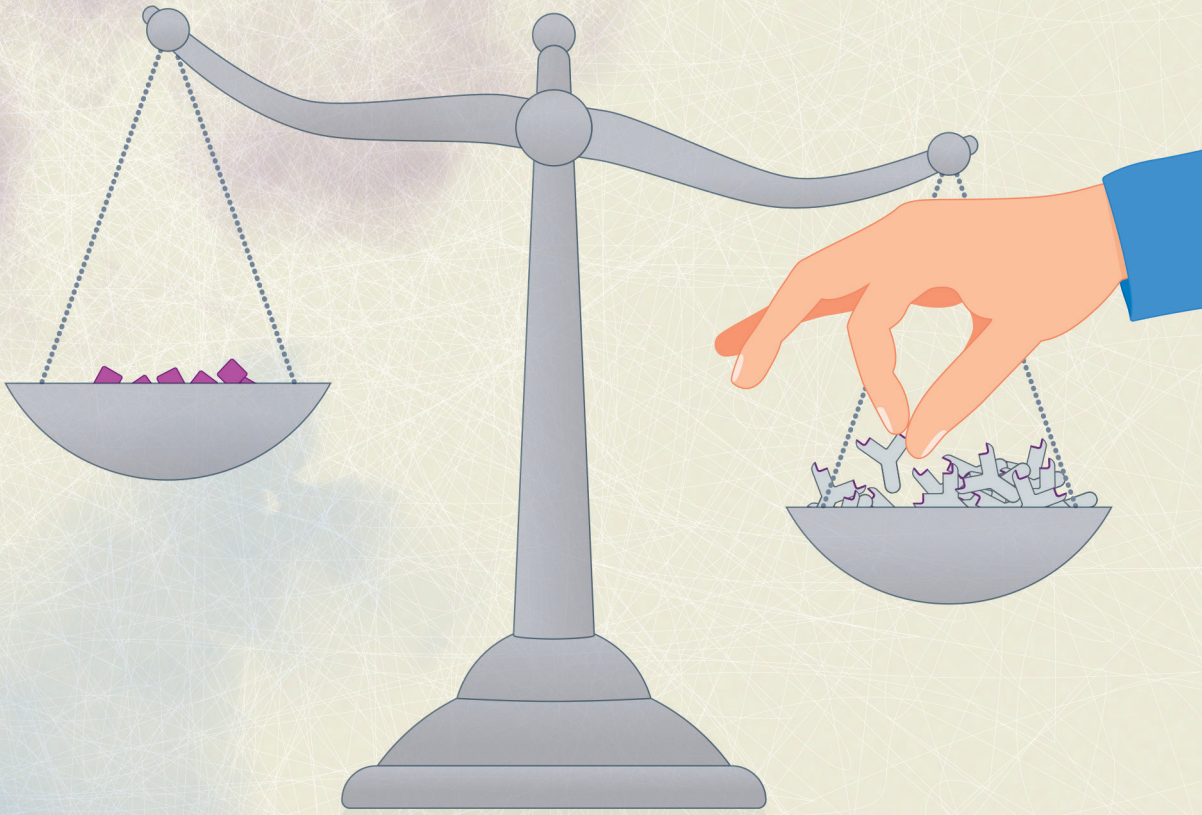
Further optimising treatment with biologicals and JAK-inhibitors in inflammatory arthritis

Focus on vaccine effectiveness and cost-effectiveness



Céleste van der Togt

Colofon

Design/lay-out and print
Promotie In Zicht | www.promotie-inzicht.nl

Publishing of this thesis was financially supported by the Sint Maartenskliniek, Nijmegen, The Netherlands.

Further optimising treatment with biologicals and JAK-inhibitors in inflammatory arthritis

Focus on vaccine effectiveness and cost-effectiveness

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 30 januari 2025
om 12.30 uur precies

door

Céleste Jeanne Theodora van der Togt
geboren op 26 februari 1994
te Wageningen

Promotoren
Dr. A.A. den Broeder
Prof. dr. B.J.F. van den Bemt

Copromotoren
Dr. L.M. Verhoef
Dr. D.F. ten Cate

Manuscriptcommissie
Prof. dr. R. van Crevel
Prof. dr. S. Repping (Amsterdam UMC)
Prof. dr. A.E.A.M. Weel-Koenders (Erasmus Universiteit Rotterdam)

Table of contents

Chapter 1

General introduction

General introduction

Inflammatory rheumatic diseases and their first-line therapy

Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), in this thesis summarized as inflammatory rheumatic diseases (IRD), are auto-immune diseases characterized by inflammation of the joints.[1] In RA and PsA, the peripheral joints are the most affected, whereas inflammation of the axial joints is the predominant feature of axSpA.[1-3] Both PsA and axSpA belong to the spectrum of spondyloarthritis (SpA), and differ in musculoskeletal and extraarticular manifestations from RA. When insufficiently treated, all three diseases can lead to pain, loss of functioning, and eventually to joint deformity and destruction.[2]

The aim of pharmacological treatment of IRD is to achieve clinical low disease activity (LDA) or preferably remission: a state in which no disease activity is present and joint damage is prevented.[4,5] It is common practice to define remission as a disease activity state using validated cut off values of composite disease activity scores. For example, in RA remission can be defined as a Disease Activity Score in 28 joints with C-reactive protein (DAS28-CRP) ≤ 2.4 and in PsA as a Psoriatic Arthritis Disease Activity Score (PASDAS) ≤ 1.9.[6,7] In some patients, remission is not an attainable target because of long-standing disease with joint damage, or specific comorbidities interfering with a composite score, such as increased joint pain scores with fibromyalgia. In these patients, LDA can be an acceptable alternative target, which is defined as a somewhat higher disease activity score (for example DAS28-CRP ≤ 2.9 or PASDAS ≤ 3.2).[4-7]

For reaching the treatment target, the treat-to-target approach is advised, as with this strategy the treatment target can be achieved more rapidly while also increasing functional outcomes, compared to routine care.[8] The treat-to-target approach includes frequent measurements of disease activity (every 1-3 months in case of active disease), the definition of the treatment target (LDA or remission), the use of a valid disease activity measurement tool (such as DAS28-CRP or PASDAS), and, most importantly, adjustment of the current therapy when the treatment target is not yet reached.[4,5] As soon as the treatment target is reached, follow-up measurements can be performed up to every 6 months.[4,5]

Among the first-line therapy of IRDs, two important groups of drugs can be distinguished: nonsteroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). For both RA and PsA, csDMARDs are advised as first-line therapy because of their disease-modifying effect, whereas NSAIDs can be used as add-on therapy for symptom relief.[9,10] The preferred first csDMARD for both diseases is methotrexate (MTX), effective in reducing musculo-

skeletal symptoms, and, in case of PsA, also skin symptoms.[11,12] As first-line therapy for axial inflammation in axSpA, only NSAIDs have shown to be effective against axial symptoms and radiographic progression, and are thus advised.[13-15] However, in axSpA patients with peripheral arthritis, the csDMARDs sulfasalazine and methotrexate can be of additional value.[14,15]

Second-line therapy: biological and targeted synthetic DMARDs

With the arrival of the biological and targeted synthetic DMARDs (bDMARDs and tsDMARDs, respectively) since 1999,[16] the pharmacological treatment options for IRD have vastly expanded. bDMARDs are proteins that are either made from, or contain components of living organisms, such as a monoclonal antibody or a soluble receptor. Because of their protein base, only parenteral administration is possible. Contrary to the bDMARDs, tsDMARDs are of a chemical origin and can be administered orally. Both types of drugs interact with a specific part of the immune system, for example by binding to cytokines, inhibiting signal transduction, preventing activation of immune cells, or inducing apoptosis. Both bDMARDs and tsDMARDs can be combined with a csDMARD to increase effectiveness of antirheumatic treatment.[12]

The b/tsDMARDs investigated in this thesis can be divided further into subclasses with different working mechanisms and indications, as shown in Table 1. Regarding bDMARDs, tumour necrosis factor (TNF) inhibitors, drugs inhibiting the cytokine TNF-alpha, are the most commonly used.[17,18] Examples of TNF-inhibitors include adalimumab and etanercept, and apart from IRD, they are also used for the treatment of inflammatory bowel diseases and psoriasis, among others.[19] Apart from the TNF-inhibitors, the bDMARDs also include medication with other working mechanisms, such as IL-6 inhibition, IL-12/23 inhibition, IL-17 inhibition, T-cell activation prevention, and B-cell depletion.[20,21] For tsDMARDs, drugs inhibiting two pathways have been developed: the Janus kinase pathway (JAK-inhibitors) and the phosphodiesterase-4 pathway (PDE-4 inhibitors).[20,21]

All aforementioned b/tsDMARDs are effective in reducing disease activity, slowing down radiological progression and improving daily functioning and are therefore used as second-line therapy for IRD after failure of one or multiple first-line therapy drugs.[15,22-24] With the large number of therapies available, remission or LDA has become an achievable goal for the majority of patients using a treat-to-target approach. A cross-sectional study of PsA patients showed remission in approximately 65% of patients[25], and for RA, LDA or remission is achievable for 75 to 80 percent of patients.[26]

Table 1. Biological and targeted synthetic DMARDs categorised by mode of action*

Mode of action	Drugs	Registered for
bDMARDs		
TNF-alpha inhibition	adalimumab, certolizumab pegol, etanercept, golimumab, infliximab	RA, PsA, axSpA
IL-6 inhibition	sarilumab, tocilizumab	RA
IL-12/23 inhibition	ustekinumab	PsA
IL-17 inhibition	ixekizumab, secukinumab	PsA, axSpA
T-cell activation inhibition	abatacept	RA, PsA
B-cell depletion	rituximab	RA
tsDMARDs		
JAK inhibition	baricitinib, filgotinib, tofacitinib, upadacitinib	RA, PsA, axSpA
PDE4 inhibition	apremilast	PsA

*Only includes the b/tsDMARDs further discussed in this thesis.
TNF: tumour necrosis factor, IL: interleukin, JAK: janus kinase, PDE4: phosphodiesterase-4.

However, b/tsDMARD therapy comes with some disadvantages, either general or drug-specific. General disadvantages of b/tsDMARDs are for example an increased infection risk[27], requirement of subcutaneous or intravenous administration (for bDMARDs), and high costs (6-12 times more expensive than csDMARDs), whereas drug-specific disadvantages include an injection site reactions for subcutaneous bDMARDs, an increased cardiovascular risk for JAK-inhibitors, and a reduced vaccination response due to rituximab.[27,28] In this thesis, I will further focus on two of these disadvantages: reduced vaccination response for rituximab and high costs of b/tsDMARD therapy. I will further elaborate on these disadvantages and explain how these might be reduced by further optimisation of treatment strategies with these drugs.

(Lower dosed) rituximab and vaccination response

Rituximab (RTX), belonging to the bDMARDs, is a chimeric monoclonal antibody drug targeting CD20 positive B-cells. Originally, it was developed for the treatment of non-Hodgkin's lymphoma but thereafter, RTX has also been shown to be safe and efficacious in the treatment of different auto-immune diseases, among which RA.[29,30] Some advantages of RTX compared to the other b/tsDMARDs could be its long treatment interval (one infusion per six to nine months), the relative safety and low costs, and high therapy adherence due to intravenous treatment.

The CD20 antigen is present on almost all types of B-cells, from precursor B-cells until B-cells differentiating into plasma cells, except for mature plasma cells.[31] Although anti-CD20 therapy does not affect mature plasma cells, the production of new plasma cells is reduced by depletion of the precursor cells.[31] During infections, plasma cells are responsible for the humoral response, which includes the production of antigen-specific antibodies. The production of these antibodies are not only induced during infection but also after vaccination, and therefore, RTX might also have an impairing effect over time on vaccination response. Indeed, a systematic literature review on influenza and pneumococcus vaccines showed a non-significantly lower humoral response after vaccination for people using RTX compared to people using other DMARDs.[32] Furthermore, additional studies investigated response after vaccination against the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) during the Coronavirus disease-19 (COVID-19) pandemic. These studies also found a significantly lower humoral response rate for RTX compared to other DMARDs.[33-35] Lower dosing and a longer time between RTX infusion and vaccinations are factors which may improve the humoral response after vaccination.

Regarding dosing, the authorised dosing schedule for RTX in the treatment of RA is two infusions of 1000 mg two weeks apart (2x 1000 mg) every six months, slightly lower than the dosing schedule for non-Hodgkin's lymphoma. However, in one of the RA registration trials, a dose of 2x 500 mg showed similar clinical efficacy to 2x 1000 mg.[36] This was later confirmed by several RCTs and a systematic review, showing that lower dosed RTX, 1x 1000 mg or 2x 500 mg every six months, indeed had similar efficacy and reduced toxicity compared to the registered dose.[37] Consequently, the European rheumatology society (EULAR) recommends using 1x 1000 mg RTX.[9]

The randomised controlled REDO-study investigated efficacy of ultra-low dose RTX, 1x 500 or 1x 200 mg, for continued treatment in patients with RA responding well to low-dose RTX.[38] Although this study could not establish formal non-inferiority between ultra-low dose and standard low-dose RTX, maintenance of response on ultra-low doses was demonstrated for a majority of patients together with significantly fewer infections.[38] Based on this outcome, it would be of interest to investigate if ultra-low dose RTX also has a positive effect on the vaccination response, leading to increased protection against the SARS-CoV-2 virus in this vulnerable group. Also, the effect of RTX dose on the effectiveness of a booster vaccination would be of interest, in case of insufficient response after the standard doses.

Regarding timing of vaccination after RTX therapy, the European guideline recommends to vaccinate at least six months after and at least four weeks before the next rituximab cycle.[28] This recommendation can easily be implemented for elective

vaccinations such as travel vaccinations, but is more difficult in case of more acute vaccinations, for example vaccinations during the SARS-CoV-2 pandemic, or a tetanus vaccination because of potential exposure. However, the recommendation of timing is merely based on expert opinion and, therefore, additional evidence on the timing of vaccination in RTX patients is required. Additionally, if humoral response is less impaired after ultra-low dose RTX, the timing of vaccination may be less important when using these doses.

Therefore, the aims of the first part of this thesis were:

- To investigate the effect of rituximab dosing and timing on humoral response against COVID-19 after two vaccinations in patients treated with rituximab (**chapter 2**);
- To investigate the effect of rituximab dosing on persistence of humoral response after two COVID-19 vaccinations (**chapter 3**);
- To investigate the effect of rituximab dosing and timing on seroconversion after a third COVID-19 vaccine dose in patients treated with rituximab (**chapter 3**).

Cost-effective use of b/tsDMARDs

As previously explained, a good level of disease control can be achieved in the majority of patients using the available b/tsDMARDs, and thus considerations other than controlling disease activity become more relevant. An important consideration in this context should be the costs of treatment. In the Netherlands, the overall health care expenditures are expected to increase until 2060 with approximately 2.8 percent per year every years, according to the calculation of the Dutch National Institute for Public Health and the Environment (RIVM).[39] Hospital care receives the largest part of the total health care budget (around 96 billion euros in 2060), partly due to increasing costs of (new) therapies.

Roughly estimated, b/tsDMARDs are around six to twelve times more expensive per year (2000 to 12000 euros per patient per year (pppy)) in the Netherlands than csDMARD therapy (200 to 1000 euros pppy).[40] This is partly due to the more expensive production process (for bDMARDs) but mainly to the current market structure. As b/tsDMARDs are relatively new on the market, a significant number of the drugs mentioned in *table 1* are still patented. The patented drugs without alternative drugs in the same subclass (e.g. abatacept, ustekinumab) are in the first market structure phase, also known as the monopoly phase, in contrast to the patented drugs with subclass alternatives (e.g. JAK-inhibitors, IL-6 inhibitors), belonging to the oligopoly phase (*figure 1*).[41] The TNF-inhibitors are in the third market structure phase, the competitive phase, in which there are a small number of similar drugs available.[41] For bDMARDs, these similar drugs are called 'biosimilars', defined as highly similar to

another biological medicine (the 'originator') already marketed in the EU.[42] A progress in market structure phase leads to cost reduction due to competition, with current b/tsDMARDs in phase 1 priced around 12000 euros pppy in contrast to 2000-3000 euros for those in phase 3.

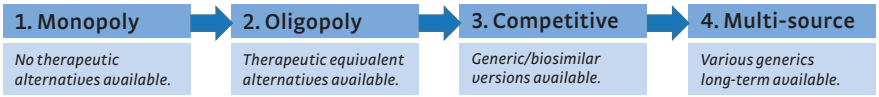


Figure 1. Phases of market structure *(based on: Van der Erf et al.[41])*

Clinicians can reduce costs by prescribing b/tsDMARDs efficiently and effectively. Therefore, strategies that reduce health care costs without affecting clinical effectiveness, also known as cost-effective strategies, are needed. Cost-effectiveness is defined as the estimated costs of a specific treatment in relation to its expected benefits, which can also be expressed as the effectiveness of therapy divided by the costs (*figure 2).*[43] Using this expression, cost-effectiveness can be increased in multiple ways, either by reducing costs, increasing effectiveness, or both.

$$\textit{Cost-effectiveness} = \frac{\textit{Effectiveness}}{\textit{Costs}}$$

Figure 2. Cost-effectiveness

So far, various strategies for more cost-effective use of b/tsDMARDs have been investigated, among which dose reduction and biosimilar use. For biosimilars specifically, there are consensus-based recommendations for use in clinical practice available.[44] However, an overview of all available and potential strategies on cost-effective use of b/tsDMARDs has not yet been composed. Moreover, evidence and consensus-based recommendations on all strategies, such as those available for biosimilars, are needed to guide cost-effective use of b/tsDMARDs in clinical rheumatology care.

A previously explored strategy is disease activity-guided dose optimisation, in which the dose of a b/tsDMARD is stepwise reduced in patients with LDA or remission, by either reducing the dose or increasing the interval between doses. This strategy requires tight monitoring of the disease activity, so that the dose of b/tsDMARD can

be increased when needed. Disease activity-guided dose optimisation has shown to be non-inferior on disease activity and cost-effective compared to continuation of b/tsDMARDs,[45-47] for example in the randomized controlled DRESS-study with an extension study up to 3 years.[48,49] However, results on the effectiveness and safety longer than three years are not yet available. Those results could for example give insight in the long-term disease activity and drug dose, the relevance of a subsequent dose optimisation attempt, and the effect of dose optimisation on radiographic joint progression.

An promising strategy is increasing drug exposure of the b/tsDMARD by interference with the pharmacokinetics of the drug. Examples are enhancement of drug absorption, inhibition of drug excretion, or inhibition of drug metabolism, the latter also named pharmacokinetic boosting.[50] Pharmacokinetic boosting is already used in the treatment of the human immunodeficiency virus (HIV), by inhibiting the cytochrome P450 isoenzyme 3A (CYP3A).[50,51] This enzyme is involved in the metabolism of several antiretroviral drugs, and when these drugs are combined with a registered CYP3A-inhibiting drug, such as cobicistat or ritonavir, the dose interval of these drugs can be halved.[50,51] Tofacitinib, one of the JAK-inhibitors, is also metabolized by the CYP3A-enzyme, and therefore the strategy of pharmacokinetic boosting could potentially be applied to tofacitinib treatment.[52]

Consequently, the aims of the second part of this thesis were:

- To provide an overview of strategies for cost-effective use of b/tsDMARDs and to formulate evidence and consensus-based recommendations on this subject (**chapter 4**);
- To investigate efficacy and safety of disease activity-guided dose optimisation of TNF-inhibitors in rheumatoid arthritis up to 10 years (**chapter 5**);
- To investigate the bioequivalence of pharmacokinetic boosting of tofacitinib with cobicistat (**chapter 6**).

Aim and outline of this thesis

In summary, this thesis consists of the following chapters:

- A prospective cohort study assessing the effect of dosage and timing of (ultra-)low dose rituximab on humoral response against COVID-19 after 2 vaccinations in RA patients (**chapter 2**);
- A follow-up study of the previously mentioned cohort investigating the efficacy of a third COVID-19 vaccine including the associations of RTX dosage and timing, and the persistence of humoral response against COVID-19 (**chapter 3**).
- A scoping review and Delphi study for development of consensus-based points-to-consider on strategies for cost-effective use of b/tsDMARDs in RA, PsA, and axSpA (**chapter 4**);
- An observational follow-up of the DRESS-study investigating 10-year effectiveness of disease activity-guided dose optimisation of b/tsDMARDs in RA (**chapter 5**);
- A pharmacokinetic crossover study assessing bioequivalence of tofacitinib with cobicistat once daily to tofacitinib twice daily (**chapter 6**).
- A general discussion of the abovementioned chapters (**chapter 7**);
- A summary of the thesis (**chapter 8**).

References

1. Saalfeld W, Mixon AM, Zelie J, Lydon EJ. Differentiating Psoriatic Arthritis from Osteoarthritis and Rheumatoid Arthritis: A Narrative Review and Guide for Advanced Practice Providers. *Rheumatol Ther.* 2021;8(4):1493-1517.
2. Mease PJ, Bhutani MK, Hass S, Yi E, Hur P, Kim N. Comparison of Clinical Manifestations in Rheumatoid Arthritis vs. Spondyloarthritis: A Systematic Literature Review. *Rheumatol Ther.* 2022;9(2):331-378.
3. Sieper J, Rudwaleit M, Baraliakos X, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis.* 2009;68 Suppl 2:ii1-44.
4. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis.* 2016;75(1):3-15.
5. Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis.* 2018;77(1):3-17.
6. Coates LC, Gladman DD, Nash P, et al. Secukinumab provides sustained PASDAS-defined remission in psoriatic arthritis and improves health-related quality of life in patients achieving remission: 2-year results from the phase III FUTURE 2 study. *Arthritis Res Ther.* 2018;20(1):272.
7. Fleischmann R, van der Heijde D, Koenig AS, et al. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? *Ann Rheum Dis.* 2015;74(6):1132-1137.
8. Stoffer MA, Schoels MM, Smolen JS, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. *Ann Rheum Dis.* 2016;75(1):16-22.
9. Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis.* 2023;82(1):3-18.
10. Coates LC, Soriano ER, Corp N, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol.* 2022;18(8):465-479.
11. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis.* 2020;79(6):700-712.
12. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis.* 2020;79(6):685-699.
13. Kroon FP, van der Burg LR, Ramiro S, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) for axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis). *Cochrane Database Syst Rev.* 2015;2015(7):Cd010952.
14. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis.* 2017;76(6):978-991.
15. Danve A, Deodhar A. Treatment of axial spondyloarthritis: an update. *Nat Rev Rheumatol.* 2022;18(4):205-216.
16. Agency. EM. Remicade. https://www.ema.europa.eu/en/medicines/human/EPAR/remicade#authorisation-details-section. Accessed 31-01-2023.
17. Fletcher A, Lassere M, March L, et al. Patterns of biologic and targeted-synthetic disease-modifying antirheumatic drug use in rheumatoid arthritis in Australia. *Rheumatology (Oxford).* 2022.
18. Kerola AM, Rollefstad S, Kazemi A, et al. Psoriatic arthritis, axial spondyloarthritis and rheumatoid arthritis in Norway: nationwide prevalence and use of biologic agents. *Scand J Rheumatol.* 2022:1-9.
19. Jang DI, Lee AH, Shin HY, et al. The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. *Int J Mol Sci.* 2021;22(5).
20. Rein P, Mueller RB. Treatment with Biologicals in Rheumatoid Arthritis: An Overview. *Rheumatol Ther.* 2017;4(2):247-261.
21. Silvagni E, Bortoluzzi A, Ciancio G, Govoni M. Biological and synthetic target DMARDs in psoriatic arthritis. *Pharmacol Res.* 2019;149:104473.

22. Kerschbaumer A, Sepriano A, Smolen JS, et al. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis.* 2020;79(6):744-759.
23. Ruyssen-Witrand A, Perry R, Watkins C, et al. Efficacy and safety of biologics in psoriatic arthritis: a systematic literature review and network meta-analysis. *RMD Open.* 2020;6(1).
24. Campanaro F, Batticciotto A, Zaffaroni A, Cappelli A, Donadini MP, Squizzato A. JAK inhibitors and psoriatic arthritis: A systematic review and meta-analysis. *Autoimmun Rev.* 2021;20(10):102902.
25. Gorlier C, Orbai AM, Puyraimond-Zemmour D, et al. Comparing patient-perceived and physician-perceived remission and low disease activity in psoriatic arthritis: an analysis of 410 patients from 14 countries. *Ann Rheum Dis.* 2019;78(2):201-208.
26. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis: A Review. *Jama.* 2018; 320(13):1360-1372.
27. Sepriano A, Kerschbaumer A, Bergstra SA, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis.* 2023;82(1):107-118.
28. Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis.* 2020;79(1):39-52.
29. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med.* 2004;350(25):2572-2581.
30. Tak PP, Rigby W, Rubbert-Roth A, et al. Sustained inhibition of progressive joint damage with rituximab plus methotrexate in early active rheumatoid arthritis: 2-year results from the randomised controlled trial IMAGE. *Ann Rheum Dis.* 2012;71(3):351-357.
31. Crickx E, Weill JC, Reynaud CA, Mahévas M. Anti-CD20-mediated B-cell depletion in autoimmune diseases: successes, failures and future perspectives. *Kidney Int.* 2020;97(5):885-893.
32. Hua C, Barnetche T, Combe B, Morel J. Effect of methotrexate, anti-tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken).* 2014;66(7):1016-1026.
33. Boekel L, Steenhuis M, Hooijberg F, et al. Antibody development after COVID-19 vaccination in patients with autoimmune diseases in the Netherlands: a substudy of data from two prospective cohort studies. *Lancet Rheumatol.* 2021;3(11):e778-e788.
34. Furer V, Eviatar T, Zisman D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis.* 2021;80(10):1330-1338.
35. Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS- CoV-2 vaccination in patients with rheumatic diseases. *Ann Rheum Dis.* 2021;80(10):1357-1359.
36. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum.* 2006;54(5):1390-1400.
37. Bredemeier M, Campos GG, de Oliveira FK. Updated systematic review and meta-analysis of randomized controlled trials comparing low- versus high-dose rituximab for rheumatoid arthritis. *Clin Rheumatol.* 2015;34(10):1801-1805.
38. Verhoef LM, den Broeder N, Thurlings RM, et al. Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial. *The Lancet Rheumatology.* 2019;1(3):e145-e153.
39. Milieu. RvVe. Toekomstverkenning zorguitgaven 2015-2060 : Kwantitatief vooronderzoek in opdracht van de Wetenschappelijke Raad voor het Regeringsbeleid (WRR). Deel 1: toekomstprojecties. https://www.rivm.nl/publicaties/toekomstverkenning-zorguitgaven-2015-2060-kwantitatief-vooronderzoek-in-opdracht-van. Published 2020. Accessed 31-01-2023.
40. Zorginstituut Nederland. Medicijnkosten.nl. www.medicijnkosten.nl. Accessed 27-09-2022.

41. van der Erf SD, F.; Heida, J.P. . Versterken inkoop geneesmiddelen. Onderzoek in opdracht van de Nederlandse Vereniging van Ziekenhuizen Web site. https://www.sirm.nl/docs/Publicaties/Eindrapport-Versterken-inkoop-geneesmiddelen_november-2016.pdf. Published 2016. Accessed 2023-08-21.
42. Agency. EM. Biosimilars in the EU : information guide for healthcare professionals. https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf. Published 2017. Accessed 2023-08-19.
43. National Institute for Health and Care Excellence (NICE). Process and methods: 7 Assessing cost effectiveness. The guidelines manual Web site. https://www.nice.org.uk/process/pmg6/chapter/assessing-cost-effectiveness. Published 2012. Accessed 25-07-2022.
44. Kay J, Schoels MM, Dörner T, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. *Ann Rheum Dis.* 2018;77(2):165-174.
45. Verhoef LM, van den Bemt BJ, van der Maas A, et al. Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. *Cochrane Database Syst Rev.* 2019;5(5):Cd010455.
46. Vasconcelos LB, Silva MT, Galvao TF. Reduction of biologics in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatol Int.* 2020;40(12):1949-1959.
47. Vinson D, Molet-Benhamou L, Degboé Y, et al. Impact of tapering targeted therapies (bDMARDs or JAKis) on the risk of serious infections and adverse events of special interest in patients with rheumatoid arthritis or spondyloarthritis: a systematic analysis of the literature and meta-analysis. *Arthritis Res Ther.* 2020;22(1):97.
48. van Herwaarden N, van der Maas A, Minten MJ, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. *Bmj.* 2015;350:h1389.
49. Bouman CA, van Herwaarden N, van den Hoogen FH, et al. Long-term outcomes after disease activity-guided dose reduction of TNF inhibition in rheumatoid arthritis: 3-year data of the DRESS study - a randomised controlled pragmatic non-inferiority strategy trial. *Ann Rheum Dis.* 2017;76(10):1716-1722.
50. Salama E, Eke AC, Best BM, Mirochnick M, Momper JD. Pharmacokinetic Enhancement of HIV Antiretroviral Therapy During Pregnancy. *J Clin Pharmacol.* 2020;60(12):1537-1550.
51. Larson KB, Wang K, Delille C, Otofokun I, Acosta EP. Pharmacokinetic enhancers in HIV therapeutics. *Clin Pharmacokinet.* 2014;53(10):865-872.
52. Xeljanz - Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf. Accessed 30-11-2021.

Chapter 2

Humoral response to Coronavirus Disease-19 Vaccines is dependent on dosage and timing of rituximab in patients with rheumatoid arthritis

Céleste J.T. van der Togt
David F. Ten Cate
Nathan den Broeder
Janette Rahamat-Langendoen
Bart J.F. van den Bemt
Alfons A. den Broeder

Published in Rheumatology (Oxford), June 2022

Abstract

Objectives

Humoral response to vaccines in rheumatoid arthritis (RA) patients treated with rituximab (RTX) in standard dosages (≥1000mg) is decreased. Ultra-low dosages (500 or 200mg) may have better response. Also, timing after latest RTX infusion may be an important variable. We aimed to investigate the influence of RTX dosage and timing on response to COVID-19 vaccination in RA patients.

Methods

A single-centre observational study (n=196) investigated the humoral response, measured by total Ig anti-COVID-19 assay (positive response ≥1.1), 2-6 weeks after complete COVID-19 vaccination. A multivariable logistic regression model was built to study the effect of RTX dosage and time between latest rituximab and vaccination on response, adjusting for age and methotrexate use.

Results

After two-dose vaccination, the response rate was significantly better for patients receiving 200 mg (n=31, 45%) rituximab compared with 1000 mg (n=98, 26%; OR 3.07, 95% CI 1.14 to 8.27) and for each additional month between latest rituximab and vaccination (OR 1.67, 1.39 to 2.01).

Conclusion

Both increased time between latest rituximab infusion and complete vaccination, and 200 mg as latest dose were associated with a better response to COVID-19 vaccination and should be considered when trying to increase vaccine response after rituximab in RA patients.

Introduction

Since the beginning of 2020, the SARS CoV-2 virus rapidly spread around the world, causing widespread coronavirus disease-19 (COVID-19) infections. Although the risk of severe SARS-CoV-2 is not increased for patients with rheumatoid arthritis (RA) in general,[1] RA patients treated with rituximab (RTX) do have an increased risk.[2] Treatment with rituximab also impairs humoral response to both COVID-19[3-6] and non-COVID-19 vaccines.[7] Thus, for optimal prevention of COVID-19 in this patient group, increasing vaccine response is of utmost importance.

Two factors could conceptually influence vaccine response in patients treated with RTX: RTX dose and vaccination timing. The effect of RTX on severity of infection and vaccination response has been shown for standard doses only (1000-2000 mg per cycle). However, data from a randomised controlled study shows that ultra-low dose rituximab, 500 or 200 mg per cycle, has similar efficacy, and halves infection risk.[8] Therefore, it would be of interest to investigate humoral response to COVID-19 vaccines after these ultra-low doses.

Recent studies on COVID-19 vaccination with small RTX populations suggest an association between longer time since latest RTX infusion at first vaccination and better humoral response.[3,4,9] Again, these studies only described patients receiving full dose RTX, indicating the importance of data on ultra-low dosed rituximab.

The Dutch nationwide COVID-19 vaccination effort started in the spring of 2021. This provided us the opportunity to study the effects of RTX dose and relative timing of vaccination on humoral response to COVID-19 vaccination in our large cohort of RA patients using regular and ultra-low dose RTX.

Patients and methods

Patients

All RA patients aged ≥ 16 years of the Sint Maartenskliniek (Nijmegen, the Netherlands) were invited to participate in the cohort, if i) they received at least one dose of rituximab (200 mg, 500 mg, or 1000 mg) in the year prior to their first dose of COVID-19 vaccination and ii) COVID-19 vaccination was performed according to the registered dose and interval. The RTX dose was based on the treating physician's discretion.

At the time of the study, the Dutch national vaccine programme included four vaccines against COVID-19, of which three were two-dose regimens: BNT162b2

(Comirnaty; Pfizer-BioNtech), ChAdOx1 nCoV-19 (Vaxzevria; AstraZeneca) and CX-024414 (Spikevax; Moderna), and one single-dose: Ad.26.COV2.S (COVID-19 vaccine Janssen).[10] If a COVID-19 infection had occurred in the six months prior to first vaccination, the Dutch government also approved one dose of a two-dose vaccine as fully vaccinated.[11]

This study has been approved by the ethics committee (CMO Arnhem-Nijmegen, 2021-7406) and the competent authority (CCMO, NL76709.091.21). The study protocol was registered in the Netherlands Trial Register (NL9342) before start. All participants provided written informed consent.

Study design

Relevant demographics and RA disease characteristics were obtained at study inclusion (**Supplementary Text 1**). Also, we recorded relevant treatment characteristics including concomitant csDMARD use, prednisolone use, current b/tsDMARD, cumulative RTX dose, and dosage and date of the latest RTX administration. Details on a previous COVID-19 infection (including date of positive test) and COVID-19 vaccination (type and dates) were provided by the participant. For humoral response assessment, blood samples were drawn two to six weeks after the second COVID-19 vaccination.[3,12] Total immunoglobulin levels (IgT, including IgA, IgG and IgM) against COVID-19 were measured in serum using a CE marked diagnostic ELISA assay (Wantai SARS-CoV-2 Ab assay®, Beijing Wantai Biological BV, Beijing, China).[13] Test results were reported by the laboratory as negative (index number <1), borderline (0.9-1.1) or positive (≥ 1.1), in accordance with the cut-off points by the manufacturer.[13,14]

Statistical analysis

Descriptive statistics were appropriately used to assess group characteristics. Fisher's Exact Test was used to univariately assess difference between the three dosage groups, and univariable logistic regression between a previous COVID-19 infection and IgG-levels, and humoral response. Variables were used in the multivariate model with highest associations in the univariate analysis or with prognostic value according to previous literature (**Supplementary Table 1**). We used a rule of thumb of 10 events per variable included in the multivariable model. A multivariable logistic regression model was built using humoral response 2-6 weeks after last vaccination as dependent variable, dose of latest RTX and time between latest RTX and first vaccination as central determinants and corrected for age, csDMARD use and prednisolone use. A cut-off point of ≥ 1.1 of the IgT index number was used to dichotomise the outcome. All data were entered in an electronic data capture database (Castor EDC, Amsterdam, Netherlands) and subsequently exported to StataIC (version 13, StataCorp LLC, TX, USA) for statistical analyses.

Results

Patients

Between April 7 and July 15, 2021, 376 patients were asked to participate. 259 (69%) provided written informed consent. Post vaccination serology was taken in 196 (52%) patients. Of these 196 participants, 31 (16%) received 200 mg rituximab as latest dose, 67 (34%) 500 mg and 98 (50%) 1000 mg, including one participant with 2x 1000 mg.

Baseline characteristics

Baseline demographic and clinical data were similar in the three groups (200 mg, 500 mg and 1000 mg) (Table 1). The median time between latest RTX and first vaccination was 128 days (IQR 90-165). Most patients received the BNT162b2 vaccine (n=153, 78%),

Table 1. Baseline characteristics

	Total (n=196)	200mg (n=31)	500mg (n=67)	1000mg# (n=98)
Age (years)‡	68 ± 11	66 ± 11	68 ± 12	64 ± 11
Female sex	138 (70)	16 (52)	55 (82)	67 (68)
Disease duration (years)†	15 (8-23)	17 (9-25)	16 (8-23)	13 (5-21)
RF and/or ACPA positive	165 (84)	29 (94)	58 (87)	78 (80)
Concomitant csDMARD use	112 (57)	18 (58)	35 (52)	59 (60)
Methotrexate	65 (33)	10 (32)	21 (31)	34 (35)
Hydroxychloroquine	20 (10)	4 (13)	5 (7)	11 (11)
Sulfasalazine	10 (5)	1 (3)	3 (4)	6 (6)
Azathioprine	7 (4)	2 (6)	3 (4)	2 (2)
Leflunomide	6 (3)	1 (3)	1 (1)	4 (4)
Multiple	4 (2)	0 (0)	2 (3)	2 (2)
Concomitant prednisolone use	36 (18)	2 (6)	7 (10)	27 (28)
Duration of rituximab use (years)‡	4.7 ± 3.4	6.2 ± 3.2	4.7 ± 2.9	4.3 ± 3.7
Days between rituximab & 1st vaccine†	128 (90-165)	126 (86-161)	131 (86-171)	128 (93-162)
Vaccine type				
BNT162b2 (BioNTech/Pfizer)	153 (78)	26 (84)	56 (84)	71 (72)
ChAdOx1 nCoV-19 (AstraZeneca)	30 (16)	5 (16)	7 (10)	18 (18)
CX-024414 (Moderna)	13 (6)	0 (0)	4 (6)	9 (9)
Prior documented COVID infection	20 (10)	2 (6)	8 (12)	10 (10)

Either displayed as number (percentage), median (interquartile range)† or mean ± standard deviation‡.
Includes 1 patient treated with 2x 1000mg.

followed by the ChAdOx1 nCoV-19 (n=30, 16%) and CX-024414 (n=13, 6%). No patients in the 200 mg group received the CX-024414 vaccine. A total of 20 (10%) reported a previous COVID-19 infection, of which five patients (25%) only received one vaccine dose.

Factors associated with vaccination response

Fifty-five patients (28%) had a vaccination response positive antibody test (IgT≥1.1). In the univariate analysis, lower dosage and later timing were associated with vaccination response (p<0.05) (**Supplementary Table 1**). Compared to the 1000 mg group, a positive vaccination response was significantly more frequent in the 200 mg group (26% versus 45% (p=0.045)) but not for 500 mg (26% versus 24%, p=0.856). Response rate was 29% (45/153) for the BNT162b2 vaccine, 20% (6/30) for the ChAdOx1 nCoV-19 vaccine and 31% (4/13) for the CX-024414 vaccine. A previous COVID-19 infection had a nonsignificant higher chance of a positive vaccination response (9/20, 45% versus 46/175, 26%, p=0.11). In the participants with a previous COVID-19 infection, response rate was 46% (7/15) for participants who received two-dose vaccination, and 40% for one-dose (2/5).

The multivariable model including time between latest rituximab infusion and first vaccination, age, concomitant csDMARD use, and prednisolone use confirmed the association between vaccination response and low dose RTX (200 mg group versus 1000 mg (OR 3.07 [95% CI 1.55 to 8.27, p=0.03]). The time between most recent infusion and first vaccination was positively associated with higher chance of vaccination response in the multivariable model (per month OR 1.67 [95% CI 1.39 to 2.01, p<0.0001], see figure 1).

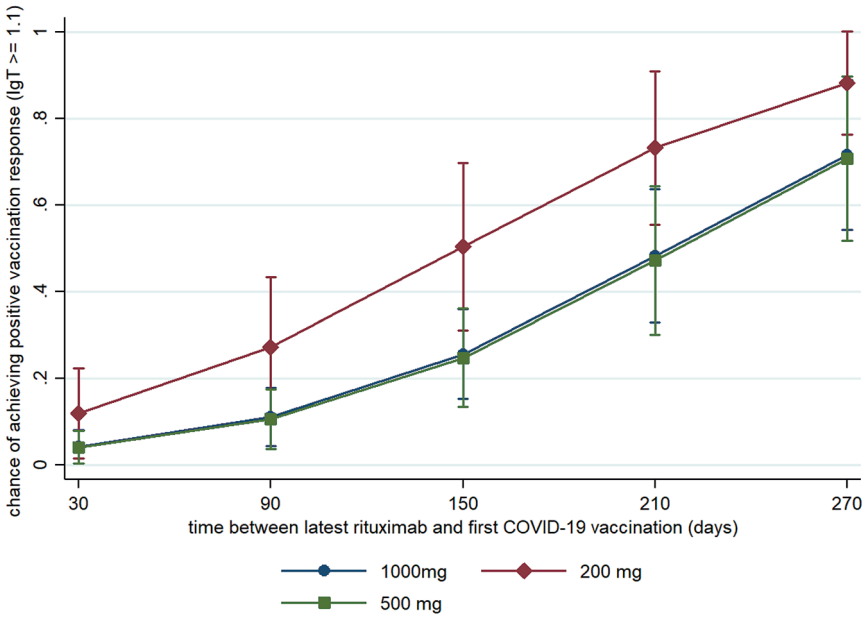


Figure 1. Cumulative humoral response on COVID-19 vaccination per dosage group, corrected for relevant confounders.

Discussion

This study is the first to show that 200 mg RTX in RA patients is associated with a significantly better humoral response to COVID-19 vaccines than higher dosages (500 mg and 1000 mg) of RTX. Also, timing the vaccination longer after the RTX infusion yields significantly better vaccination response, confirming data in the literature.[3,4,9]

Although this study is the largest cohort investigating humoral response to COVID-19 vaccines in RA patients using (ultra-low dose) RTX, this study has some limitations. First, a relatively small number of patients received 200 mg. Nonetheless, statistically significant factors were identified. Another limitation may be the lack of a comparison group of RA patients with other DMARDs. However, COVID-19 vaccination response in patients with other DMARDs and has been extensively investigated in other studies and the focus of the study was different RTX dosages, not co-DMARDs.[3,5] Last, because of study feasibility, only one surrogate vaccination response outcome was investigated, namely humoral response, and not T-cell response nor clinical vaccine efficacy. A clear cut-off in amount of protective antibodies measured by commercial

assays is yet unclear, however the assay used in this study has been clinically validated.[13,15] Besides, T-cell response is associated with humoral response.[9] Therefore, we think that the differences in vaccination response could indeed translate to differences in clinical vaccine efficacy.

Based on our findings, two recommendations can be formulated. First, COVID-19 vaccination should be timed as late as possible after the latest rituximab infusion, preferably more than one rituximab cycle (6 months). Second, RTX should be dosed as low as possible, preferably 200 mg. The safety and feasibility of this dosage is supported by high quality evidence.[8,16]

Some important questions remain, including the effects of a third booster vaccination in patients who did not show response to the first vaccination, and the optimal timing for RTX retreatment after the vaccination. Also, it would be important to see whether these differences between dose and timing on vaccination response can be extrapolated to COVID-19 infection risk and infection outcome. Last, it would be of interest to investigate how long vaccination response lasts.
In conclusion, COVID-19 vaccination response can be improved in RTX treated RA patients by adjusting the dose and time between rituximab treatment and vaccination.

References

1. Wang Q, Liu J, Shao R, et al. Risk and clinical outcomes of COVID-19 in patients with rheumatic diseases compared with the general population: a systematic review and meta-analysis. Rheumatol Int. 2021;41(5):851-61.
2. Avouac J, Drumez E, Hachulla E, et al. COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. Lancet Rheumatol. 2021;3(6):e419-e26.
3. Furer V, Eviatar T, Zisman D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis. 2021;80(10):1330-8.
4. Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS- CoV-2 vaccination in patients with rheumatic diseases. Ann Rheum Dis. 2021;80(10):1357-9.
5. Boekel L, Steenhuis M, Hooijberg F, et al. Antibody development after COVID-19 vaccination in patients with autoimmune diseases in the Netherlands: a substudy of data from two prospective cohort studies. Lancet Rheumatol. 2021.
6. Benucci M, Damiani A, Infantino M, et al. Correspondence on "SARS-CoV-2 vaccination in rituximab-treated patients: evidence for impaired humoral but inducible cellular immune response"by Bonelli et al. Ann Rheum Dis. 2021;80(10):e166.
7. Hua C, Barnetche T, Combe B, et al. Effect of methotrexate, anti-tumor necrosis factor α, and rituximab on the immune response to influenza and pneumococcal vaccines in patients with rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2014;66(7):1016-26.
8. Verhoef LM, den Broeder N, Thurlings RM, et al. Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial. . Lancet Rheumatol. 2019;1:145-53.
9. Moor MB, Suter-Riniker F, Horn MP, et al. Humoral and cellular responses to mRNA vaccines against SARS-CoV-2 in patients with a history of CD20 B-cell-depleting therapy (RituxiVac): an investigator-initiated, single-centre, open-label study. Lancet Rheumatol. 2021.
10. RIVM (Dutch National Institute for Public Health and the Environment). The COVID-19 vaccines. Access date: 07-10-2021. Available from: https://www.rivm.nl/en/covid-19-vaccination/covid-19-vaccines.
11. Government of the Netherlands. Using proof of vaccination to generate a COVID Certificate. Access date: 07-10-2021. Available from: https://www.government.nl/topics/coronavirus-covid-19/covid-certificate/proof-of-vaccination.
12. Walsh EE, Frenck RW, Jr., Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med. 2020;383(25):2439-50.
13. Beijing Wantai Biological Pharmacy Enterprise Co. L. WANTAI SARS-CoV-2 Ab ELISA. Access date: 07-10-2021. Available from: https://www.fda.gov/media/140929/download.
14. Trabaud MA, Icard V, Milon MP, et al. Comparison of eight commercial, high-throughput, automated or ELISA assays detecting SARS-CoV-2 IgG or total antibody. J Clin Virol. 2020;132:104613.
15. GeurtsvanKessel CH, Okba NMA, Igloi Z, et al. An evaluation of COVID-19 serological assays informs future diagnostics and exposure assessment. Nat Commun. 2020;11(1):3436.
16. den Broeder N, Verhoef LM, De Man Y, et al. Long-term Effectiveness of Ultra-Low Doses of Rituximab in Rheumatoid Arthritis [abstract]. Arthritis Rheumatol. 2021;73.

Supplementary data

Supplementary text 1. Relevant demographics and disease characteristics obtained Relevant demographics obtained for this study: gender, age, tobacco use (current/past/never), alcohol use (current/past/never), previous COVID-infection including date and severity (no symptoms/mild symptoms/fever/hospitalization/ICU admission), and relevant comorbidities (multiple possible): hypertension/diabetes/obesity/ischemic heart disease/asthma or COPD/CVID (common variable immunodeficiency disorder)/haematologic malignancy/other).

Relevant RA disease characteristics obtained for this study: year of RA diagnosis, rheumatoid factor positivity, ACPA (anti-citrullinated protein antibodies) positivity, presence of erosions, extra-articular manifestation of RA, immunoglobulin levels including date and IgA/IgG/IgM subtypes (if previously measured), and last DAS28 before first vaccine including its relevant variables (any available): swollen joint count, tender joint count, VAS global disease activity by patient, ESR, CRP.

Supplementary table 1. univariate logistic regression of included variables with response (IgT 2-6 weeks after last vaccination ≥ 1.1) as dependent variable, sorted by P-value.

Variable	P-value	OR	95% CI
Days between latest RTX and 1st vacc	**<0.0001**	1.02	1.01-1.02
Current use of RTX	**0.004**	0.27	0.11-0.66
IgG-levels [n=149]	**0.008**	1.24	1.06-1.46
Latest RTX dose of 200mg (vs 1000mg)	**0.041**	2.40	1.04-5.57
Second latest RTX dose of 200mg	0.059	2.39	0.97-5.87
Previous COVID infection	0.084	2.29	0.89-5.89
Last DAS28 before 1st vaccine	0.111	0.77	0.56-1.06
ACPA positivity	0.117	1.90	0.85-4.26
IgA-levels [n=149]	0.149	1.19	0.94-1.50
Concomitant csDMARD use	0.156	0.64	0.34-1.19
Current smoking	0.193	0.47	0.15-1.46
Concomitant oral prednisolone use	0.207	0.56	0.23-1.37
AstraZeneca vaccine (vs Pfizer)	0.297	0.6	0.23-1.57
Extra-articular manifestation of RA	0.386	0.56	0.15-2.06
Years of RTX use	0.398	1.04	0.95-1.14
Age	0.418	0.99	0.96-1.02
Concomitant MTX use	0.450	0.77	0.39-1.52
RF and/or ACPA positivity	0.461	1.41	0.57-3.48
Presence of relevant comorbidity	0.523	0.81	0.43-1.54
Gender	0.548	1.23	0.63-2.40
Current alcohol use	0.577	1.20	0.63-2.27
Cumulative RTX dose	0.582	1.00	1.00-1.00
RF positivity	0.608	1.22	0.57-2.63
IgM-levels [n=149]	0.625	1.26	0.50-3.14
Years since RA diagnosis	0.784	1.00	0.97-1.03
Latest RTX dose of 500mg (vs 1000mg)	0.812	0.92	0.44-1.89
Presence of erosions	0.850	0.96	0.61-1.51
Moderna vaccine (vs Pfizer)	0.918	1.07	0.31-3.64
Second latest RTX dose of 500mg	0.922	1.04	0.48-2.23
Days between last vaccination and IgT	0.945	1.00	0.96-1.04

Chapter 3

Seroconversion after a third COVID-19 vaccine is affected by rituximab dose but persistence is not in patients with rheumatoid arthritis

Céleste J.T. van der Togt
David F. Ten Cate
Bart J.F. van den Bemt
Janette Rahamat-Langendoen
Nathan den Broeder
Alfons A. den Broeder

Published in Rheumatology (Oxford), April 2023

Abstract

Objectives

In patients with rheumatoid arthritis (RA) treated with (ultra-)low dose rituximab (RTX), we investigated the association of dosing and timing of RTX on sero-conversion after third COVID-19 vaccination, and the persistence of humoral response after a two-dose vaccination.

Methods

In this monocentre observational study, patients from the COVAC cohort were included in the third vaccine analysis if humoral response was obtained 2-6 weeks after third vaccination in previous non-responders, and in the persistence analysis if a follow-up humoral response was obtained before third vaccination in previous responders. Dichotomization between 'positive' and 'negative' response was based on the assay cut-off. The association between latest the RTX dose before first vaccination, timing between latest RTX and vaccination, and response was analysed with univariable logistic regression.

Results

Of the 196 patients in the cohort, 98 were included in the third vaccine analysis and 23 in the persistence analysis. Third vaccination response was 19/98 (19%) and higher for 200 mg RTX users (5/13, 38%) than 500 and 1000 mg (7/37, 19% and 7/48, 15%, respectively). Non-significant trends were seen for higher response with lower dosing (200 versus 1000 mg: OR 3.66, 95% CI 0.93-14.0) and later timing (per month since infusion: OR 1.16, 0.97-1.35). Humoral response persisted in 96% (22/23) and in 89% (8/9) of patients who received RTX between the two measurements.

Conclusion

Repeated vaccination as late as possible after the lowest RTX dose possible seems the best vaccination strategy. A once positive humoral response after COVID-19 vaccination persists irrespective of intercurrent rituximab infusion.

Introduction

The coronavirus disease-19 (COVID-19) pandemic has led to large numbers of COVID-19-related hospitalizations and death. Several vaccines against COVID-19 are available, which have shown to induce humoral and cellular response and to reduce the risk and severity of COVID-19. Rheumatoid arthritis (RA) patients treated with rituximab (RTX) have both an increased risk of COVID-19 hospitalization[1] and a reduced humoral response after two-dose vaccination,[2] when compared to other disease modifying antirheumatic drugs (DMARDs). Therefore, to optimise management of COVID-19 risk in these patients, it is important to identify strategies for increasing response in this population.

Previously we demonstrated that both use of an ultra-low dose of 200 mg RTX and a longer time between latest RTX and vaccination are associated with positive humoral response after two-dose vaccination, with the effect of timing also confirmed by a recent meta-analysis.[3,4] Now that (at least) a third dose vaccination has been advised for these patients, it is of interest whether these factors also positively influence humoral response after follow-up COVID-19 vaccines. Previous studies found a seroconversion in ~20% of patients, but mostly included patients treated with registered dose RTX (≥1000 mg).[5-7]

Additionally, there is scarce data on humoral response persistence in RA patients treated with rituximab. So far, persistence of humoral response after two-dose vaccination was investigated in one study, which found a persistence rate of 88% after 6 months in a population with a median dose of 1000 mg RTX.[7]

Therefore, we aimed to investigate the association of dosing and timing of RTX on humoral response after three dose vaccination in previous non-responders, and the persistence of an initial positive humoral response after two dosages of the COVID-19 vaccination in RA patients treated with (ultra-)low dose RTX.

Patients and methods

Study design and participants

This is a follow-up study of the RTX-COVAC cohort in which we demonstrated that the humoral response after two-dose COVID-19 vaccination in rheumatoid arthritis patients treated with (ultra-) low dose rituximab is dependent on both dosage and timing.[4] In the current study, the first aim was to investigate the efficacy of a third vaccine and the second to investigate persistence of response after two-dose

COVID-19 vaccination. Patients were included in the first analysis if they had a negative humoral response after two doses, had received a third COVID-19 vaccination and had drawn a blood sample 2-6 weeks thereafter ('third dose sample'). Patients were included in the second analysis if they had a previous positive humoral response and have drawn a blood sample ≥ 6 weeks after second SARS-CoV-2 vaccination but before the third vaccination ('persistence sample'). All participants provided written informed consent. This study was registered at the Netherlands Trial Registry (www.trialregister.nl, NL9342). The follow-up study took place from June 2021 to January 2022 in the Sint Maartenskliniek, Nijmegen, the Netherlands and was approved by the local ethics committee (CMO Arnhem-Nijmegen, 2021-7406).

Procedures

All participants received their COVID-19 vaccinations through the Dutch national vaccine programme. For the first two vaccinations, patients in the cohort either received BNT162b2 (Comirnaty; Pfizer-BioNtech), ChAdOx1 nCoV-19 (Vaxzevria; AstraZeneca), or mRNA-1273 (Spikevax; Moderna). For the third vaccination, only the mRNA vaccines BNT162b2 and mRNA-1273 were approved for RTX patients in the Netherlands.

Relevant demographics and RA disease characteristics were obtained at baseline. Also, we recorded relevant treatment characteristics including concomitant conventional synthetic DMARD (csDMARD) use, prednisolone use, current biological/targeted synthetic DMARD (b/tsDMARD), cumulative RTX dose, and dosage and date of the latest RTX administration. Details on a previous COVID-19 infection (including date of positive test, and dichotomized between before or after second vaccination) and COVID-19 vaccination dates were provided by the participant.

The 'persistence samples' were evaluated using the Wantai SARS-CoV-2 Ab assay measuring ratio of total immunoglobulin (IgT) with a cut-off of positive (≥ 1.1).[8] Most samples of the 'third dose sample' were evaluated with the prementioned assay, however, not all patients were able to visit our clinic during the established time frame. Therefore, humoral response measured with routinely used and validated assays at a local laboratory was also accepted, and results were categorised as either 'positive' or 'negative' based on assay specific cut-offs. Follow-up of patients ended after the last blood sample was drawn for the study.

Outcomes

The main outcomes of the study were to assess the proportion of patients with a seroconversion after third vaccination and the association with dosing and timing of rituximab, and the proportion of patients with persistence of humoral response after second vaccination.

Statistical analysis

All eligible patients from the first study were included.[4] Three dosage groups (200 mg, 500 mg, and 1000 mg) were defined based on the last received RTX dose before first vaccination, similar to our first study. We used a dichotomous outcome to assess seroconversion, based on the cut-off of ≥ 1.1 of the IgT index number for the Wantai assay, and for other assays we used the dichotomous outcome as provided by the local laboratory.[8] Descriptive statistics were appropriately used to assess group characteristics.

We used the 'third dose sample' (figure 1) for the efficacy after third vaccine analysis. Fisher's Exact Test was used to test the differences between the vaccine types on third vaccine efficacy. To assess the associations between dosing and timing on humoral response in the 'efficacy after third vaccine analysis', we used univariable logistic regression with humoral response 2-6 weeks after third vaccination as dependent variable, and latest RTX dose before baseline and time between latest RTX and first vaccination as central determinant.

The 'persistence sample' was used for the secondary analysis, investigating persistence o f humoral response. All data were entered in an electronic data capture database (Castor EDC, Amsterdam, Netherlands) and subsequently exported to StataIC (version 13, StataCorp LLC, TX, USA) for statistical analyses.

Results

Patients

At total of 98 patients provided a 'third dose sample' for third vaccine analysis and 23 a 'persistence sample' for persistence analysis (Figure 1). The baseline characteristics of the patients included in this study are displayed in **Supplementary Table 1**.

Factors associated with seroconversion after a third vaccine dose

Third vaccinations took place between 5 October 2021 and 9 January 2022. RTX dose at baseline did not differ between before and after the respective vaccinations in 89% of patients. The median time between second and third vaccination was 145 days (IQR 130-160). Samples for third vaccine efficacy were drawn in 98 patients 2-6 weeks after third vaccination and took place between 28 October 2021 and 9 February 2022. Of the 98 patients, 13 (13%) had received 200 mg as latest RTX dose before first vaccination, 37 (38%) 500 mg, and 48 (49%) 1000 mg (Table 1).

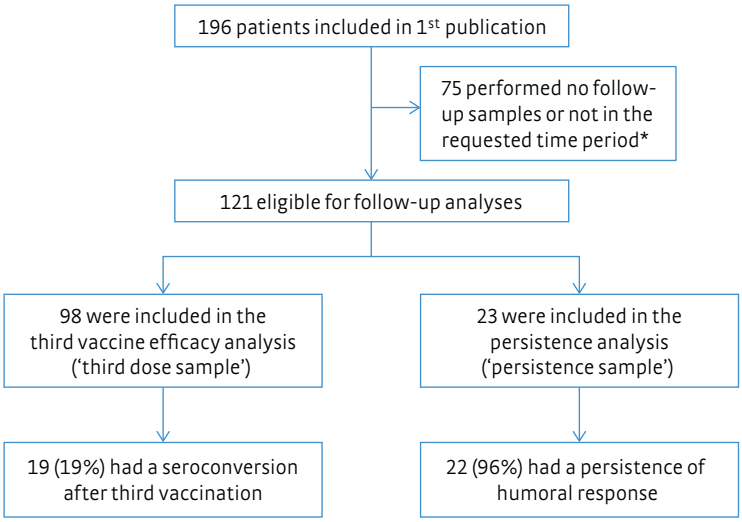


Figure 1. Study flow chart

* for third vaccine analysis: non-response after two vaccines and blood sample taken 2-6 weeks after third vaccination. for persistence analysis: previous response after two vaccines and follow-up blood sample taken after second COVID-19 vaccination but before third vaccination.

Nineteen patients (19%) reached a positive response after third vaccination, of which two had a COVID-19 infection between second and third vaccination. Response rates were numerically higher for patients who received AstraZeneca as the first two COVID-19 vaccines (5/19, 26%) versus the Pfizer and Moderna vaccines (combined; 10/79, 13%, p=0.16).

Between 200 mg and 1000 mg as latest rituximab dose for first vaccination, the percentage of humoral response after third vaccination was higher for the 200 mg group (5/13, 38%) versus the 1000 mg group (7/48, 15%) although not significantly (OR 3.66, 95% CI 0.93 to 14, *p*=0.06). Between 500 mg and 1000 mg, response rates were similar: 19% (7/37) versus 15% (7/48), respectively (OR 1.37, 95% CI 0.43 to 4.3, *p*=0.59). These values were similar when analysing with the latest RTX dose before third vaccination.

The median time between third vaccination and the latest RTX treatment was 138 days (IQR 111-156) for responders and 119 days (IQR 91-147) for non-responders, resulting in a non-significant association between humoral response and timing (OR 1.16, 95% CI 0.97 to 1.35 per month increased time, *p*=0.10).

Table 1. Third vaccine efficacy

RTX dose* (mg)	Positive response *n*(%)	Negative response *n*(%)	Total
200	5 (38%)	8 (62%)	13
500	7 (19%)	30 (81%)	37
1000	7 (15%)	41 (85%)	48
Total	19	79	98

Displayed as number (percentage). *Latest RTX dose before first COVID-19 vaccination

Humoral response persistence

Samples for humoral response persistence were drawn between 30 June and 4 November 2021, with a median time after second vaccination of 83 days (IQR 66-122). Detectable response persisted in 96% (22/23; Table 2). Nine patients with a previous positive response had received a RTX dose between both samples, of which four a dose of 1000 mg (44%), three 500 mg (33%), and two 200 mg (22%). Response persisted in 8/9 patients who retrieved intercurrent rituximab (89%), except for one patient who received 500 mg.

Table 2. Humoral response persistence

RTX dose* (mg)	Positive response *n*(%)	Negative response *n*(%)	Total
200	5 (100%)	0 (0%)	5
500	5 (83%)	1 (17%)	6
1000	12 (100%)	0 (0%)	12
Total	22	1	23

Displayed as number (percentage). *Latest RTX dose before first COVID-19 vaccination

Discussion

Our main results illustrate that humoral response after third vaccination occurs in a relevant proportion of patients who did not respond to earlier vaccination. Also, with a similar odds ratio as in our first study[4] – although not significantly so due to a smaller study population – humoral response was associated with 200 mg RTX and longer time between RTX infusion and vaccination. Additionally, we have shown that persistence of humoral response is very high even in context of intercurrent RTX infusions.

The association between 200 mg RTX and positive response after two-dose and three-dose vaccination could be explained by faster B-cell repletion. Previous studies showed that B-cell repopulation is associated with humoral response,[3,9] and that B-cell numbers are non-significantly higher at six months after a dose of 200 mg RTX compared to 1000 mg.[10] Unfortunately, B-cell counts were not performed in our current study. We also found a non-significant higher response rate after third vaccination for patients receiving AstraZeneca for the first two vaccinations in comparison to Pfizer or Moderna. This may be explained by the beneficial effect of a heterologous booster,[11] as only mRNA vaccines were approved for third vaccination.

A limitation of this study is the smaller sample size compared to the first study, possibly leading to reduced power. Also, T-cell measurements were not performed which may lead to an underrepresentation of responders in our study, as T-cell responses are present in the majority of RTX patients after two-dose vaccination.[12] To extend this, the optimal outcome would of course be the COVID-19 occurrence, but this would require a longer follow-up, more patients, and is dependent on COVID-19 incidence in the population. Of note, this study did not include patients with other diseases in which RTX is used, therefore extrapolation of our recommendations to treatment with RTX in general may be difficult.

Based on the results of our study, repeated vaccination as late as possible after the lowest RTX dose possible seems the best vaccination strategy. Once seroconversion is achieved, humoral response persists despite rituximab continuation.

References

1. Avouac J, Drumez E, Hachulla E, et al. COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. Lancet Rheumatol. 2021;3(6):e419-e26.
2. Furer V, Eviatar T, Zisman D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis. 2021;80(10):1330-8.
3. Schietzel S, Anderegg M, Limacher A, et al. Humoral and cellular immune responses on SARS-CoV-2 vaccines in patients with anti-CD20 therapies: a systematic review and meta-analysis of 1342 patients. RMD Open. 2022;8(1).
4. van der Togt CJT, Ten Cate DF, den Broeder N, et al. Humoral response to Coronavirus Disease-19 vaccines is dependent on dosage and timing of rituximab in patients with rheumatoid arthritis. Rheumatology (Oxford). 2022.
5. Bonelli M, Mrak D, Tobudic S, et al. Additional heterologous versus homologous booster vaccination in immunosuppressed patients without SARS-CoV-2 antibody seroconversion after primary mRNA vaccination: a randomised controlled trial. Ann Rheum Dis. 2022.
6. Jyssum I, Kared H, Tran TT, et al. Humoral and cellular immune responses to two and three doses of SARS-CoV-2 vaccines in rituximab-treated patients with rheumatoid arthritis: a prospective, cohort study. Lancet Rheumatol. 2021.
7. Sidler D, Born A, Schietzel S, et al. Trajectories of humoral and cellular immunity and responses to a third dose of mRNA vaccines against SARS-CoV-2 in patients with a history of anti-CD20 therapy. RMD Open. 2022;8(1).
8. Beijing Wantai Biological Pharmacy Enterprise Co. L. WANTAI SARS-CoV-2 Ab ELISA https://www.fda.gov/media/140929/download Access date: 07-10-2021.
9. Avouac J, Miceli-Richard C, Combier A, et al. Risk factors of impaired humoral response to COVID-19 vaccination in rituximab treated patients. Rheumatology (Oxford). 2021.
10. Wientjes MHM, Gijzen TMG, den Broeder N, et al. Drug levels, anti-drug antibodies and B-cell counts were not predictive of response in rheumatoid arthritis patients on low dose rituximab. Rheumatology (Oxford). 2022.
11. Liu X, Munro APS, Feng S, et al. Persistence of immunogenicity after seven COVID-19 vaccines given as third dose boosters following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK: Three month analyses of the COV-BOOST trial. J Infect. 2022;84(6):795-813.
12. Prendecki M, Clarke C, Edwards H, et al. Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. Ann Rheum Dis. 2021;80(10):1322-9.

Supplementary data

Supplementary table 1. Baseline characteristics

	Third vaccine analysis (n=98)	Persistence analysis (n=23)
Age (years) ‡	66 ± 11	66 ± 10
Female sex	69 (70)	15 (65)
Disease duration (years)†	17 (8-25)	19 (9-27)
RF and/or ACPA positive	78 (80)	20 (87)
MTX use	36 (37)	10 (43)
Concomitant prednisolone use	19 (19)	2 (8)
Duration of rituximab use (years) ‡	4.8 ± 3.1	4.2 ± 3.0
Latest RTX dose before first vaccination		
200 mg	13 (13)	5 (22)
500 mg	37 (38)	6 (26)
1000 mg	48 (49)	12 (52)
Days between RTX and 1st vaccine†	119 (83-154)	175 (135-225)
Type of first 2 vaccinations		
BioNTech/Pfizer	76 (78)	18 (78)
AstraZeneca	15 (15)	2 (9)
Moderna	7 (7)	3 (13)

Either displayed as number (percentage), median (interquartile range)† or mean ± standard deviation‡.

Chapter 4

Points to consider for cost-effective use of biological and targeted synthetic DMARDs in inflammatory rheumatic diseases: results from an umbrella review and international Delphi study

Céleste J.T. van der Togt
Bart J.F. van den Bemt
Daniel Aletaha
Rieke Alten
Katerina Chatzidionysiou
James B. Galloway
John D. Isaacs
Denis Mulleman
Patrick Verschueren
Arnold G. Vulto
Paco M.J. Welsing
Lise M. Verhoef
Alfons A. den Broeder

Published in RMD Open, March 2023

Abstract

Objectives

To develop evidence-based points-to-consider for cost-effective use of biological and targeted disease modifying antirheumatic drugs (b/tsDMARDs) in the treatment of inflammatory rheumatic diseases, specifically rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis.

Methods

Following EULAR procedures, an international task force was formed, consisting of 13 experts in rheumatology, epidemiology, and pharmacology from seven European countries. Twelve strategies for cost-effective use of b/tsDMARDs were identified through individual and group discussion. For each strategy, PubMed and Embase were systematically searched for relevant English-language systematic reviews and, for 6 strategies, additionally for RCTs. Thirty systematic reviews and twenty-one RCTs were included. Based on the evidence, a set of overarching principles and points-to-consider was formulated by the task force using a Delphi procedure. Level of evidence (1a-5) and grade (A-D) were determined for each point-to-consider. Individual voting on the level of agreement (LoA; between 0 (completely disagree) and 10 (completely agree)) was performed anonymously.

Results

The task force agreed on five overarching principles. For ten of twelve strategies, the evidence was sufficient to formulate ≥1 point-to-consider, leading to 20 in total, regarding response prediction, drug formulary use, biosimilars, loading doses, low-dose initial therapy, concomitant csDMARD use, route of administration, medication adherence, disease activity guided dose optimisation and non-medical drug switching. Ten points-to-consider (50%) were supported by level 1 or 2 evidence. The mean LoA (SD) varied between 7.9 (1.2) and 9.8 (0.4).

Conclusion

These points-to-consider can be used in rheumatology practices and complement inflammatory rheumatic diseases treatment guidelines to incorporate cost-effectiveness in b/tsDMARD treatment.

Introduction

In the last two decades, pharmacological treatment options for inflammatory rheumatic diseases (IRD), including specifically rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), have vastly expanded. In particular, the biological and targeted synthetic disease modifying antirheumatic drugs (bDMARDs and tsDMARDs, respectively) have taken an important place in IRD treatment, as they have shown to reduce disease activity, slow down radiological progression and improve daily functioning.[1-3]

Although b/tsDMARD therapy is effective, it has disadvantages, such as adverse events, the need for parenteral administration (for bDMARDs), and high costs. Concerning the costs, b/tsDMARDs are substantially more expensive per year than conventional synthetic DMARDs (csDMARDs),[4] are used by an increasing number of patients, and in principle require chronic use. With the arrival of biosimilars, some bDMARDs have become somewhat less expensive,[5] but their impact on a pressured healthcare budget remains.

When following the current disease specific recommendations, many patients can reach good disease control. Therefore, the current challenge for clinicians is not only controlling the disease, but also achieving this in the most cost-effective way, to provide optimal rheumatology care from a societal perspective. This viewpoint has been adopted in the EULAR RA recommendations as follows: "RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist".[6] However, specific recommendations or points-to-consider on how to optimize cost-effectiveness have not been formulated.

Cost-effectiveness, expressed as the effect on health divided by the costs of an intervention, can be improved by either increasing effectiveness or reducing costs.[7] So far, several strategies for improving cost-effectiveness of b/tsDMARDs have been investigated, with dose reduction and biosimilar use being the most systematically studied.[8,9] Concerning the use of biosimilars, recommendations for clinical practice have been formulated by Kay et al.[9] However, to facilitate that clinicians and rheumatology practices choose the optimal strategy in their specific situation, a systematic overview of all (possible and attempted) strategies to optimise cost-effectiveness with points-to-consider for all strategies, including less-known options, is needed.

Therefore, the aim of this project was to provide a systematic overview of evidence regarding strategies aimed at improving cost effective use, and to develop international, consensus based, interdisciplinary points-to-consider on cost-effective prescribing of b/tsDMARDs in IRD from a societal perspective.

Methods

These consensus- and evidence-based points-to-consider were developed for individual rheumatologists or groups of rheumatologists (e.g., in a hospital). They were designed to be applicable across different health care systems. For development of the points-to-consider, we used the EULAR standardized operating procedure for recommendations[10] and the additional EULAR guidance on methodology.[11] Of note, where the word 'rheumatologist' is used, the task force means any rheumatology health care provider prescribing b/tsDMARDs, including amongst others rheumatology trainees, and in some countries also nurse specialists and physician assistants. For the definition of cost-effectiveness, we used an adapted version of the NICE-definition: ""Guideline recommendations should be based on the estimated costs of the interventions or services in relation to their expected health benefits (that is, their 'cost effectiveness'), rather than on the total cost or resource impact of implementing them."[7]

Task force

In September 2020, an international interdisciplinary task force of 13 experts from seven European countries was formed for this study, consisting of 7 rheumatologists (DA, RA, KC, JBG, JDI, DM and PV), 1 pharmacist (AV), 1 epidemiologist-health technology assessment expert (PMJW), 1 research fellow (CJTvdT), 1 epidemiologist (LMV), 1 pharmacist-clinical pharmacologist (BJFvdB), and 1 rheumatologist-epidemiologist (AAdB). The steering committee, consisting of CJTvdT, BJFvdB, LMV, and AAdB, performed the scoping review and hosted the task force meetings. All task force members were involved in formulating the points-to-consider and voting for level of agreement.

Phase I: Scope and strategies

In October and November 2020, one-to-one open interviews with all members of the task force were performed by CJTvdT to identify all relevant strategies on cost-effective use of b/tsDMARDs (Figure 1). Thereafter, in November 2020, an online kick-off meeting took place to reach consensus on the included b/tsDMARDs (table 1), the definition of a strategy for cost-effective use, the included strategies with their definitions, and the protocol of the scoping review. A study was considered eligible if

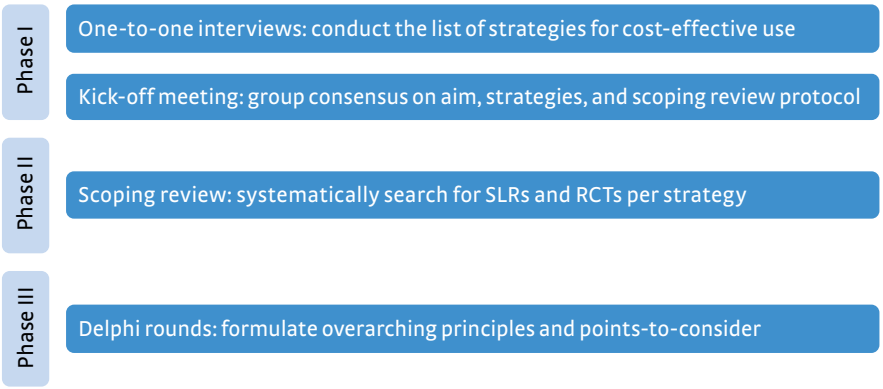


Figure 1. Study phases

SLR: systematic literature review, RCT: randomized controlled trial.

it included: patients with RA, PsA or axSpA, (planning to be) treated with b/tsDMARDs [Population], comparison of treatment with and without a strategy [Intervention/Comparison], and any of the following outcomes: cost-effectiveness, costs, efficacy, safety, or patient reported outcomes (PROMs) [Outcome]. Of note, formal cost-effectiveness assessment was considered the primary outcome for our review. However, when not available, a more informal approach for assessing costs and resource use in relation to effectiveness outcomes was performed. Only systematic literature reviews (SLRs) and randomized controlled trials (RCTs) were included, to search for available high-quality evidence and to conserve feasibility. Moreover, the panel agreed on two further limitations: 1) publications in English only, as this was the only language understood by every participant in the project, and 2) studies published in 2000 or thereafter, since we did not expect any relevant publications beforehand.

Phase II: Existing evidence

PubMed and Embase were systematically searched for each strategy using a two-step approach: an initial search for SLRs by filtering for systematic reviews in both PubMed and Embase, and a second search for RCTs for the remaining research gaps by adding the Cochrane high sensitivity RCT search string in both PubMed and Embase.[12] In addition, reference lists of included articles were screened for relevant studies. In general, the search string consisted of three parts: [IRDs] AND [drugs] AND [strategy]. The first part [IRDs] was identical for all strategies, and the second part [drugs] for every strategy except for route of administration, of which this part only focussed on drugs with multiple administration routes available (ABA, IFX, TCZ).

Table 1. Included drugs with abbreviation and their indications, authorised dose, interval and route of administration

Drug	Abbr.	Indication for RA, PsA, axSpA? (EMA)	RoA	Authorised dosing scheme (EMA)		Different registration for FDA?
				Loading dose	Maintenance dose	
Abatacept	ABA	RA, PsA	IV	Weight-based infusion at week 0, 2, 4	Weight-based infusion every 4 weeks: < 60 kg 500 mg, 60-100 kg 750 mg, > 100 kg 1000 mg	No
			SC	Weight-based infusion	125 mg/week	No
Adalimumab	ADA	RA, PsA, axSpA	SC	None	40 mg/2 weeks	No
Apremilast	APR	PsA	oral	None	30 mg once daily	No
Baricitinib	BARI	RA	oral	None	4 mg once daily	Yes, 2 mg once daily
Certolizumab pegol	CER	RA, PsA, axSpA	SC	400 mg at week 0, 2, 4	200 mg/2 weeks or 400 mg/4 weeks.	No
Etanercept	ETN	RA, PsA, axSpA	SC	None	50 mg/week	No
Filgotinib	FILG	RA	oral	None	200 mg once daily	Not available in US
Golimumab	GOL	RA, PsA, axSpA	SC	None	50 mg/month. If weight is >100 kg and response is insufficient: increase to 100 mg/month.	No
Infliximab	IFX	RA, PsA, axSpA	IV	Disease-based mg/kg infusion at week 0, 2, 6	3 mg/kg every 8 weeks for RA; 5 mg/kg every 8 weeks for PsA and axSpA.	No
		RA, PsA, axSpA	SC		120 mg/2 weeks	Not available in US
Ixekizumab	IXE	PsA, axSpA	SC	160 mg at week 0	80 mg every 4 weeks	No
Rituximab	RTX	RA	IV	None	1000 mg/6 months	No
Sarilumab	SARI	RA	SC	None	200 mg/2 weeks	No
Secukinumab	SECU	PsA, axSpA	SC	150 mg at week 0, 1, 2, 3, 4	150 mg/month	No

Tocilizumab	TCZ	RA	IV	None	8 mg/kg every 4 weeks (max. 800 mg)	Yes, 4 mg/kg.
			SC	None	162 mg/week	Yes, 162 mg/2 weeks if weight < 100 kg
Tofacitinib	TOFA	RA, PsA, axSpA	oral	None	5 mg twice daily or 11 mg XR once daily	No
Upadacitinib	UPA	RA, PsA, axSpA	oral	None	15 mg once daily	No
Ustekinumab	UST	PsA	SC	45 mg at week 0, 4. 90 mg if weight > 100 kg.	45 mg/12 weeks. 90 mg if weight > 100 kg	No

Abbr.: abbreviation (as used in this publication and the supplementary data), EMA: European medicines agency, IV: intravenous, RA: rheumatoid arthritis, PsA: psoriatic arthritis, RoA: route of administration, SC: subcutaneous, SpA: spondyloarthritis, US: United States, XR: extended release

The outcomes were not included in the search string, but checked for in the title/abstract screening. Further information on the search strategies and searches is included in the supplementary data.

Title/abstract screening was performed by two steering committee members separately. Disagreements were discussed by the two reviewers until agreement was reached, or, if persistent, were resolved by the vote of another steering committee member. If more than five SLRs were accepted after title/abstract screening, full-texts of recent SLRs (published in 2019 or thereafter) were screened first. Full-texts of older reviews were only screened in case of research gaps. Full-text screening combined with Risk of Bias (RoB) assessment was performed by the same reviewers as title/abstract screening independently, using AMSTAR-2 for SLRs[13] and the Cochrane RoB tool 2 for RCTs.[14] The data extraction form was designed by LMV and CJTvdT. CJTvdT performed the data-extraction.

Phase III: Consensus

The steering committee drafted a first version of the overarching principles and points-to-consider, the latter including level of evidence (LoE) and grade of recommendation (GR), based on the underlying evidence. Thereafter, a summary of the evidence and the proposed points-to-consider were communicated to all task force members prior to the meetings. In total, five online task force Delphi meetings took place between June and December 2021. In the first meeting, the overarching principles were discussed and accepted with 'no objection' during the meeting. In the following meetings, we discussed content and phrasing of the definitive points-to-consider. Also, LoE and GR were determined, in accordance with the EULAR additional guidance.[11] If consensus was reached on the formulation of the point-to-consider in the group meeting, task force members were asked afterwards by e-mail to vote on its level of agreement (LoA). LoA score ranged from 0 (completely disagree) to 10 (completely agree), based on the 2014 EULAR SOP.[10]

Results

Phase I: Scope and strategies

The task force formulated a definition for strategies of cost-effective b/tsDMARD use (see Box 1). Of note, we assumed that the diagnosis of the patients should be sufficiently certain.

Box 1. Definition for strategies of cost-effective b/tsDMARD use

"Strategies on the level of an individual patient or a hospital, concerning cost-effective prescribing[1] or use of biological and targeted synthetic DMARDs in the treatment of rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis."

[1] includes the indication, selection, dose, interval, route of administration and monitoring of the drug, and any co-medication interfering pharmacokinetically or -dynamically.

The task force identified four distinct ways for a strategy to increase cost-effectiveness ("benefits"): 1) a direct reduction of drug price per mg, 2) a lower drug quantity needed (dose/interval), 3) lower direct additional non-medication costs (e.g., day care costs for infusion), and 4) improved efficacy or safety, or reduced patient burden. Furthermore, the task force identified twelve strategies: 1) response prediction, 2) drug formulary policy, 3) biosimilar/generic drug use, 4) avoid dose loading, 5) initial lower dose, 6) optimizing pharmacokinetic exposure, 7) combination therapy, 8) route of administration, 9) drug wastage, 10) medication adherence, 11) disease activity guided dose optimisation (DAGDO), and 12) non-medical drug switching. An overview of the strategies including their definition and potential benefits is displayed in table 2.

Phase II: Existing evidence

The SLR searches, performed on 24-02-2021 and 1-11-2021 (initial lower dose), identified 1104 publications. Of those, 57 were accepted after title-abstract screening. After full-text screening, 30 SLRs in total could be included. For five strategies, no systematic reviews could be included. Except for the strategy biosimilar/generic drug use, additional RCT searches were performed for the other 11 strategies between 22-03-2021 and 17-11-2021, identifying 4804 publications. Of those, 25 were accepted after title-abstract screening and eventually 21 full-text publications were included for six strategies. For four strategies no articles could be accepted, including: drug formulary policy, optimizing pharmacokinetic exposure, reducing drug wastage and non-medical drug switching (excluding biosimilar transitioning). The searches, output flowcharts per strategy, and extracted data are included in the supplementary data.

Phase III: Consensus

In the Delphi meetings, the task force agreed on five overarching principles and twenty points-to-consider (see table 3), which are explained in the following paragraphs. The overall mean LoA was 8.9 (range 7.9-9.7). Of the 240 votes received, four times a 5 was voted (2%), five times a 6 (2%) and nine times a 7 (4%). All other votes were ≥8. Except for the strategy 'avoid dose loading', all other strategies required only one Delphi meeting to agree with the completeness of the search and to reach consensus on the phrasing of the recommendation. Regarding the strategy 'avoid dose loading', the task force requested for an additional search in the 'summary of the product characteristics' of the included drugs but no additional information was found.

Overarching principles

A. Treatment choices must be based on shared decision making between the patient and the rheumatologist.

RA, PsA and axSpA are diseases with a chronic course and require chronic treatment in the vast majority of patients. Shared decision making can enhance medication adherence, by adapting treatment to a patient's personal life/preferences, leading to increased satisfaction and control of treatment.

B. Treat-to-target is the cornerstone of b/tsDMARD based treatment in RA, PsA and axSpA.

The treat-to-target (T2T) approach comprises tight monitoring of disease activity for evaluation of treatment. This approach is recommended for RA, PsA and axSpA.[15-17] T2T should be the standard background strategy for b/tsDMARD treatment.

C. Cost-effectiveness considerations are an important aspect of treatment, and rheumatologists should have a leading role regarding this.

Currently, there are many drugs available for inflammatory arthritis. As most of these drugs are comparable in efficacy and safety, we believe that cost-effectiveness should be an additional selection criterium. Antirheumatic treatment has a significant impact on the rheumatology health care budget and as explained further in this paper, multiple strategies for more cost-effective use are available. Moreover, we believe that rheumatologists should have a leading role in this, because of their knowledge, training, experience, and direct involvement in b/tsDMARD prescription and the hospital's drug formulary.

Table 2. Definition of strategies and how cost-effectiveness can be optimised

Strategy	Definition	Benefit(s)*
Response prediction	To use a predictor for optimizing any drug use intervention, such as drug selection, drug dose reduction or drug discontinuation.	4
Drug formulary policy	To prescribe b/tsDMARDs in a preferential order for the rheumatology practice, primarily based on effectiveness and safety but in case of equality also on cost-effectiveness.	1
Biosimilar/generic drug use	To (allow the) start of or transition to the best value drug variant (biosimilar/generic or originator) of a b/tsDMARD	1
Avoid dose loading	To avoid the loading dose (initial higher dose than maintenance dose) that is part of authorised dosing	2, 4
Initial lower dose	To use a lower dose than the authorised dose in the maintenance phase	2, 4
Optimizing pharmacokinetic exposure	To improve exposure to the b/tsDMARD by influencing pharmacokinetic parameters	2, 4
Combination therapy	To choose for either combined treatment of a b/tsDMARD with a csDMARD or monotherapy of a specific b/tsDMARD	2, 3, 4
Route of administration	To start with or to transition to the most cost-effective route of administration for bDMARDs of which multiple routes are available.	2, 3, 4
Drug wastage	To reduce wastage of the b/tsDMARD to reduce total amount of drug needed.	2, 3
Medication adherence	To improve the extent to which a person's medication intake corresponds with agreed treatment decisions with the health care provider	3, 4
Disease activity guided dose optimisation	To gradually reduce drug dosage or lengthen the interval of the b/tsDMARD to the minimal effective dose or discontinuation guided by the disease activity	2, 4
Non-medical drug switching	To switch patients to another more cost-effective b/tsDMARD (within or between classes), excluding biosimilars, to reduce drug costs.	1

*1. A direct reduction of drug price per mg; 2. A lower needed drug quantity (dose/interval); 3. Lower direct additional drug costs; 4. Improved efficacy or safety, or reduced patient burden.

D. Reimbursement policies should cover cost-effective use of pharmacological treatments, both on- and off-label, when it is evidence based and supported by (inter)national guidelines.

Some of these recommendations require off-label use of b/tsDMARDs, for example a reduced dose, a prolonged interval or removal of a loading dose. We acknowledge that off-label use of medication is sometimes not included in reimbursement policies or not financially beneficial for the hospital while this could have multiple advantages regarding outcomes and/or costs at a societal level. We believe that every opportunity for healthcare cost reduction (without significant impact on the quality of care) should be taken advantage of for the preservation of affordable healthcare. We therefore advocate that reimbursement policies, either from governments or healthcare insurance companies, include off-label medication use in case of proven added value. We consider these recommendations a first step towards removing barriers for providing cost-effective care.

E. Bio-originators and approved biosimilars are considered similar, and thus all recommendations apply equally to bio-originators and biosimilars.

As further explained in the supplementary text of the fourth recommendation (on biosimilar/generic drug use), we consider bio-originators and approved biosimilars clinically similar, in agreement with the ACR RA guideline.[17] Therefore, all points-to-consider apply equally to biosimilars.

Consensus recommendations

Response prediction

1. *Therapeutic drug monitoring of b/tsDMARDs in patients with RA, PsA and axSpA is not advised because of absence of evidence on efficacy and safety.*

Therapeutic drug monitoring (TDM) is a clinical practice in which adjustments of dose and/or interval are made based on drug serum levels and/or antidrug antibodies (ADAb).[18] One can distinguish 'proactive TDM' in which drug levels and/or ADAb are measured with the aim to proactively adjust treatment, regardless of the clinical response, and 'reactive TDM' in which drug levels and/or ADAb are measured in case of loss of efficacy or side effects.[18] A recent systematic review on clinical effectiveness of TDM of anti-TNF in RA found one clinical study on this subject but could not draw conclusions because of serious risk of bias of this study.[19] We found another RCT (NORDRUM I), which compared proactive TDM of induction of infliximab treatment to standard care and did not find a difference in clinical remission at week 30.[20] Based on the available evidence, the task force concluded that TDM can currently not be advised because of absence of evidence on superiority.

2. *Using other predictors for either choosing or tapering a particular b/tsDMARD is not advised because none have demonstrated superiority to standard care.*

Other predictors could include either biomarkers, genetic markers or clinical markers. Disease activity was not included as a clinical marker because T2T is already incorporated in the overarching principles and disease activity-based tapering in the DAGDO section. Four systematic reviews found no clinical test-treatment trials with these markers.[21-24] A RCT on circulating TNF-alpha levels as a predictor for increasing infliximab dosage in RA found no differences in sustained remission.[25] Therefore, using other predictors for selecting or tapering a b/tsDMARD is not advised.

Drug formulary policy

3. *Rheumatologists might consider to adopt and use a drug formulary for their practice, primarily based on effectiveness and safety, and cost-effectiveness thereafter.*

A drug formulary is a preferred order of b/tsDMARDs, established for a hospital, region or country. Formularies provide a structure for safe, rational and cost-effective drug use. As formularies uniformalise and prioritize drug therapy strategies, they are also an important instrument for cost-conscious procurement of the medication. We found no supporting SLRs or RCTs on this topic. However, as these points-to-consider aim to inform rheumatologists on incorporating cost-effectiveness in their practice, and drug formulary policy was seen as an important strategy, the task force agreed on a point-to-consider based on expert opinion only.

Biosimilar/generic drug use

4. *A biosimilar, if approved by a drug regulating authority in a highly regulated area, should be preferred if it is the most cost-effective version of the drug.*

Biosimilars are available for an increasing number of bDMARDs, and from 2027 on, generic drug variants of tsDMARDs can also be expected. We found two systematic reviews supporting the use of biosimilars but both of low-quality.[26,27] As mentioned in the introduction, the expert group of Kay et al. has formulated consensus-based recommendations for biosimilar use in clinical care.[9] The current point-to-consider is directly adapted from one of their overarching principles, which states that approved biosimilars in highly regulated areas are neither better nor worse in efficacy and non-inferior in safety to bio-originators. Our task force agreed on this principle with the addition that initiating therapy with a biosimilar can contribute to cost-effectiveness.

5. *A single transition from a bio-originator to one of its biosimilars should be considered if it contributes to the cost-effectiveness of the treatment.*

There is high-quality evidence available for the efficacy and safety of a single transition from bio-originator to biosimilar. Twelve RCTs regarding transitioning of infliximab (6), adalimumab (5), and etanercept (1) were included in three systematic

reviews, which demonstrated efficacy and safety of a single switch.[28-30] Furthermore, transitioning is also supported by the recommendations of Kay et al.[9] Regarding multiple switching, there was no evidence available at the time of the systematic search. Therefore, only a single transition is included in the second point-to-consider.

Avoid dose loading

6. *When initiating abatacept or certolizumab in RA, or secukinumab in PsA or axSpA, rheumatologists might consider to initiate treatment using the maintenance dose, as dose loading has not shown superior efficacy.*
7. *For the other b/tsDMARDs, there is no information on the effect of dose loading. Therefore, these drugs should be used as authorised.*

A loading dose is a higher initial dose given at the beginning of a treatment course with the aim to achieve steady-state concentrations of a drug earlier in time, especially when a drug has a long half-life. For six bDMARDs, a loading dose is advised (table 1). The task force advocates that a loading dose should not be used when superiority on effectiveness has not been demonstrated in a head-to-head study. A systematic review on this subject found comparative studies with/without loading dose for abatacept and certolizumab in RA, and secukinumab in both PsA and axSpA.[31] The authors concluded that there is insufficient evidence on superiority of dose loading for these drugs. For the other drugs authorised with a loading dose, no comparative studies were found. Thus, the task force concluded that for the aforementioned drugs, a regimen without loading dose could optimize cost-effectiveness. However, these drugs were studied and authorised with loading dose, and therefore the decision should be made carefully and with shared decision to the patient. For the other drugs, more research is required to evaluate additional value of the loading dose.

Initial lower dose

8. *In RA, low-dose rituximab (1*1000mg or 2*500mg per cycle) has similar efficacy and less toxicity compared to authorised-dose rituximab (2*1000mg) and should thus be preferred over the authorised dose.*

For some b/tsDMARDs, an initial dose lower than the authorised dose may be as efficacious. The authorised dose of rituximab is two infusions of 1000mg (14 days apart) every six months (2*1000 mg). An updated systematic review of Bredemeier et al. based on three RCTs concluded that there were no significant differences between 2*1000mg and 1*1000mg rituximab in the primary efficacy outcomes.[32] Moreover, 1*1000mg rituximab was associated with a lower incidence of first infusion reactions. Based on this systematic review, 1*1000 mg could be advised over 2*1000 mg for the treatment of rheumatoid arthritis.

9. *In patients with RA, rheumatologists might start with the lower dose of baricitinib or tocilizumab because of a more favourable safety and/or cost-effectiveness profile.*

For both tocilizumab and baricitinib, the authorised doses in the EU and the US are different. Baricitinib is dosed as 2 mg daily for RA in the US, in contrast to 4 mg daily in the EU, and tocilizumab as 162 mg every 2 weeks (SC) or 4 mg/kg (IV) in the US, in contrast to 162 mg weekly (SC) or 8 mg/kg (IV) in the EU. Although no formal cost-benefit study has been performed between the two regimens, the task force suggests that, based on the evidence,[33-36] these lower doses could also be used as initial dose in European clinical practice. The use of baricitinib 2 mg might not lead to lower drug costs due to flat pricing of 2 and 4 mg tablets. As lower-dosed tocilizumab was associated with numerically lower infection rates, and fewer cases of hypercholesterolemia and neutropenia,[34] this regimen could especially be suitable for patients with safety concerns.

Combination therapy

Combining a b/tsDMARD with a csDMARD is known to increase effectiveness of therapy and drug survival, and therefore cost-effectiveness. For this strategy, we specifically looked for evidence on starting a b/tsDMARD with or without concomitant csDMARD.

10. *In patients with RA, rheumatologists should combine the b/tsDMARD with methotrexate to maximise efficacy; in patients who cannot use methotrexate as comedication, IL-6 pathway inhibitors and JAK inhibitors might be preferred over other bDMARDs.*

For RA, there is high quality evidence supporting combination therapy. A meta-analysis investigated studies comparing b/tsDMARD treatment with and without methotrexate and found significantly better efficacy outcomes (ACR20/ACR50 response) for combination therapy for all bDMARDs.[37] For tsDMARDs, this effect was not significant. Two other reviews specifically investigated tocilizumab and found comparable ACR20 responses[38] and effectiveness measured with PROMs.[39] Regarding sarilumab, no specific evidence was found. In the 2019 EULAR recommendations, combination therapy is advised for all b/tsDMARDs, and therapy with a IL-6 inhibitor or a JAK-inhibitor alone, if combination therapy is not possible.[6] We formulated the point-to-consider in line with the EULAR RA recommendation but with a specific focus on methotrexate instead of csDMARDs, based on the available evidence. In addition, a dose of 10 mg MTX weekly may be sufficient for the effect.[40]

11. *For patients with PsA or axSpA, combination therapy of a TNF-inhibitor with methotrexate cannot be advised, because increased efficacy compared to TNF-inhibitor monotherapy is not shown.*

For PsA and axSpA, two systematic reviews on combination therapy of TNFi[41,42] found no additional effect of combination therapy on efficacy outcomes. However,

the drug survival of TNFi, specifically infliximab, seemed somewhat better when combined with methotrexate in PsA according to registry data.[41] The current EULAR guideline on management of PsA therefore advises to continue methotrexate, but to reduce the dose in good responders. We advise, in the light of cost-effectiveness, to taper the csDMARD to full discontinuation when the bDMARD is efficacious, although stopping the csDMARD when starting the bDMARD is an alternative possibility.

12. *For patients with PsA or axSpA, combination therapy of non-TNF inhibitors with methotrexate cannot be advised because of absence of evidence on efficacy and safety.*

We found no systematic reviews or RCTs on combination therapy for non-TNFi in psoriatic arthritis or axial spondyloarthritis. Therefore, an expert opinion point-to-consider was formed in which combination therapy for non-TNFi in these diseases was not advised.

Route of administration

13. *For patients with RA, non-inferiority of subcutaneous versus intravenous treatment of abatacept, infliximab and tocilizumab has been shown, and thus rheumatologists can choose the most cost-effective route of administration when initiating one of those drugs.*

For abatacept, infliximab and tocilizumab, both an intravenous and subcutaneous formulation are available which may differ in yearly medication costs. However, intravenous administration of the medication comes with additional costs for day-care treatment. Both routes of administration for those three drugs have shown to be non-inferior regarding efficacy and without differences in safety.[43-45] Therefore, we advise that a rheumatologist chooses the most cost-effective route of administration, whenever possible.

14. *For patients with RA, a single switch from subcutaneous to intravenous tocilizumab or vice versa did not affect efficacy or safety, and thus rheumatologists might consider this for cost-effectiveness reasons.*

The extension of the SUMMACTA study investigated switching from intravenous to subcutaneous tocilizumab or vice versa in a subpopulation and found maintained efficacy and similar safety profiles.[46] For abatacept and infliximab, this has not yet been investigated. Therefore, the current point-to-consider is that a switch in route of administration might be advised for tocilizumab to increase cost-effectiveness.

Table 3. Overarching principles and consensus-based points-to-consider

Overarching principles			
A. Treatment choices must be based on shared decision making between the patient and the rheumatologist.			
B. Treat-to-target is the cornerstone of b/tsDMARD based treatment in RA, PsA and axSpA.			
C. Cost-effectiveness considerations are an important aspect of treatment, and rheumatologists should have a leading role regarding this.			
D. Reimbursement policies should cover cost-effective use of pharmacological treatments, both on- and off-label, when it is evidence based and supported by (inter)national guidelines.			
E. Bio-originators and biosimilars are considered similar, and thus all recommendations apply equally to bio-originators and biosimilars.			
Points-to-consider	**LoE**	**GR**	**LoA**
Response prediction			
1. Therapeutic drug monitoring[1] of b/tsDMARDs in patients with RA, PsA and axSpA is not advised because of absence of evidence[2] on efficacy and safety.	5	D	8.3±1.4 (6-10)
2. Using other predictors for either choosing or tapering a particular b/tsDMARD is not advised because none have demonstrated superiority to standard care.	5	D	8.3±1.0 (7-10)
Drug formulary policy*			
3. Rheumatologists might consider to adopt and use a drug formulary for their practice, primarily based on effectiveness and safety, and cost-effectiveness thereafter.	5	D	9.1±1.0 (7-10)
Biosimilar/generic drug use			
4. A biosimilar, if approved by a drug regulating authority in a highly regulated area, should be preferred if it is the most cost-effective version of the drug.	1b	A	9.8±0.39 (9-10)
5. A single transition from a bio-originator to one of its biosimilars should be considered if it contributes to the cost-effectiveness of the treatment.	1b	A	9.4±0.51 (9-10)
Avoid dose loading			
6. When initiating abatacept or certolizumab in RA, or secukinumab in PsA or axSpA, rheumatologists might consider to initiate treatment using the maintenance dose, as dose loading has not shown superior efficacy.	1b	B	8.5±1.5 (5-10)
7. For the other b/tsDMARDs, there is no information on the effect of dose loading. Therefore, these drugs should be used as authorised.	5	D	9.4±1.0 (7-10)
Initial lower dose			
8. In RA, low-dose rituximab (1*1000mg or 2*500mg per cycle) has similar efficacy and less toxicity compared to authorised-dose rituximab (2*1000mg) and should thus be preferred over the authorised dose.	1a	A	9.3±1.3 (6-10)

Table 3. Continued

Points-to-consider	LoE	GR	LoA
Initial lower dose			
9. In patients with RA, rheumatologists might start with the lower dose[3] of baricitinib or tocilizumab because of a more favourable safety and/or cost-effectiveness profile.	4	D	7.9±1.2 (5-10)
Combination therapy			
10. In patients with RA, rheumatologists should combine the b/tsDMARD with methotrexate to maximise efficacy; in patients who cannot use methotrexate as comedication, IL-6 pathway inhibitors and JAK-inhibitors[4] might be preferred over other bDMARDs.	1a 2a[4]	A	9.5±0.78 (8-10)
11. For patients with PsA or axSpA, combination therapy of a TNF-inhibitor with methotrexate cannot be advised, because increased efficacy compared to TNF-inhibitor monotherapy is not shown.	1a	A	8.4±1.3 (5-10)
12. For patients with PsA or axSpA, combination therapy of non-TNF inhibitors with methotrexate cannot be advised because of absence of evidence on efficacy and safety.	5	D	8.7±1.2 (6-10)
Route of administration			
13. For patients with RA, non-inferiority of subcutaneous versus intravenous treatment of abatacept, infliximab and tocilizumab has been shown, and thus rheumatologists can choose the most cost-effective route of administration when initiating one of those drugs.	1b	A	9.5±0.52 (9-10)
14. For patients with RA, a single switch from subcutaneous to intravenous tocilizumab or vice versa did not affect efficacy or safety, and thus rheumatologists might consider this for cost-effectiveness reasons.	2b	C	8.9±1.0 (7-10)
Medication adherence			
15. Rheumatologists should take adherence into account in the management of their patients by using the current points to consider[5] to manage non-adherence of b/tsDMARDs.	5	D	9.5±0.52 (9-10)
Disease activity guided dose optimisation			
16. For patients with RA in whom the treatment target is reached and sustained, rheumatologists should consider disease activity guided dose optimisation of anti-TNF drugs.	1	A	9.6±0.90 (7-10)
17. For patients with RA in whom the treatment target is reached and sustained, rheumatologists might consider disease activity guided dose optimisation of IL-6 inhibitors, rituximab, baricitinib or abatacept.	1b	B	8.8±0.87 (7-10)
18. For patients with axSpA[6] and PsA[7] in whom the treatment target is reached and sustained, rheumatologists might consider disease activity guided dose optimisation of anti-TNF drugs.	1a[6] 5[7]	B[6] D[7]	8.2±1.1 (6-10)

Table 3. Continued

Points-to-consider	LoE	GR	LoA
Disease activity guided dose optimisation			
19. Rheumatologists can use any disease activity guided dose optimisation scheme, as none is preferential based on the evidence.	5	D	8.9±1.4 (5-10)
Non-medical drug switching*			
20. Non-medical switching within or between b/tsDMARD classes is not advised because of absence of evidence on efficacy and safety.	5	D	9.7±0.65 (8-10)

LoE: level of evidence; GR: grade of point-to-consider; LoA: level of agreement on a numeric rating scale from 0 (completely disagree) to 10 (completely agree), displayed as mean ± standard deviation (range).
[1] adjustments of dose and/or interval based on drug serum levels and/or antidrug antibodies.
[2] Except for 1) proactive TDM (drug doses and timing of doses are based on serum drug levels) of infliximab in RA, PsA and axSpA, and 2) dose increase of infliximab based on baseline TNF-a for RA, this has not shown superiority (both level of evidence 1b, strength B).
[3] 2mg once daily for baricitinib; and 4 mg/kg (IV)† or 162mg every 2 weeks (SC)† for tocilizumab, all three authorised doses in the United States. †Only for patients with a body weight < 100kg
[4] Lower LoE for baricitinib
[5] Ritschl V, et al. Ann Rheum Dis. 2020.[58]
[6]+[7] different LoE and GR for PsA and axSpA
* No evidence (SLR or RCT) found for this strategy.

Medication adherence

15. Rheumatologists should take adherence into account in the management of their patients by using the current points to consider to manage non-adherence of b/tsDMARDs.

Even the most perfectly prescribed drug cannot have its desired effect in the case of non-adherence. Therefore, medication adherence should be included in points-to-consider for cost-effectiveness. We did not find any supporting systematic reviews or RCTs on this topic but refer to the current EULAR points to consider on non-adherence,[47] which can help rheumatologists to manage non-adherence.

Disease activity guided dose optimisation (DAGDO)

Disease activity guided dose optimisation (DAGDO, also known as tapering) is a strategy that includes a stepwise dose reduction (often by interval lengthening between injections) with or without complete discontinuation as final step. According to the task force, DAGDO should also fulfil the following criteria: 1) following the treat-to-target principle with regular visits (every 1-3 months or up to every 6 months if there is sustained remission), 2) measurement of disease activity with a valid tool, 3) agreement on treatment target (remission or low disease activity), and 4) switching/

intensifying treatment if treatment target is not reached. DAGDO should only be performed when the treatment target is sustained, defined as a ≥3 months on target with ≥2 formal disease activity measurements.

16. *For patients with RA in whom the treatment target is reached and sustained, rheumatologists should consider disease activity guided dose optimisation of anti-TNF drugs.*
17. *For patients with RA in whom the treatment target is reached and sustained, rheumatologists might consider disease activity guided dose optimisation of IL-6 inhibitors, rituximab, baricitinib or abatacept.*

DAGDO of TNF-inhibitors in RA is supported by two systematic reviews[8,48] and should therefore be considered in patients in which the treatment target is reached and sustained. DAGDO of abatacept and tocilizumab is also supported by two reviews[48,49] but with less evidence compared to TNF-inhibitors. Dose reduction of rituximab (to 1*500 or 1*200 mg every six months) was investigated in a double-blinded RCT and advised by the authors, although formal non-inferiority criteria were not met.[50] A study investigating dose reduction of baricitinib to 2 mg found that many patients could maintain control of disease activity, and if not, disease control could be recaptured with return to 4 mg.[51]

18. *For patients with axSpA and PsA in whom the treatment target is reached and sustained, rheumatologists might consider disease activity guided dose optimisation of anti-TNF drugs.*

Evidence on DAGDO of TNFi in axSpA has been included in two low-quality reviews, supporting step-wise tapering of these drugs.[49,52] One review also looked into DAGDO of PsA, but was not able to draw conclusions because of absence of evidence.[49] Therefore, the point-to-consider for PsA is expert opinion level only.

19. *Rheumatologists can use any disease activity guided dose optimisation scheme, as none is preferential based on the evidence.*

An expert opinion point-to-consider was formulated on the dose reduction scheme. Although no scheme is preferential, the task force advises dose reduction by interval lengthening in 1-4 steps with or without complete discontinuation, for example 100%-50%-0% or 100%-66%-50%-33%-0%. Whenever a flare or loss of disease control occurs, it is advised to return to last effective dose.

Non-medical drug switching

20. *Non-medical switching within or between b/tsDMARD classes is not advised because of absence of evidence on efficacy and safety.*

Non-medical drug switching is drug switching for other reasons than (loss of) efficacy, side effects or adherence, for example to reduce drug costs.[53] For these

recommendations, this includes switching within or between a drug class but excludes non-medical biosimilar transitioning (which is addressed as a separate strategy). We found no supporting evidence on this topic. Therefore, non-medical drug switching is not advised and should be further investigated. Of note, when a drug is not available temporarily or definitively, which was the case for example for tocilizumab, sarilumab and abatacept in COVID times, non-medical switching cannot be avoided and should be offered of course.

Discussion

In this study, we were able to identify twelve strategies for cost-effective use of b/tsDMARDs in IRD: response prediction, drug formulary policy, biosimilar/generic drug use, avoid dose loading, initial lower dose, optimizing pharmacokinetic exposure, combination therapy, route of administration, drug wastage, medication adherence, disease activity guided dose optimisation, and non-medical drug switching. Moreover, we formulated high-quality clinical points-to-consider for the majority of those strategies, based on an extensive literature review and stakeholder engagement. These points-to-consider can be used in addition to the recommendations for management of RA, PsA or axSpA and are broadly applicable across many healthcare environments.

Our points-to-consider have some limitations. First, we did not include patient representatives to our task force, but we would fully recommend this for an updated version. Second, because of feasibility, we only included systematic reviews and RCTs as a consequence of which we could have missed some important non-randomized clinical studies. For the strategy of initial lower dose specifically, our plan was to look in registration data of all b/tsDMARDs to check for lower effective doses tested in phase 1 and 2 trials, but this was deemed not feasible. Third, most included systematic reviews were of low or critically low AMSTAR-2 quality. Nevertheless, we were able to combine multiple reviews with high-quality RCTs to form high-quality points-to-consider. Fourth, we mainly focused on drug costs as the main cost-component of cost-effectiveness and might have missed other important costs which can influence cost-effectiveness of therapy. Also, net drug costs fluctuate over time which may affect the points-to-consider. Last, because of contextual differences in health care systems and reimbursement policies across countries, the generalizability of these points-to-consider may be limited in certain contexts.

Although we could form points-to-consider for most strategies, some research gaps have been identified through the scoping review. An important one is less overall

evidence for PsA and axSpA compared to RA at the time of our search, for example for DAGDO and combination therapy. Moreover, for four strategies there was no SLR or RCT evidence available. A research agenda is included in the supplementary data (supplementary box 1). Of note, important studies have been published after our search which could not be included when formulating the points-to-consider, such as the NOR-DRUM B study and a DAGDO RCT in PsA and axSpA.[54,55]

Changes in b/tsDMARD prices require these points-to-consider to be kept under review and, if necessary, updated. As an increasing number of b/tsDMARDs will lose their patent and thus the possibility for biosimilar or generic drug variants becomes available, this might lead to increased competition and lower drug prices. However, the drug losing patent protection does not equate to direct availability of a biosimilar, for example for rituximab (4 years after patent expiry), and tocilizumab and abatacept (no biosimilars available yet). Also, new b/tsDMARDs are still entering the market, leading to an increased number to choose from and more price competition. Finally, some points-to-consider are of value to the patient also when leaving costs out of the equation, for example lower-dosed rituximab for the same effect but with less infusion time and side effects. Therefore, we think that these points-to-consider on cost-effectiveness will remain of value and require an update in the future.

In conclusion, healthcare costs are spiralling up, and yet we have a finite financial envelope. For clinicians to provide the best care to the greatest number, it is our responsibility to be cognisant of costs and use high-cost medications wisely. This framework of strategies and corresponding points-to-consider for cost-effective use of b/tsDMARDs in IRD can be a starting point to incorporate cost-effectiveness into clinical care.

References

1. Kerschbaumer A, Sepriano A, Smolen JS, et al. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2020;79(6):744-59.
2. Kerschbaumer A, Smolen JS, Dougados M, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis. Ann Rheum Dis. 2020;79(6):778-86.
3. Cruz-Machado AR, Rodrigues-Manica S, Silva JL, et al. Effect of biologic disease-modifying anti-rheumatic drugs targeting remission in axial spondyloarthritis: systematic review and meta-analysis. Rheumatology (Oxford). 2020;59(11):3158-71.
4. John M. Eisenberg Center for Clinical Decisions and Communications Science. Medicines for Rheumatoid Arthritis: A Review of the Research for Adults. https://www.ncbi.nlm.nih.gov/books/NBK115126/table/consra2.tu2/ Access date: 25-07-2022.
5. Brkic A, Diamantopoulos AP, Haavardsholm EA, et al. Exploring drug cost and disease outcome in rheumatoid arthritis patients treated with biologic and targeted synthetic DMARDs in Norway in 2010-2019 - a country with a national tender system for prescription of costly drugs. BMC Health Serv Res. 2022;22(1):48.
6. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79(6):685-99.
7. National Institute for Health and Care Excellence (NICE). Process and methods: 7 Assessing cost effectiveness https://www.nice.org.uk/process/pmg6/chapter/assessing-cost-effectiveness Access date: 25-07-2022.
8. Verhoef LM, van den Bemt BJ, van der Maas A, et al. Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. Cochrane Database Syst Rev. 2019;5(5):Cd010455.
9. Kay J, Schoels MM, Dörner T, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis. 2018;77(2):165-74.
10. van der Heijde D, Aletaha D, Carmona L, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. Ann Rheum Dis. 2015;74(1):8-13.
11. Van der Heijde D, De Thurah A. Additional guidance on the methodology for the development/update of EULAR recommendations https://www.eular.org/myUploadData/files/additional_guidance_sop_eular_endorsed_recommendations_v2_june2018.pdf Access date: 25-07-2022.
12. The Cochrane Collaboration. The Cochrane highly sensitive search strategies for identifying randomized trials in PubMed https://work.cochrane.org/pubmed.
13. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj. 2017;358:j4008.
14. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.
15. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis. 2016;75(1):3-15.
16. Smolen JS, Schöls M, Braun J, et al. Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis. 2018;77(1):3-17.
17. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2021;73(7):924-39.
18. Shmais M, Regueiro M, Hashash JG. Proactive versus Reactive Therapeutic Drug Monitoring: Why, When, and How? Inflamm Intest Dis. 2022;7(1):50-8.
19. Tikhonova IA, Yang H, Bello S, et al. Enzyme-linked immunosorbent assays for monitoring TNF-alpha inhibitors and antibody levels in people with rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess. 2021;25(8):1-248.

20. Syversen SW, Goll GL, Jørgensen KK, et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Infliximab Induction on Disease Remission in Patients With Chronic Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. Jama. 2021;325(17):1744-54.
21. Pouw J, Leijten E, Radstake T, et al. Emerging molecular biomarkers for predicting therapy response in psoriatic arthritis: A review of literature. Clin Immunol. 2020;211:108318.
22. Schlager L, Loiskandl M, Aletaha D, et al. Predictors of successful discontinuation of biologic and targeted synthetic DMARDs in patients with rheumatoid arthritis in remission or low disease activity: a systematic literature review. Rheumatology (Oxford). 2020;59(2):324-34.
23. Tweehuysen L, van den Ende CH, Beeren FM, et al. Little Evidence for Usefulness of Biomarkers for Predicting Successful Dose Reduction or Discontinuation of a Biologic Agent in Rheumatoid Arthritis: A Systematic Review. Arthritis Rheumatol. 2017;69(2):301-8.
24. Ingegnoli F, Favalli EG, Meroni PL. Does polymorphysm of genes coding for pro-inflammatory mediators predict the clinical response to tnf alpha blocking agents? A review analysis of the literature. Autoimmun Rev. 2011;10(8):460-3.
25. Tanaka Y, Oba K, Koike T, et al. Sustained discontinuation of infliximab with a raising-dose strategy after obtaining remission in patients with rheumatoid arthritis: the RRRR study, a randomised controlled trial. Ann Rheum Dis. 2020;79(1):94-102.
26. Kim JW, Jung JY, Suh CH. Real-world observational study of biosimilars in inflammatory arthritis treatment: a systematic literature review. Expert Opin Biol Ther. 2021;21(1):57-73.
27. Cantini F, Benucci M, Li Gobbi F, et al. Biosimilars for the treatment of psoriatic arthritis. Expert Rev Clin Immunol. 2019;15(11):1195-203.
28. Numan S, Faccin F. Non-medical Switching from Originator Tumor Necrosis Factor Inhibitors to Their Biosimilars: Systematic Review of Randomized Controlled Trials and Real-World Studies. Adv Ther. 2018;35(9):1295-332.
29. Feagan BG, Lam G, Ma C, et al. Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. Aliment Pharmacol Ther. 2019;49(1):31-40.
30. Mezones-Holguin E, Gamboa-Cardenas RV, Sanchez-Felix G, et al. Efficacy and Safety in the Continued Treatment With a Biosimilar Drug in Patients Receiving Infliximab: A Systematic Review in the Context of Decision-Making From a Latin-American Country. Front Pharmacol. 2019;10:1010.
31. Geurts-Voerman GE, Verhoef LM, van den Bemt BJF, et al. The pharmacological and clinical aspects behind dose loading of biological disease modifying anti-rheumatic drugs (bDMARDs) in auto-immune rheumatic diseases (AIRDs): rationale and systematic narrative review of clinical evidence. BMC Rheumatol. 2020;4:37.
32. Bredemeier M, Campos GG, de Oliveira FK. Updated systematic review and meta-analysis of randomized controlled trials comparing low- versus high-dose rituximab for rheumatoid arthritis. Clin Rheumatol. 2015;34(10):1801-5.
33. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. 2006;54(9):2817-29.
34. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987-97.
35. Ogata A, Atsumi T, Fukuda T, et al. Sustainable Efficacy of Switching From Intravenous to Subcutaneous Tocilizumab Monotherapy in Patients With Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2015;67(10):1354-62.
36. Weng C, Xue L, Wang Q, et al. Comparative efficacy and safety of Janus kinase inhibitors and biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and network meta-analysis. Ther Adv Musculoskelet Dis. 2021;13:1759720x21999564.
37. Tarp S, Jørgensen TS, Furst DE, et al. Added value of combining methotrexate with a biological agent compared to biological monotherapy in rheumatoid arthritis patients: A systematic review and meta-analysis of randomised trials. Semin Arthritis Rheum. 2019;48(6):958-66.

38. Teitsma XM, Marijnissen AK, Bijlsma JW, et al. Tocilizumab as monotherapy or combination therapy for treating active rheumatoid arthritis: a meta-analysis of efficacy and safety reported in randomized controlled trials. Arthritis Res Ther. 2016;18(1):211.
39. Jansen JP, Buckley F, Dejonckheere F, et al. Comparative efficacy of biologics as monotherapy and in combination with methotrexate on patient reported outcomes (PROs) in rheumatoid arthritis patients with an inadequate response to conventional DMARDs--a systematic review and network meta-analysis. Health Qual Life Outcomes. 2014;12:102.
40. Burmester GR, Kivitz AJ, Kupper H, et al. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Ann Rheum Dis. 2015;74(6):1037-44.
41. Behrens F, Cañete JD, Olivieri I, et al. Tumour necrosis factor inhibitor monotherapy vs combination with MTX in the treatment of PsA: a systematic review of the literature. Rheumatology (Oxford). 2015; 54(5):915-26.
42. Lin S, He M, Chen J. Tumor necrosis factor-alpha inhibitor combined with methotrexate for ankylosing spondylitis: a systematic review and meta-analysis. Rheumatology Reports. 2014;6(5127):6-11.
43. Burmester GR, Rubbert-Roth A, Cantagrel A, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). Ann Rheum Dis. 2014;73(1):69-74.
44. Westhovens R, Wiland P, Zawadzki M, et al. Efficacy, pharmacokinetics and safety of subcutaneous versus intravenous CT-P13 in rheumatoid arthritis: a randomized phase I/III trial. Rheumatology (Oxford). 2021;60(5):2277-87.
45. Genovese MC, Covarrubias A, Leon G, et al. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. Arthritis Rheum. 2011;63(10):2854-64.
46. Burmester GR, Rubbert-Roth A, Cantagrel A, et al. Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA). Ann Rheum Dis. 2016;75(1):68-74.
47. Ritschl V, Stamm TA, Aletaha D, et al. 2020 EULAR points to consider for the prevention, screening, assessment and management of non-adherence to treatment in people with rheumatic and musculoskeletal diseases for use in clinical practice. Ann Rheum Dis. 2021;80(6):707-13.
48. Vasconcelos LB, Silva MT, Galvao TF. Reduction of biologics in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatol Int. 2020;40(12):1949-59.
49. Edwards CJ, Fautrel B, Schulze-Koops H, et al. Dosing down with biologic therapies: a systematic review and clinicians' perspective. Rheumatology (Oxford). 2017;56(11):1847-56.
50. Verhoef LM, den Broeder N, Thurlings RM, et al. Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial. The Lancet Rheumatology. 2019;1(3):e145-e53.
51. Takeuchi T, Genovese MC, Haraoui B, et al. Dose reduction of baricitinib in patients with rheumatoid arthritis achieving sustained disease control: results of a prospective study. Ann Rheum Dis. 2019;78(2):171-8.
52. Navarro-Compán V, Plasencia-Rodríguez C, de Miguel E, et al. Anti-TNF discontinuation and tapering strategies in patients with axial spondyloarthritis: a systematic literature review. Rheumatology (Oxford). 2016;55(7):1188-94.
53. Dolinar R, Kohn CG, Lavernia F, et al. The non-medical switching of prescription medications. Postgrad Med. 2019;131(5):335-41.
54. Syversen SW, Jørgensen KK, Goll GL, et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Maintenance Infliximab Therapy on Disease Control in Patients With Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. Jama. 2021;326(23):2375-84.
55. Michielsens CA, den Broeder N, van den Hoogen FH, et al. Treat-to-target dose reduction and withdrawal strategy of TNF inhibitors in psoriatic arthritis and axial spondyloarthritis: a randomised controlled non-inferiority trial. Ann Rheum Dis. 2022.

Supplementary appendix of the RECORD study

Table of contents

Section 1. Additional information on the search strategy

In general, the search string consisted of three parts: [IRDs] AND [drugs] AND [strategy]. The first part [IRDs] was identical for all strategies, and the second part [drugs] for every strategy except for route of administration, of which this part only focussed on drugs with multiple administration routes available (ABA, IFX, TCZ). Within each part, we combined both MeSH terms and title/abstract of the relevant keywords for PubMed, and Emtree terms and explode for Embase. If an additional search for RCTs was performed, only the relevant IRDs and drugs were included in the [IRDs] and [drugs] queries. For the SLR search, we filtered for 'systematic reviews' or 'reviews'. For the RCT search, we added the Cochrane maximum sensitivity search string.

Section 2. Core searches

Search string for inflammatory rheumatic diseases (IRD)

IRD – PubMed

(arthritis, rheumatoid[MeSH Terms]) OR (arthritis, psoriatic[MeSH Terms]) OR (ankylosing spondylitis[MeSH Terms]) OR (Rheumatoid arthritis[Title/Abstract]) OR (Psoriatic arthritis[Title/Abstract]) OR (axial spondyloarthritis[Title/Abstract]) OR (spondyloarthritis[Title/Abstract]) OR (ankylosing spondylitis[Title/Abstract]) OR (auto immune rheumatic disease*[Title/Abstract]) OR (immune-mediated inflammatory disease*[Title/Abstract])

IRD – Embase

1. rheumatoid arthritis/
2. exp rheumatoid arthritis/
3. psoriatic arthritis/
4. ankylosing spondylitis/
5. exp spondylarthritis/
6. rheumatoid arthritis.ti,ab,kw.
7. psoriatic arthritis.ti,ab,kw.
8. ankylos* spondyl*.ti,ab,kw.
9. spondyl?arthr*.ti,ab,kw.
10. AIRD.ti,ab,kw.
11. autoimmune rheumat* disease.ti,ab,kw.
12. IMID.ti,ab,kw.
13. immune-mediated inflammatory disease.ti,ab,kw.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

Search string for b/tsDMARDs

The searches are divided in 'drug name' and 'drug class'. For the part [drugs] we combined 'drug name' with 'drug class' using AND.

Drug name – PubMed

((((((((((((((((((((((((((((((adalimumab[MeSH Terms]) OR (certolizumab pegol[MeSH Terms])) OR (etanercept[MeSH Terms])) OR (infliximab[MeSH Terms])) OR (ustekinumab[MeSH Terms])) OR (rituximab[MeSH Terms])) OR (abatacept[MeSH Terms])) OR (adalimumab[Title/Abstract])) OR (certolizumab[Title/Abstract])) OR (golimumab[Title/Abstract])) OR (infliximab[Title/Abstract])) OR (tocilizumab[Title/Abstract])) OR (sarilumab[Title/Abstract])) OR (ustekinumab[Title/Abstract])) OR (secukinumab[Title/Abstract])) OR (ixekizumab[Title/Abstract])) OR (rituximab[Title/Abstract])) OR (abatacept[Title/Abstract])) OR (tofacitinib[Title/Abstract])) OR (baricitinib[Title/Abstract])) OR (upadacitinib[Title/Abstract])) OR (filgotinib[Title/Abstract])) OR (apremilast[Title/Abstract])) OR (golimumab[Supplementary Concept])) OR (tocilizumab[Supplementary Concept])) OR (sarilumab[Supplementary Concept])) OR (secukinumab[Supplementary Concept])) OR (ixekizumab[Supplementary Concept])) OR (tofacitinib[Supplementary Concept])) OR (baricitinib[Supplementary Concept])) OR (upadacitinib[Supplementary Concept])) OR (filgotinib[Supplementary Concept])) OR (apremilast[Supplementary Concept])) OR (etanercept[Title/Abstract])

Drug class – PubMed

((tumor necrosis factor inhibitors[MeSH Terms]) OR (janus kinase inhibitors[MeSH Terms])) OR (phosphodiesterase 4 inhibitors[MeSH Terms])) OR (TNF inhibitor*[Title/Abstract])) OR (TNF Antagonist*[Title/Abstract])) OR (TNF blocker[Title/Abstract])) OR (bDMARD[Title/Abstract])) OR (tsDMARD[Title/Abstract])) OR (biological agent*[Title/Abstract])) OR (biologicals[Title/Abstract])) OR (biological drug*[Title/Abstract])) OR (biological medication[Title/Abstract])) OR (biologics[Title/Abstract])) OR (targeted small molecules[Title/Abstract])) OR (janus kinase inhibitor*[Title/Abstract])) OR (JAK inhibitor*[Title/Abstract])) OR (Phosphodiesterase 4 inhibitor*[Title/Abstract])) OR (PDE 4 inhibitor*[Title/Abstract])) OR (PDE4 inhibitor[Title/Abstract])) OR (IL6R inhibitor*[Title/Abstract])) OR (IL-6R inhibitor*[Title/Abstract])) OR (IL6R blocker*[Title/Abstract])) OR (IL-6R blocker*[Title/Abstract])) OR (IL6R antagonist*[Title/Abstract])) OR (IL-6R antagonist*[Title/Abstract])) OR (anti IL6[Title/Abstract])) OR (anti IL-6[Title/Abstract])) OR (IL12/23 inhibitor*[Title/Abstract])) OR (IL-12/23 inhibitor*[Title/Abstract])) OR (IL12/IL23 inhibitor*[Title/Abstract])) OR (IL-12/IL-23 inhibitor*[Title/Abstract])) OR (IL12/23 blocker*[Title/Abstract])) OR (IL-12/23 blocker*[Title/Abstract])) OR (IL-12/IL-23 blocker*[Title/Abstract])) OR (IL12/23 antagonist*[Title/Abstract])) OR (IL-12/IL-23 antagonist*[Title/Abstract])) OR (anti IL12/23[Title/Abstract])) OR (anti IL-12/23[Title/Abstract])) OR (anti IL-12/IL-23[Title/Abstract])) OR (anti IL12/IL23[Title/Abstract])) OR (IL17 inhibitor*[Title/Abstract])) OR (IL-17 inhibitor*[Title/Abstract])) OR (IL17 blocker*[Title/Abstract])) OR (IL-17 blocker*[Title/Abstract])) OR (IL17 antagonist*[Title/Abstract])) OR (IL-17 antagonist*[Title/Abstract])) OR (anti IL17[Title/Abstract])) OR (anti IL-17[Title/Abstract])

Drug name – Embase

1. adalimumab.ti,ab,kw. or exp adalimumab/
2. etanercept.ti,ab,kw. or exp etanercept/
3. golimumab.ti,ab,kw. or exp golimumab/
4. infliximab.ti,ab,kw. or exp infliximab/
5. certolizumab pegol.ti,ab,kw. or exp certolizumab pegol/
6. certolizumab.ti,ab,kw.
7. tofacitinib.ti,ab,kw. or exp tofacitinib/
8. baricitinib.ti,ab,kw. or exp baricitinib/
9. filgotinib.ti,ab,kw. or exp filgotinib/
10. tocilizumab.ti,ab,kw. or exp tocilizumab/
11. sarilumab.ti,ab,kw. or exp sarilumab/
12. secukinumab.ti,ab,kw. or exp secukinumab/
13. ustekinumab.ti,ab,kw. or exp ustekinumab/
14. ixekizumab.ti,ab,kw. or exp ixekizumab/
15. abatacept.ti,ab,kw. or exp abatacept/
16. rituximab.ti,ab,kw. or exp rituximab/
17. upadacitinib.ti,ab,kw. or exp upadacitinib/
18. apremilast.ti,ab,kw. or exp apremilast/
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

Drug class – Embase

1. tumor necrosis factor inhibitors.ti,ab,kw. or exp tumor necrosis factor inhibitor/
2. exp tumor necrosis factor antibody/
3. exp Janus kinase inhibitor/ or janus kinase inhibitor*.ti,ab,kw.
4. exp phosphodiesterase IV inhibitor/ or phosphodiesterase 4 inhibitor*.ti,ab,kw.
5. bDMARD*.ti,ab,kw.
6. tsDMARD*.ti,ab,kw.
7. biological*.ti,ab,kw.
8. biological drug*.ti,ab,kw.
9. biologics.ti,ab,kw.
10. JAK inhibitor*.ti,ab,kw.
11. PDE4 inhibitor*.ti,ab,kw.
12. IL6R inhibitor*.ti,ab,kw.
13. IL6R blocker*.ti,ab,kw.
14. IL6R antagonist*.ti,ab,kw.
15. anti IL6.ti,ab,kw.
16. exp interleukin 12 antibody/
17. IL 23 inhibitor*.ti,ab,kw.
18. IL17 inhibitor*.ti,ab,kw.
19. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

Cochrane search for RCTs with maximum sensitivity

RCT search – PubMed

((((((((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (drug therapy[MeSH Subheading])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])) NOT ((animals[MeSH Terms]) NOT (humans[MeSH Terms]))

RCT search – Embase

1. Randomized controlled trial/
2. Controlled clinical study/
3. random$.ti,ab.
4. randomization/
5. intermethod comparison/
6. placebo.ti,ab.
7. (compare or compared or comparison).ti.
8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9. (open adj label).ti,ab.
10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
11. double blind procedure/
12. parallel group$1.ti,ab.
13. (crossover or cross over).ti,ab.
14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
15. (assigned or allocated).ti,ab.
16. (controlled adj7 (study or design or trial)).ti,ab.
17. (volunteer or volunteers).ti,ab.
18. human experiment/
19. trial.ti.
20. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. (random$ adj sampl$ adj7 (“cross section$” or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
22. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)
23. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
24. (Systematic review not (trial or study)).ti.
25. (nonrandom$ not random$).ti,ab.

26. Random field$.ti,ab.
27. (random cluster adj3 sampl$).ti,ab.
28. (review.ab. and review.pt.) not trial.ti.
29. we searched.ab. and (review.ti. or review.pt.)
30. update review.ab.
31. (databases adj4 searched).ab.
32. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
33. Animal experiment/ not (human experiment/ or human/)
34. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 20 not 34

Section 3. Response prediction

Strategy specific search

PubMed search

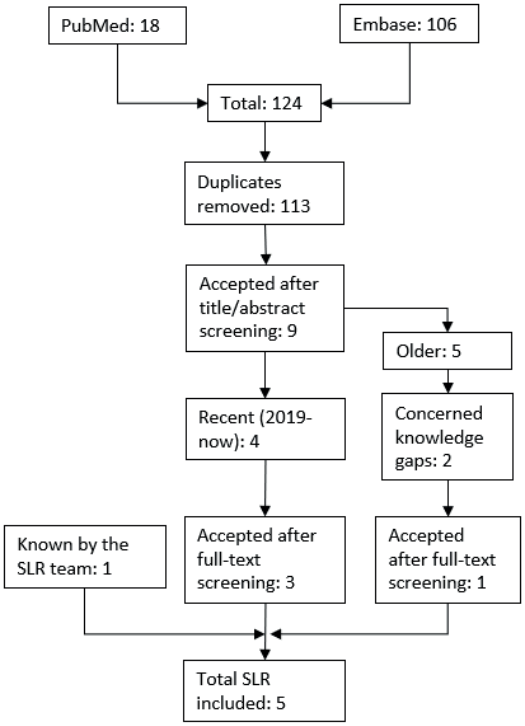
(predictive value of tests[MeSH Terms]) OR (response prediction[Title/Abstract]) OR (personalized treatment[Title/Abstract]) OR (prediction[Title/Abstract]) OR (drug monitoring, therapeutic[MeSH Terms]) OR (drug monitoring[MeSH Terms]) OR (therapeutic drug monitoring[Title/Abstract]) OR (drug level[Title/Abstract]) OR (serum level[Title/Abstract])

Embase search

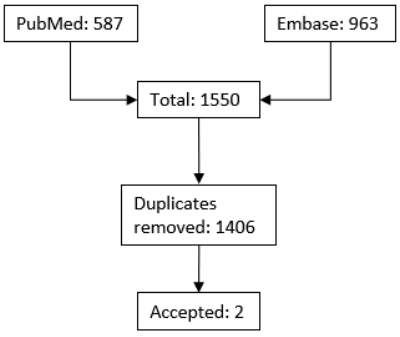
predictive value/ or response prediction.ti,ab,kw. or personalized treatment.ti,ab,kw. or predict*.ti,ab,kw. or drug monitoring/ or therapeutic drug monitoring.ti,ab,kw. or drug level.ti,ab,kw. or serum level.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic literature reviews for response prediction:



The flow diagram for the search strategy of randomized controlled trials for response prediction:



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Tikhonova[1]	2021	P: patients with RA I: treatment decisions based on drug levels or anti-drug antibodies C: regular treatment O: clinical or patient related outcomes	anti-TNF	Moderate	1=yes, 2=yes, 3=no, 4=partial yes, 5=yes, 6=yes, 7=yes, 8=yes, 9=yes, 10=yes, 11=0, 12=0, 13=yes, 14=yes, 15=0, 16=yes
Pouw[2]	2019	P: patients with PsA I: biomarkers C: not clearly mentioned O: not clearly mentioned	bDMARDs	Low	1=no, 2=no, 3=no, 4=partial yes, 5=no, 6=no, 7=no, 8=no, 9=no, 10=no, 11=0, 12=0, 13=no, 14=no, 15=0, 16=yes.
Schlager[3]	2019	P: RA, receiving b/tsDMARD I: discontinuation of the b/tsDMARD in remission or LDA C: continuation O: % remaining in remission or LDA, to identify predictors.	bDMARDs	Critically low	1=yes, 2=no, 3=no, 4=no, 5=yes, 6=no, 7=no, 8=partial yes, 9=yes, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=yes
Tweehuysen[4]	2018	P: RA treated with bDMARD I: biomarker C: no biomarker O: successful dose reduction or discontinuation	bDMARDs	Moderate	1=yes, 2=no, 3=yes, 4=partial yes, 5=yes, 6=yes, 7=partial yes, 8=partial yes, 9=0, 10=no, 11=0, 12=0, 13=yes, 14=yes, 15=0, 16=no.
Ingegnoli[5]	2011	P: RA starting an anti-TNF drug I: genetic polymorphism in TNF, interleukin, interferon gamma or TGF beta. C: not clearly mentioned O: not clearly mentioned.	anti-TNF	Critically low	1=no, 2=no, 3=no, 4=no, 5=no, 6=no, 7=no, 8=no, 9=no, 10=no, 11=0, 12=0, 13=no, 14=no, 15=0, 16=no.

Included RCTs

Full RCT search performed.

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Syversen[6]	2021	NOR-DRUM A	P: patients with RA, PsA, axSpA initiating IFX treatment I: IFX TDM: serum trough levels entered in eCRF which provides recommended dose and interval C: standard clinical practice O: % clinical remission at week 30	IFX	Some concerns
Tanaka[7]	2020	RRRR	P: RA, active disease despite MTX I: IFX dose reduction at 14 weeks based on TNF-a antigen level C: standard IFX, no dose reduction O: % patients who sustained discontinuation at week 54.	IFX	Some concerns

Section 4. Drug formulary policy

Strategy specific search

PubMed search

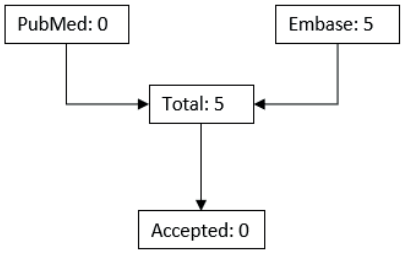
((drug formulary[title/abstract]) OR (drug policy[title/abstract]))

Embase search

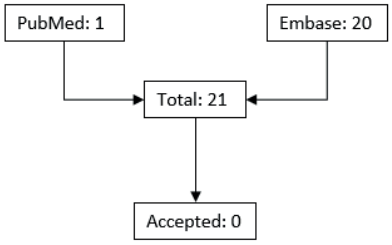
exp drug formulary/ or exp health care policy/ or drug formulary policy.ti,ab,kw. or drug formulary.ti,ab,kw. or drug policy.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic reviews for 'drug formulary policy':



The flow diagram for the search strategy of randomized controlled trials for 'drug formulary policy':



Included SLRs

None of the found publications matched our research question and could be included.

Included RCTs

None of the found publications matched our research question and could be included.

Section 5. Biosimilar/generic drug use

Strategy specific search

PubMed search

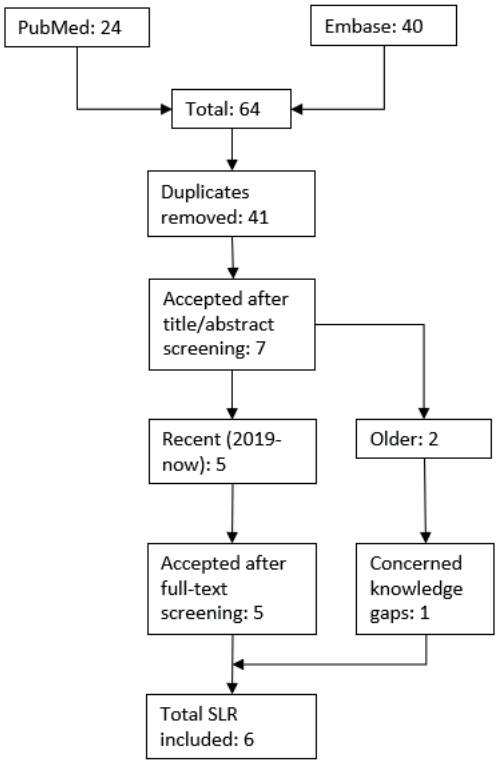
((biosimilar pharmaceuticals[MeSH Terms]) OR (biosimilar[Title/Abstract])) OR (follow-on biologics[Title/Abstract])

Embase search

exp biosimilar agent/ or biosimilar*.ti,ab,kw. or follow-on biologic*.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic reviews for 'Biosimilar/generic drug use':



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Kim[8]	2021	P: RA, PsA, axSpA I/C: not entirely clear, they mention the keywords: biosimilar, adalimumab, etanercept, infliximab, rituximab O: effectiveness	bDMARDs	Critically low	1=no, 2=no, 3=yes, 4=partial yes, 5=yes, 6=no, 7=partial yes, 8=partial yes, 9=no, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=yes

Included SLRs *(Continued)*

Author	Year	PICO	Drugs	Study quality	Amstar score
Luttropp[9]	2020	P: inflammatory arthritis I/C: bio-originator to biosimilar switch, bio-originator to bio-originator or biosimilar to bio-originator. O: switch or discontinue treatment	bDMARDs	Low	1=yes, 2=no, 3=yes, 4=partial yes, 5=no, 6=no, 7=yes, 8=yes, 9=no, 10=no, 11=0, 12=0, 13=yes, 14=yes, 15=0, 16=yes
Feagan[10]	2019	P: RA, PsA, axSpA I/C: bio-originator to biosimilar switch, bio-originator to bio-originator or biosimilar to bio-originator. O: efficacy, safety, immunogenicity	IFX	Critically low	1=yes, 2=no, 3=yes, 4=partial yes, 5=no, 6=no, 7=partial yes, 8=partial yes, 9=no, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=yes
Cantini[11]	2019	P: RA I/C: not entirely clear, they mention biosimilars of adalimumab, etanercept and infliximab O: efficacy and safety	ADA, ETN, IFX	Critically low	1=yes, 2=no, 3=yes, 4=no, 5=no, 6=no, 7=no, 8=no, 8=no, 9=no, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=yes
Mezones-Holguin[12]	2019	P: RA, PsA, axSpA I: switch to biosimilar infliximab C: continuation with originator O: efficacy and safety	IFX	Critically low	1=yes, 2=no, 3=no, 4=no, 5=yes, 6=yes, 7=no, 8=partial yes, 9=yes, 1=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=no
Numan[13]	2018	P: RA, PsA, axSpA I/C: double-blind RCT in which multiple biosimilar/bio-originator switches are perfomed. O: immunogenicity, patient-level	anti-TNF	Critically low	1=no, 2=no, 3=yes, 4=no, 5=yes, 6=no, 7=partial yes, 8=partial yes, 9=no, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=no

Included RCTs

None, our research question was answered after the SLR search.

Section 6. Avoid dose loading

Strategy specific search

PubMed search

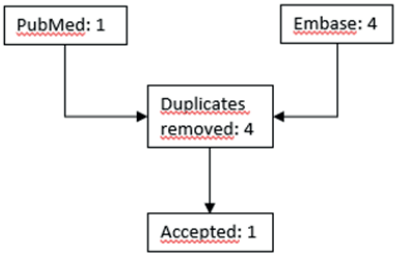
(dose loading[Title/Abstract]) OR (loading dose[Title/Abstract])

Embase search

(dose loading or loading dose).ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic literature reviews for dose loading:



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Geurts-Voerman[14]	2020	P: RA, PsA, axSpA I: dose loading C: no dose loading O: efficacy (disease activity)	CER, IFX, ABA, SEC or UST	Critically low	1=yes, 2=no, 3=yes, 4=yes, 5=yes, 6=no, 7=yes, 8=partial yes, 9=no, 10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=yes.

Included RCTs

None. The SLR covered our research question regarding bDMARDs. We performed an additional search regarding tsDMARDs but found no hits in either PubMed or Embase.

Section 7. Initial lower dose

Strategy specific search

PubMed search

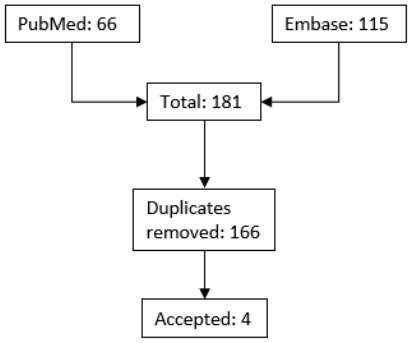
(low-dose*[Title/Abstract]) OR (low-dosage*[Title/Abstract]) OR (reduced-dose*-[Title/Abstract]) OR (reduced-dosage*[Title/Abstract]) OR (half-dose*[Title/Abstract])

Embase search

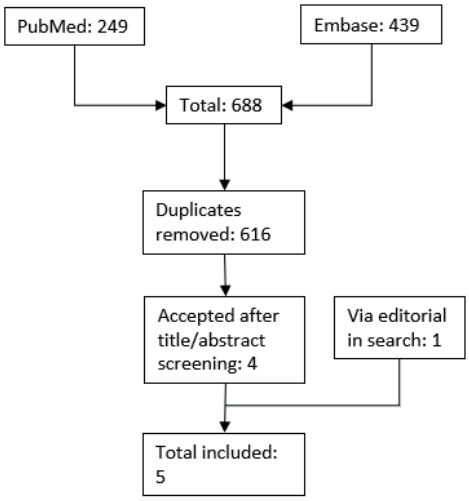
1. (low adj3 dose?).ti,ab,kw.
2. (reduc* adj3 dose?).ti,ab,kw.
3. (low* adj3 dosage?).ti,ab,kw.
4. (reduc* adj3 dosage?).ti,ab,kw.
5. (half adj3 dose?).ti,ab,kw.
6. 1 or 2 or 3 or 4 or 5
7. exp low dose/
8. 6 or 7
9. limit 8 to (human and english language and embase)

Strategy output

The flow diagram for the search strategy of systematic literature reviews for initial lower dose:



The flow diagram for the search strategy of randomized controlled trials for initial lower dose:



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Weng[15]	2021	P: RA with inadequate response to at least one DMARD I: JAK-inhibitors (including bari 2 & 4) C: bDMARDs O: efficacy and safety	BARI	Critically low	1=yes, 2=yes, 3=no, 4=no, 5=yes, 6=yes, 7=no, 8=partial yes, 9=yes, 10=no, 11=yes, 12=no, 13=no, 14=yes, 15=yes
Bae[16]	2018	P: RA I: SAR 200 mg (mono or with MTX) C: SAR 150 mg + MTX, other bDMARD, or MTX mono O: Clinical efficacy and tolerability	SAR	Low	1=yes, 2=no, 3=yes, 4=partial yes, 5=no, 6=yes, 7=no, 8=partial yes, 9=no, 10=no, 11=yes, 12=yes, 13=yes, 14=yes, 15=no, 16=yes.

Included SLRs *(Continued)*

Author	Year	PICO	Drugs	Study quality	Amstar score
Bredemeier (update)[17]	2015	P: RA I: low-dose RTX (1*1000 or 2*500) C: registered dose RTX (2*1000) O: efficacy	RTX	Critically low	1=yes, 2=no, 3=no, 4=yes, 5=yes, 6=yes, 7=no, 8=no, 9=yes, 10=no, 11=yes,12=yes, 13=yes, 14=yes, 15=yes, 16=yes
Bredemeier[18]	2014	P: RA I: low-dose RTX (1*1000 or 2*500) C: registered dose RTX (2*1000) O: efficacy	RTX	Critically low	1=yes, 2=no, 3=no, 4=yes, 5=yes, 6=yes, 7=no, 8=no, 9=yes, 10=no, 11=yes,12=yes, 13=yes, 14=yes, 15=yes, 16=yes

Included RCTs

Full RCT search performed.

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Tada[19]	2012	PRECEPT	P: RA I: ETN 25 mg/week C: ETN 50 mg/week O: radiographic damage at week 52	ETN	Low
Tanaka[20]	2011	-	P: RA and inadequate response to MTX I: TOFA 2dd 1, 3, 5 or 10 mg + MTX C: placebo + MTX O: ACR20 response rate at week 12	TOFA	Some concerns
Smolen[21]	2008	OPTION	P: RA and inadequate response to MTX I: TCZ 4 mg/kg + MTX or TCZ 8 mg/kg + MTX C: placebo + MTX O: ACR20 response rate at week 24	TCZ	Some concerns
Maini[22]	2006	CHARISMA	P: RA and inadequate response to MTX I: TCZ 2 mg/kg + MTX, TCZ 4 mg/kg + MTX or TCZ 8 mg/kg + MTX C: placebo + MTX O: ACR20 response rate at week 16	TCZ	Some concerns

Section 8. Optimizing pharmacokinetic exposure

Strategy specific search

PubMed search

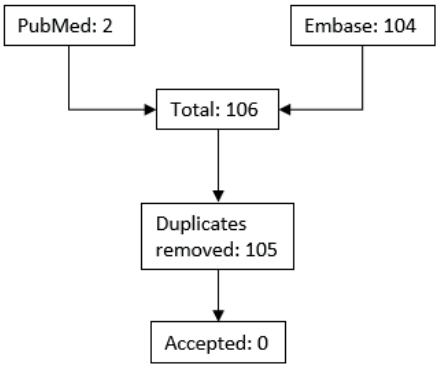
(((bioavailability[MeSH Terms]) OR (drug metabolism[Title/Abstract]) OR (drug excretion[Title/Abstract]) OR (drug absorption[Title/Abstract]) OR (drug distribution-[Title/Abstract])) OR (pharmacokinetics[MeSH Terms]))

Embase search

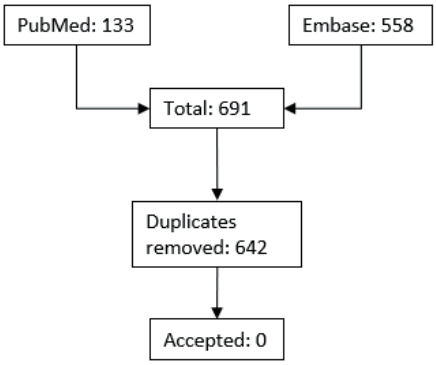
exp drug bioavailability/ or exp pharmacokinetics/ or exp drug metabolism/ or exp drug absorption/ or exp drug distribution/ or exp drug excretion/ or bioavailability.ti,ab,kw. or pharmacokinetics.ti,ab,kw. or drug metabolism.ti,ab,kw. or drug absorption.ti,ab,kw. or drug distribution.ti,ab,kw. or drug excretion.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic literature reviews for pharmacokinetics:



The flow diagram for the search strategy of randomized controlled trials for pharmacokinetics:



Included SLRs

None of the found publications matched our research question and could be included.

Included RCTs

None of the found publications matched our research question and could be included.

Section 9. Combination therapy

Strategy specific search

PubMed search

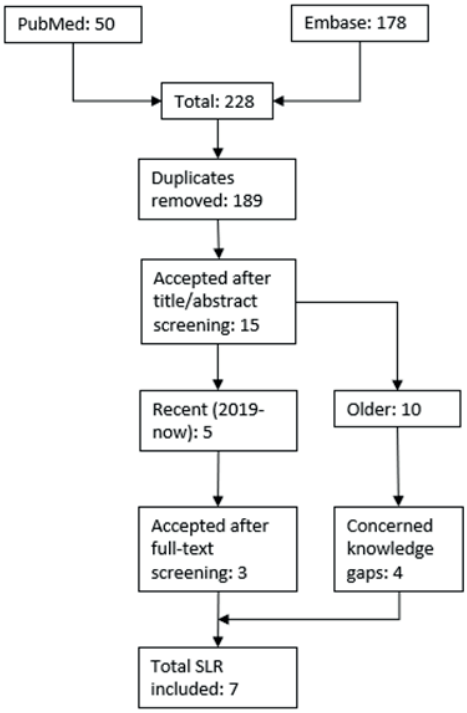
((Combination therapy[Title/Abstract]) OR (Combin*[Title/Abstract])) AND ((methotrexate[Title/Abstract]) OR (leflunomide[Title/Abstract]) OR (sulfasalazine[Title/Abstract]) OR (hydroxychloroquine[Title/Abstract]) OR (azathioprine[Title/Abstract]) OR (methotrexate[MeSH Terms]) OR (leflunomide[MeSH Terms]) OR (sulfasalazine[MeSH Terms]) OR (hydroxychloroquine[MeSH Terms]) OR (azathioprine[MeSH Terms]) (sulfasalazine[Title/Abstract]) OR (hydroxychloroquine[Title/Abstract]) OR (azathioprine[Title/Abstract]) OR (methotrexate[MeSH Terms]) OR (leflunomide-[MeSH Terms]) OR (sulfasalazine[MeSH Terms]) OR (hydroxychloroquine[MeSH Terms]) OR (azathioprine[MeSH Terms]))

Embase search

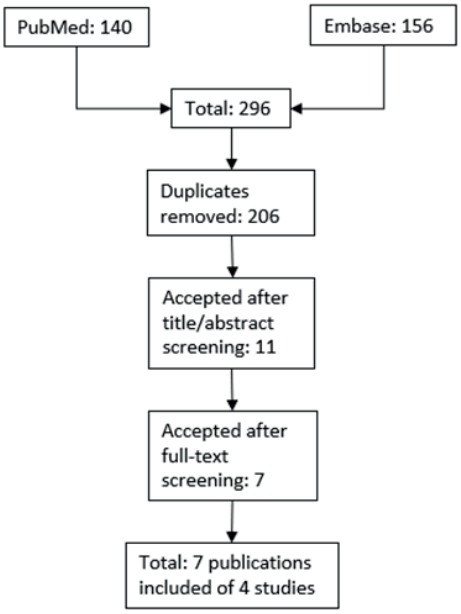
1. exp methotrexate/ or exp leflunomide/ or exp salazosulfapyridine/ or exp hydroxychloroquine/ or exp azathioprine/ or methotrexate.ti,ab,kw. or leflunomide.ti,ab,kw. or salazosulfapyridine.ti,ab,kw. or hydroxychloroquine.ti,ab,kw. or azathioprine.ti,ab,kw.
2. (combination therapy or combin*).ti,ab,kw.
3. 1 and 2

Strategy output

The flow diagram for the search strategy of systematic reviews for 'Combination therapy':



The flow diagram for the search strategy of randomised controlled trials for 'Combination therapy':



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Paul[23]	2020	P: RA I: monotherapy of ABA C: combination therapy of ABA + csDMARD or multiple csDMARDs O: efficacy and safety	ABA	Critically low	1=yes, 2=no, 3=no, 4=partial yes, 5=yes, 6=yes, 7=partial yes, 8=partial yes, 9=yes/no, 10=no, 11=no, 12=yes, 13=no, 14=no, 15=no, 16=no.

Included SLRs *(Continued)*

Author	Year	PICO	Drugs	Study quality	Amstar score
Donahue[24]	2019	P: RA I/C: head-to-head RCTs, nRCTs and prospective controlled cohort studies on bDMARD monotherapy or combination therapy for a network meta-analysis. O: Efficacy, PROMs, safety	bDMARDs	Critically low	1=yes, 2=no, 3=yes, 4=no, 5=yes, 6=yes, 7=yes, 8=partial yes, 9=yes, 10=no, 11=yes, 12=no, 13=no, 14=yes, 15=yes, 16=yes.
Tarp[25]	2019	P: RA I: combination therapy of bDMARD + MTX C: monotherapy of bDMARD O: ACR50, AEs	bDMARDs + tofa	Low	1=yes, 2=no, 3=no, 4=partial yes, 5=yes, 6=yes, 7=yes, 8=no, 9=yes, 10=no, 11=yes, 12=yes, 13=yes, 14=yes, 15=no, 16=yes
Teitsma[26]	2016	P: RA I: TCZ monotherapy C: TCZ combination therapy O: efficacy and safety	TCZ	Critically low	1=yes, 2=no, 3=no, 4=no, 5=yes, 6=yes, 7=no, 8=yes, 9=yes, 10=no, 11=yes, 12=no, 13=no, 14=yes, 15=yes, 16=yes.
Behrens[27]	2015	P: PsA I: TNFi + MTX C: TNF monotherapy O: efficacy, safety, immunogenicity	anti-TNF	Critically low	1=yes, 2=no, 3=no, 4=no, 5=no, 6=no, 7=no, 8=partial yes, 9=no, 10=no, 11=0, 12=0, 13=no, 14=no, 15=0, 16=no
Lin[28]	2014	P: axSpA I: TNFi + MTX C: TNFi monotherapy or TNFi + placebo O: efficacy, safety, PROMs, radiographic damage	anti-TNF	Low	1=yes, 2=no, 3=no, 4=no, 5=no, 6=yes, 7=no, 8=partial yes, 9=yes, 10=no, 11=yes, 12=yes, 13=yes, 14=yes, 15=no, 16=yes.
Jansen[29]	2014	P: RA I/C: bDMARD monotherapy and combiniation therapy or placebo O: PROMs	bDMARDs	Critically low	1=yes, 2=no, 3=no, 4=no, 5=no, 6=no, 7=no, 8=no, 9=no, 10=no, 11=yes, 12=no, 13=no, 14=no, 15=no, 16=no

Included RCTs

An additional RCT search was performed for the following questions:

- Combination therapy of tsDMARDs
- Recent information on PsA (from 2015)
- Recent information on axSpA (from 2015)

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Westhovens[30]	2021	FINCH-3	P: active RA, no DMARDs used I: FIL 200 mg + MTX, FIL 200 mg mono or FIL 100 mg + MTX C: MTX O: ACR20 response rate at week 24	FILG	Some concerns
Mease[31]	2019	SEAM-PsA	P: active PsA, no DMARDs used I: ETN + MTX or ETN + placebo C: MTX + placebo O: ACR20 response rate at week 24	ETN	Low
Strand[32]	2019	ORAL strategy	P: active RA despite MTX therapy I: TOFA 2dd 5 mg mono or + MTX C: ADA + MTX O: ACR50 response rate at 6 months (F), PROMs (S)	TOFA	Low
Fleischmann[33]	2017				
Van der Heijde[34]	2018	RA-BEGIN	P: active RA, no DMARDs used I: BARI 4 mg monotherapy or + MTX C: MTX monotherapy O: ACR20 response rate at week 24 (F), PROMs (S), radiographic damage (vdH)	BARI	Some concerns
Schiff[35]	2017				
Fleischmann[36]	2017				

Section 10. Route of administration

Strategy specific search

For this strategy, we only sought for articles concerning infliximab, abatacept and tocilizumab, since those drugs both have an intravenous and subcutaneous route of administration registered.

PubMed search (add this search to 'IRD')

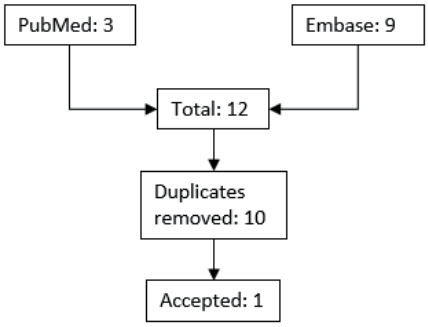
(((subcutan*[title/abstract]) AND (intraven*[title/abstract])) AND ((((((infliximab-[MeSH Terms]) OR (abatacept[MeSH Terms])) OR (tocilizumab[Supplementary Concept])) OR (infliximab[Title/Abstract])) OR (abatacept[Title/Abstract])) OR (tocilizumab[Title/Abstract])))

Embase search (add this search to 'IRD')

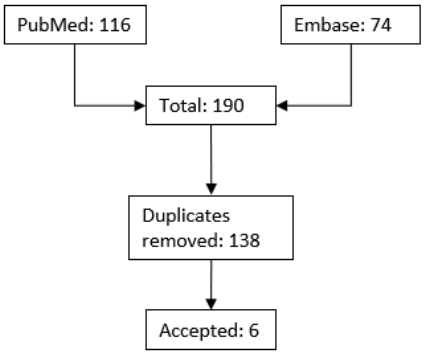
1. exp infliximab/ or exp abatacept/ or exp tocilizumab/ or infliximab.ti,ab,kw. or abatacept.ti,ab,kw. or tocilizumab.ti,ab,kw.
2. exp subcutaneous drug administration/ or subcutan*.ti,ab,kw.
3. exp intravenous drug administration/ or intraven*.ti,ab,kw.
4. 1 and 2 and 3

Strategy output

The flow diagram for the search strategy of systematic literature reviews for route of administration:



The flow diagram for the search strategy of randomized controlled trials for route of administration:



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Caporali[37]	2021	P: RA I/C: combine efficacy and safety data of IFX sc with historical data on IFX iv, ADA, ETN O: Efficacy, safety	IFX	Moderate	1=yes, 2=no, 3=yes, 4=partial yes, 5=yes, 6=no, 7=yes, 8=partial yes, 9=yes, 10=no, 11=yes, 12=yes, 13=yes, 14=yes, 15=no, 16=no.

Included RCTs

Full RCT search performed.

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Westhovens[38]	2021	-	P: active RA and inadequate response to MTX I: IFX sc 120 mg every 2 weeks from week 6 (after IV loading dose on week 0 and 2) C: IFX IV 3 mg/kg every 8 weeks O: Efficacy, PROMs, pharmacokinetics	IFX	Low

Included RCTs *(Continued)*
Full RCT search performed.

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Burmester[39]	2016	SUMMACTA extension	P: SUMMACTA participants I/C: SC group: randomization 11:1 to continue sc or switch to iv; IV group: randomization 2:1 to continuation of iv or switch to sc.	TCZ	Some concerns
Ogata[40]	2014	MUSASHI	P: active RA and inadequate response to previous tx I: TCZ sc 162 mg every 2 weeks C: TCZ iv 8 mg/kg every 4 weeks O: ACR20 response rate	TCZ	Some concerns
Burmester[41]	2014	SUMMACTA	P: active RA and inadequate response to csDMARD I: TCZ sc 162 mg once weekly C: TCZ iv 8 mg/kg every 4 weeks O: ACR20 response rate	TCZ	Low
Iwahashi[42]	2014	-	P: RA and inadequate response to MTX I: ABA sc 125 mg/week C: ABA iv 10 mg/kg every 4 weeks O: ACR20 response rate, safety, pharmacokinetics and immunogenicity.	ABA	Low
Genovese[43]	2011	ACQUIRE	P: active RA and inadequate response to MTX I: ABA sc 125 mg/week C: ABA iv 10 mg/kg every 4 weeks O: ACR20 response rate, safety, immunogenicity.	ABA	Low

Section 11. Drug wastage

Strategy specific search

PubMed search

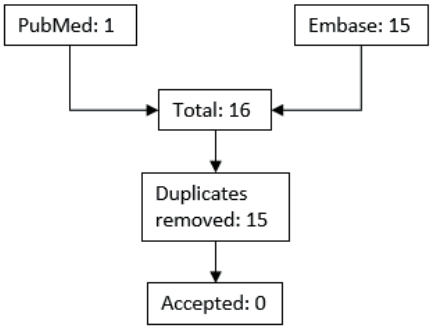
(redispens*[Title/Abstract]) OR (waste[Title/Abstract]) OR (wastage[Title/Abstract]) OR (compounding[Title/Abstract]) OR (dispens*[Title/Abstract]) OR (spillage[Title/Abstract]) OR (reuse[title/abstract]) OR (unused[title/abstract])

Embase search

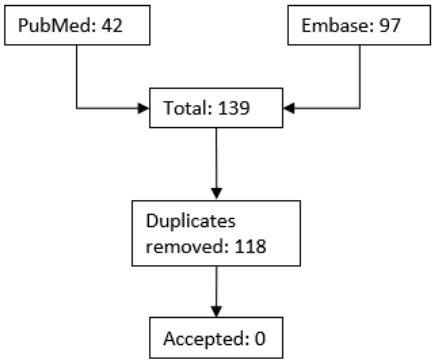
(redispens or waste or wastage or compound* or dispens* or spillage or reuse or unused).ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic literature reviews for drug wastage:



The flow diagram for the search strategy of randomized controlled trials for drug wastage:



Included SLRs
None of the found publications matched our research question and could be included.

Included RCTs
None of the found publications matched our research question and could be included.

Section 12. Medication adherence

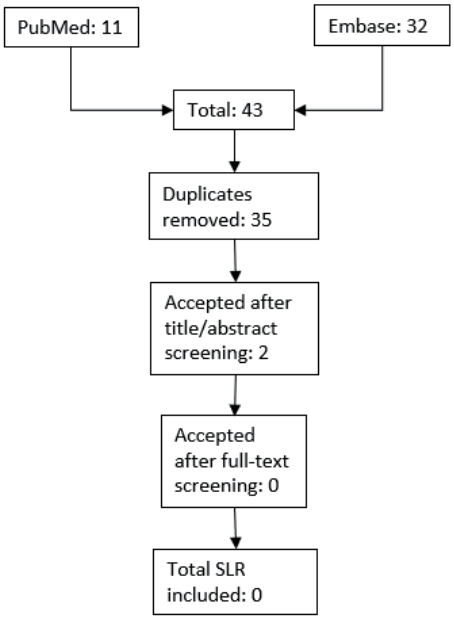
Strategy specific search

PubMed search
(medication adherence[MeSH Terms]) OR (medication adherence[Title/Abstract]) OR (drug adherence[Title/Abstract]) OR (adherence[Title/Abstract]) OR (patient compliance[Title/Abstract]) OR (medication compliance[Title/Abstract]) OR (drug compliance[Title/Abstract]) OR (non adherence[Title/Abstract]) OR (medication persistence[Title/Abstract]) OR (drug persistence[Title/Abstract]) OR (administration, self[MeSH Terms]) OR (self injection[Title/Abstract]) OR (self administration[Title/Abstract])

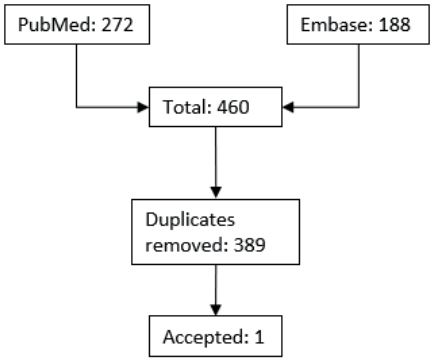
Embase search
medication compliance/ or adherence.ti,ab,kw. or patient compliance.ti,ab,kw. or compliance.ti,ab,kw. or non adherence.ti,ab,kw. or medication persistence.ti,ab,kw. or drug persistence.ti,ab,kw. or self administration.ti,ab,kw. or self injection.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic literature reviews for medication adherence:



The flow diagram for the search strategy of randomized controlled trials for medication adherence:



Included SLRs

None. None of the found publications matched our research question and could be included.

Included RCTs

Full RCT search performed.

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Gutermann[44]	2021	-	P: axSpA patients with stable disease activity for 6 months and treatment with sc bDMARD I: Pharmacist' educational interview C: Regular care O: Change in patients' knowledge score about sc bDMARD management at month 6, change in medication possession rate.	bDMARD	Low

We formed an expert opinion point-to-consider only, referring to the current EULAR points to consider for management of non-adherence, because the evidence we found was very limited and not general enough to form a point-to-consider by itself.

Section 13. Disease activity guided dose optimisation (DAGDO)

Strategy specific search

PubMed search

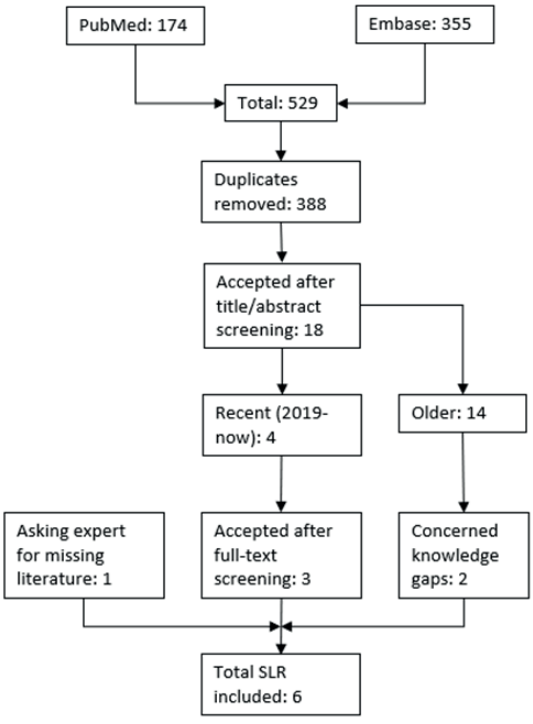
((((((((((((titrat*[Title/Abstract]) OR (down titrat*[Title/Abstract])) OR (reduc*[Title/Abstract])) OR (dose reduc*[Title/Abstract])) OR (dose de-escalat*[Title/Abstract])) OR (discontinu*[Title/Abstract])) OR (dose taper*[Title/Abstract])) OR (taper*[Title/Abstract])) OR (spac*[Title/Abstract])) OR (cessat*[Title/Abstract])) OR (stop*[Title/Abstract])) OR (withdraw*[Title/Abstract])) OR (dose titrat*[Title/Abstract])) OR (interval widen*[Title/Abstract])

Embase search

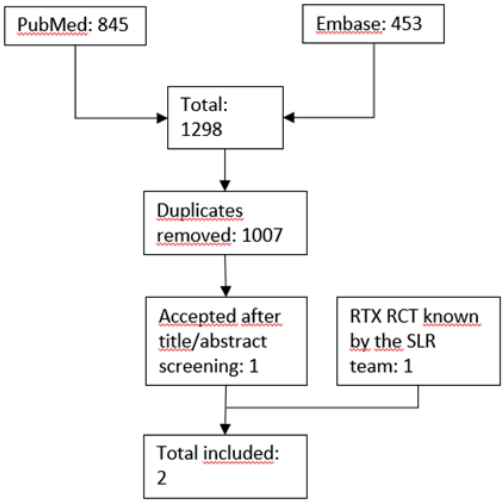
exp drug dose reduction/ or taper*.ti,ab,kw. or dose reduc*.ti,ab,kw. or down titrat*.ti,ab,kw. or reduc*.ti,ab,kw. or dose de-escalat*.ti,ab,kw. or discontinu*.ti,ab,kw. or dose taper*.ti,ab,kw. or spac*.ti,ab,kw. or cessat*.ti,ab,kw. or stop*.ti,ab,kw. or withdraw*.ti,ab,kw. or dose titrat*.ti,ab,kw. or interval widen*.ti,ab,kw.

Strategy output

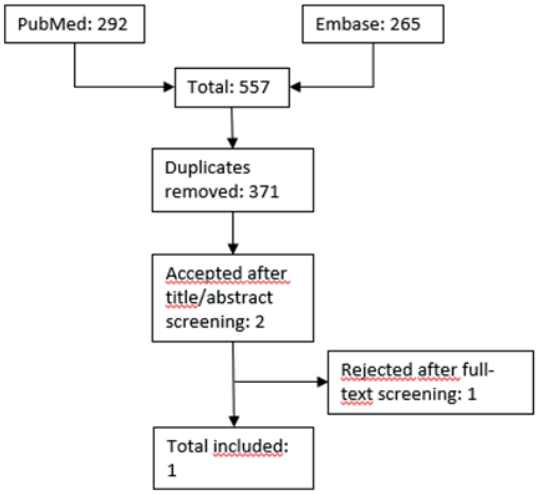
The flow diagram for the search strategy of systematic reviews for 'DAGDO':



The flow diagram for the search of RCTs for 'DAGDO in PsA, with the addition of the RTX RCT':



The flow diagram for the search of RCTs for DAGDO of tsDMARDs:



Included SLRs

Author	Year	PICO	Drugs	Study quality	Amstar score
Lawson[45]	2021	P: axSpA treated with TNFi I: dose reduction C: maintenance of standard dose O: efficacy, safety, QoL	TNFi	High	1=yes, 2=yes, 3=yes, 4=yes, 5=yes, 6=yes, 7=partial yes, 8=yes, 9=yes, 10=yes, 11=yes, 12=no, 13=yes, 14=yes, 15=yes, 16=yes
Vasconcelos[46]	2020	P: RA I: reducing or spacing bDMARD C: dose maintenance of bDMARD O: efficacy, safety, radiographic progression	ABA, ADA, CER, ETN, TCZ	Moderate	1=yes, 2=no, 3=yes, 4=partial yes, 5=yes, 6=yes, 7=partial yes, 8=yes, 9=yes, 10=yes, 11=yes, 12=yes, 13=yes, 14=yes, 15=yes, 16=yes
Vinson[47]	2020	P: RA I: tapering (dose reduction or spacing) C: continuation O: serious infections and AEs	bDMARDs, JAKi	Critically low	1=yes, 2=no, 3=yes, 4=partial yes, 5=yes, 6=no, 7=yes, 8=no, 9=yes, 10=no, 11=yes, 12=no, 13=no, 14=yes, 15=yes, 16=yes
Verhoef[48]	2019	P: RA and LDA I: down-titration of anti-TNF C: usual care O: efficacy, functioning, costs, safety and radiographic progression	anti-TNF	Moderate	1=yes, 2=no, 3=yes, 4=yes, 5=yes, 6=yes, 7=yes, 8=yes, 9=yes, 10=yes, 11=0, 12=0, 13=yes, 14=yes, 15=0, 16=yes.
Edwards[49]	2017	P: RA, PsA, axSpA I: tapering C: not clearly mentioned O: efficacy, patient perspective	bDMARDs	Critically low	1=no, 2=no, 3=no, 4=partial yes, 5=yes, 6=yes, 7=no, 8=no, 9=no,10=no, 11=0, 12=0, 13=no, 14=yes, 15=0, 16=no

Included SLRs *(Continued)*

Author	Year	PICO	Drugs	Study quality	Amstar score
Navarro-Compan[50]	2016	P: axSpA I: discontinuation or tapering C: maintaining dose of anti-TNF O: flare or change on disease activity parameters.	ADA, ETN, IFX	Critically low	1=yes, 2=no, 3=yes, 4=partial yes, 5=yes, 6=yes, 7=yes, 8=yes, 9=no, 10=no, 11=0, 12=0, 13=yes, 14=yes, 15=0, 16=no

Included RCTs

Author	Year	Acronym	PICO	Drugs	RoB-2 conclusion
Coates[51]	2021	SPIRIT-P3	P: participant in the SPIRIT-P3 study (PsA, biologic-naïve, treated with IXE in the study for 36 weeks) I: continuation of IXE 80 mg/2 weeks C: switch to placebo O: time to relapse	IXE	Low
Verhoef[52]	2019	REDO	P: RA patients on RTX with low disease activity for at least 6 months I: dose reduction to 200 mg or 500 mg RTX C: continuation of 1000 mg RTX O: change from baseline in DAS28-CRP at 3 and 6 months	RTX	Low
Takeuchi[53]	2018	-	P: RA, treated with BARI 4 mg in phase 3 trials I: dose reduction to BARI 2 mg C: continuation of BARI 4 mg O: proportion maintaining CDAI ≤ 10 at 3 months	BARI	Some concerns

Section 14. Non-medical drug switching

Strategy specific search

PubMed search

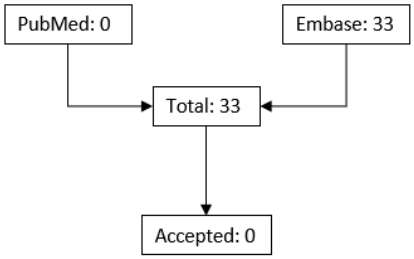
(drug switch*[Title/Abstract]) OR (drug transition*[Title/Abstract])

Embase search

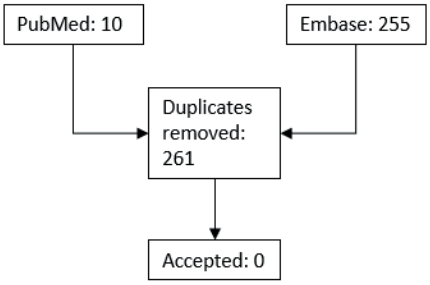
drug substitution/ or drug switch*.ti,ab,kw. or drug transition*.ti,ab,kw.

Strategy output

The flow diagram for the search strategy of systematic reviews for 'nonmedical drug switching':



The flow diagram for the search strategy of RCTs for 'nonmedical drug switching':



Included SLRs

None of the found publications matched our research question and could be included.

Included RCTs

None of the found publications matched our research question and could be included.

Section 15. Research agenda

Supplementary box 1. Research agenda

1. Is optimizing pharmacokinetic exposure of b/tsDMARDs possible?
2. Does the use of a drug formulary policy contribute to cost-effectiveness?
3. How can wastage of b/tsDMARDs be reduced?
4. Is non-medical drug switching efficacious, safe and acceptable for patients?
5. What are effective strategies to improve medication adherence of b/tsDMARDs?
6. What predictors for choosing or tapering a b/tsDMARD are effective?
7. Does combination therapy of non-TNFi with MTX (or another csDMARD) for PsA and axSpA have additional value on efficacy and drug survival, compared to monotherapy?
8. Does combination therapy of sarilumab with MTX (or another csDMARD) in RA have additional value on efficacy and drug survival, compared to monotherapy?
9. Is switching from intravenous to subcutaneous administration or vice versa of infliximab effective and safe?
10. Is subcutaneous administration of rituximab effective and safe in RA?
11. What is the most effective DAGDO strategy in IRD?
12. What is the long-term effectiveness and safety of DAGDO in IRD?

Appendix references

1. Tikhonova IA, Yang H, Bello S, et al. Enzyme-linked immunosorbent assays for monitoring TNF-alpha inhibitors and antibody levels in people with rheumatoid arthritis: a systematic review and economic evaluation. *Health Technol Assess.* 2021;**25**(8):1-248.
2. Pouw J, Leijten E, Radstake T, et al. Emerging molecular biomarkers for predicting therapy response in psoriatic arthritis: A review of literature. *Clin Immunol.* 2020;**211**:108318.
3. Schlager L, Loiskandl M, Aletaha D, et al. Predictors of successful discontinuation of biologic and targeted synthetic DMARDs in patients with rheumatoid arthritis in remission or low disease activity: a systematic literature review. *Rheumatology (Oxford).* 2020;**59**(2):324-34.
4. Tweehuysen L, van den Ende CH, Beeren FM, et al. Little Evidence for Usefulness of Biomarkers for Predicting Successful Dose Reduction or Discontinuation of a Biologic Agent in Rheumatoid Arthritis: A Systematic Review. *Arthritis Rheumatol.* 2017;**69**(2):301-8.
5. Ingegnoli F, Favalli EG, Meroni PL. Does polymorphysm of genes coding for pro-inflammatory mediators predict the clinical response to tnf alpha blocking agents? A review analysis of the literature. *Autoimmun Rev.* 2011;**10**(8):460-3.
6. Syversen SW, Goll GL, Jørgensen KK, et al. Effect of Therapeutic Drug Monitoring vs Standard Therapy During Infliximab Induction on Disease Remission in Patients With Chronic Immune-Mediated Inflammatory Diseases: A Randomized Clinical Trial. *Jama.* 2021;**325**(17):1744-54.
7. Tanaka Y, Oba K, Koike T, et al. Sustained discontinuation of infliximab with a raising-dose strategy after obtaining remission in patients with rheumatoid arthritis: the RRRR study, a randomised controlled trial. *Ann Rheum Dis.* 2020;**79**(1):94-102.
8. Kim JW, Jung JY, Suh CH. Real-world observational study of biosimilars in inflammatory arthritis treatment: a systematic literature review. *Expert Opin Biol Ther.* 2021;**21**(1):57-73.
9. Luttropp K, Dalén J, Svedbom A, et al. Real-World Patient Experience of Switching Biologic Treatment in Inflammatory Arthritis and Ulcerative Colitis - A Systematic Literature Review. *Patient Prefer Adherence.* 2020;**14**:309-20.
10. Feagan BG, Lam G, Ma C, et al. Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. *Aliment Pharmacol Ther.* 2019;**49**(1):31-40.
11. Cantini F, Benucci M, Li Gobbi F, et al. Biosimilars for the treatment of psoriatic arthritis. *Expert Rev Clin Immunol.* 2019;**15**(11):1195-203.
12. Mezones-Holguin E, Gamboa-Cardenas RV, Sanchez-Felix G, et al. Efficacy and Safety in the Continued Treatment With a Biosimilar Drug in Patients Receiving Infliximab: A Systematic Review in the Context of Decision-Making From a Latin-American Country. *Front Pharmacol.* 2019;**10**:1010.
13. Numan S, Faccin F. Non-medical Switching from Originator Tumor Necrosis Factor Inhibitors to Their Biosimilars: Systematic Review of Randomized Controlled Trials and Real-World Studies. *Adv Ther.* 2018;**35**(9):1295-332.
14. Geurts-Voerman GE, Verhoef LM, van den Bemt BJF, et al. The pharmacological and clinical aspects behind dose loading of biological disease modifying anti-rheumatic drugs (bDMARDs) in auto-immune rheumatic diseases (AIRDs): rationale and systematic narrative review of clinical evidence. *BMC Rheumatol.* 2020;**4**:37.
15. Weng C, Xue L, Wang Q, et al. Comparative efficacy and safety of Janus kinase inhibitors and biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and network meta-analysis. *Ther Adv Musculoskelet Dis.* 2021;**13**:1759720x21999564.
16. Bae SC, Lee YH. Comparative efficacy and tolerability of sarilumab 150 and 200 mg in patients with active rheumatoid arthritis : A Bayesian network meta-analysis of randomized controlled trials. *Z Rheumatol.* 2018;**77**(5):421-8.
17. Bredemeier M, Campos GG, de Oliveira FK. Updated systematic review and meta-analysis of randomized controlled trials comparing low- versus high-dose rituximab for rheumatoid arthritis. *Clin Rheumatol.* 2015;**34**(10):1801-5.
18. Bredemeier M, de Oliveira FK, Rocha CM. Low- versus high-dose rituximab for rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken).* 2014;**66**(2):228-35.

19. Tada M, Koike T, Okano T, et al. Comparison of joint destruction between standard- and low-dose etanercept in rheumatoid arthritis from the Prevention of Cartilage Destruction by Etanercept (PRECEPT) study. *Rheumatology (Oxford).* 2012;**51**(12):2164-9.
20. Tanaka Y, Suzuki M, Nakamura H, et al. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res (Hoboken).* 2011;**63**(8):1150-8.
21. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet.* 2008;**371**(9617):987-97.
22. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum.* 2006;**54**(9):2817-29.
23. Paul D, Fazeli MS, Mintzer L, et al. Comparative efficacy and safety of current therapies for early rheumatoid arthritis: a systematic literature review and network meta-analysis. *Clin Exp Rheumatol.* 2020;**38**(5):1008-15.
24. Donahue KE, Schulman ER, Gartlehner G, et al. Comparative Effectiveness of Combining MTX with Biologic Drug Therapy Versus Either MTX or Biologics Alone for Early Rheumatoid Arthritis in Adults: a Systematic Review and Network Meta-analysis. *J Gen Intern Med.* 2019;**34**(10):2232-45.
25. Tarp S, Jørgensen TS, Furst DE, et al. Added value of combining methotrexate with a biological agent compared to biological monotherapy in rheumatoid arthritis patients: A systematic review and meta-analysis of randomised trials. *Semin Arthritis Rheum.* 2019;**48**(6):958-66.
26. Teitsma XM, Marijnissen AK, Bijlsma JW, et al. Tocilizumab as monotherapy or combination therapy for treating active rheumatoid arthritis: a meta-analysis of efficacy and safety reported in randomized controlled trials. *Arthritis Res Ther.* 2016;**18**(1):211.
27. Behrens F, Cañete JD, Olivieri I, et al. Tumour necrosis factor inhibitor monotherapy vs combination with MTX in the treatment of PsA: a systematic review of the literature. *Rheumatology (Oxford).* 2015;**54**(5):915-26.
28. Lin S, He M, Chen J. Tumor necrosis factor-alpha inhibitor combined with methotrexate for ankylosing spondylitis: a systematic review and meta-analysis. *Rheumatology Reports.* 2014;**6**(5127):6-11.
29. Jansen JP, Buckley F, Dejonckheere F, et al. Comparative efficacy of biologics as monotherapy and in combination with methotrexate on patient reported outcomes (PROs) in rheumatoid arthritis patients with an inadequate response to conventional DMARDs--a systematic review and network meta-analysis. *Health Qual Life Outcomes.* 2014;**12**:102.
30. Westhovens R, Rigby WFC, van der Heijde D, et al. Filgotinib in combination with methotrexate or as monotherapy versus methotrexate monotherapy in patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: the phase 3, randomised controlled FINCH 3 trial. *Ann Rheum Dis.* 2021;**80**(6):727-38.
31. Mease PJ, Gladman DD, Collier DH, et al. Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial. *Arthritis Rheumatol.* 2019;**71**(7):1112-24.
32. Strand V, Mysler E, Moots RJ, et al. Patient-reported outcomes for tofacitinib with and without methotrexate, or adalimumab with methotrexate, in rheumatoid arthritis: a phase IIIB/IV trial. *RMD Open.* 2019;**5**(2):e001040.
33. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet.* 2017;**390**(10093):457-68.
34. van der Heijde D, Durez P, Schett G, et al. Structural damage progression in patients with early rheumatoid arthritis treated with methotrexate, baricitinib, or baricitinib plus methotrexate based on clinical response in the phase 3 RA-BEGIN study. *Clin Rheumatol.* 2018;**37**(9):2381-90.
35. Schiff M, Takeuchi T, Fleischmann R, et al. Patient-reported outcomes of baricitinib in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. *Arthritis Res Ther.* 2017;**19**(1):208.

36. Fleischmann R, Schiff M, van der Heijde D, et al. Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. *Arthritis Rheumatol.* 2017;**69**(3):506-17.
37. Caporali R, Allanore Y, Alten R, et al. Efficacy and safety of subcutaneous infliximab versus adalimumab, etanercept and intravenous infliximab in patients with rheumatoid arthritis: a systematic literature review and meta-analysis. *Expert Rev Clin Immunol.* 2021;**17**(1):85-99.
38. Westhovens R, Wiland P, Zawadzki M, et al. Efficacy, pharmacokinetics and safety of subcutaneous versus intravenous CT-P13 in rheumatoid arthritis: a randomized phase I/III trial. *Rheumatology (Oxford).* 2021;**60**(5):2277-87.
39. Burmester GR, Rubbert-Roth A, Cantagrel A, et al. Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA). *Ann Rheum Dis.* 2016;**75**(1):68-74.
40. Ogata A, Atsumi T, Fukuda T, et al. Sustainable Efficacy of Switching From Intravenous to Subcutaneous Tocilizumab Monotherapy in Patients With Rheumatoid Arthritis. *Arthritis Care Res (Hoboken).* 2015;**67**(10):1354-62.
41. Burmester GR, Rubbert-Roth A, Cantagrel A, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). *Ann Rheum Dis.* 2014;**73**(1):69-74.
42. Iwahashi M, Inoue H, Matsubara T, et al. Efficacy, safety, pharmacokinetics and immunogenicity of abatacept administered subcutaneously or intravenously in Japanese patients with rheumatoid arthritis and inadequate response to methotrexate: a Phase II/III, randomized study. *Mod Rheumatol.* 2014;**24**(6):885-91.
43. Genovese MC, Covarrubias A, Leon G, et al. Subcutaneous abatacept versus intravenous abatacept: a phase IIIb noninferiority study in patients with an inadequate response to methotrexate. *Arthritis Rheum.* 2011;**63**(10):2854-64.
44. Gutermann L, Dumas S, Lopez-Medina C, et al. Impact of a pharmacist-led programme on biologics knowledge and adherence in patients with spondyloarthritis. *Clin Exp Rheumatol.* 2021;**39**(4):811-8.
45. Lawson DO, Eraso M, Mbuagbaw L, et al. Tumor Necrosis Factor Inhibitor Dose Reduction for Axial Spondyloarthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Arthritis Care Res (Hoboken).* 2021;**73**(6):861-72.
46. Vasconcelos LB, Silva MT, Galvao TF. Reduction of biologics in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatol Int.* 2020;**40**(12):1949-59.
47. Vinson D, Molet-Benhamou L, Degboé Y, et al. Impact of tapering targeted therapies (bDMARDs or JAKis) on the risk of serious infections and adverse events of special interest in patients with rheumatoid arthritis or spondyloarthritis: a systematic analysis of the literature and meta-analysis. *Arthritis Res Ther.* 2020;**22**(1):97.
48. Verhoef LM, van den Bemt BJ, van der Maas A, et al. Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. *Cochrane Database Syst Rev.* 2019;**5**(5):Cd010455.
49. Edwards CJ, Fautrel B, Schulze-Koops H, et al. Dosing down with biologic therapies: a systematic review and clinicians' perspective. *Rheumatology (Oxford).* 2017;**56**(11):1847-56.
50. Navarro-Compán V, Plasencia-Rodríguez C, de Miguel E, et al. Anti-TNF discontinuation and tapering strategies in patients with axial spondyloarthritis: a systematic literature review. *Rheumatology (Oxford).* 2016;**55**(7):1188-94.
51. Coates LC, Pillai SG, Tahir H, et al. Withdrawing Ixekizumab in Patients With Psoriatic Arthritis Who Achieved Minimal Disease Activity: Results From a Randomized, Double-Blind Withdrawal Study. *Arthritis Rheumatol.* 2021;**73**(9):1663-72.
52. Verhoef LM, den Broeder N, Thurlings RM, et al. Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial. *The Lancet Rheumatology.* 2019;**1**(3):e145-e53.
53. Takeuchi T, Genovese MC, Haraoui B, et al. Dose reduction of baricitinib in patients with rheumatoid arthritis achieving sustained disease control: results of a prospective study. *Ann Rheum Dis.* 2019;**78**(2):171-8.

Chapter 5

Disease activity-guided dose optimisation including discontinuation of TNF-inhibitors in rheumatoid arthritis is effective for up to 10 years

Céleste J.T. van der Togt
Nathan den Broeder
Aatke van der Maas
Alfons A. den Broeder
Noortje van Herwaarden

Published in Rheumatology (Oxford), February 2024

Abstract

Objectives

To investigate safety and effectiveness of disease activity-guided dose optimisation of TNF-inhibitors in rheumatoid arthritis over 10 years.

Methods

Observational long-term extension of a randomised study of participants who completed the 3-year extension of the DRESS-study. After the randomised phase (month 0-18), disease activity-guided dose optimisation was allowed for all. Main outcomes were mean time-weighted DAS28-CRP; biological and targeted synthetic anti-rheumatic drug (b/tsDMARD) use per year as proportion of daily defined dose; proportion of patients reaching discontinuation; durability, effectiveness of subsequent dose reduction attempts; and radiographic progression between 3 and 10 years using the Sharp-van der Heijde score.

Results

170 patients were included of whom 127 completed 10-year follow-up. The mean disease activity remained low (DAS28-CRP 2.13, 95% confidence interval 2.10 to 2.16), whilst the b/tsDMARD dose reduced from 97% at baseline (95% CI 96% to 99%, n=170) to 56% at year 10 (49% to 63%, n=127). 119 of 161 participants (74%) with an optimisation attempt reached discontinuation, with a median duration of 7 months (interquartile range 3 to 33 months), and 25 participants never had to restart their b/tsDMARD (21%, 14% to 29%). The mean dose reduction after dose optimisation was 48% (n=159) for the first optimisation attempt and 33% for subsequent attempt (n=86). Of the 86 participants, 41 (48%) had radiographic progression exceeding the smallest detectable change (5.7 units), and progression was associated with disease activity, not b/tsDMARD use.

Conclusion

Long-term disease activity-guided dose optimisation of TNF-inhibitors in rheumatoid arthritis, including discontinuation and multiple tapering attempts, remains safe and effective.

Introduction

Tumour necrosis factor inhibitors (TNFi) have shown to be effective and safe in the treatment of rheumatoid arthritis (RA),[1] but have drawbacks, including infusion or injection site reactions, a somewhat higher risk of serious infections,[2] and high costs.[3] In patients with controlled RA, these drawbacks can be reduced using disease activity-guided dose optimisation. This includes a stepwise decrease of the TNFi dose (with or without discontinuation as final step) together with treat-to-target, so that treatment can be intensified in case of a flare.[4]

The 'Dose REduction Strategy of Subcutaneous TNF inhibitors' (DRESS) study was the first randomised controlled study in RA investigating disease activity-guided dose optimisation of adalimumab or etanercept compared with continuation over a period of 18 months.[5] In this study, non-inferiority regarding major flare risk between the groups was shown, and dose reduction or discontinuation was found to be possible in the majority of patients of the dose optimisation group. Interestingly, the radiographic progression was slightly higher in the dose optimisation group and, specifically in this group, associated with increased disease activity, but not with TNFi dose.[5,6]

The extension of the DRESS study investigated effectiveness and safety of dose optimisation up to three years, with dose optimisation allowed for both groups.[7] No differences were seen in major flare incidences or disease activity, nor in radiographic progression. Moreover, the cost-effectiveness of dose optimisation was confirmed.[8] Following the DRESS study, effectiveness of TNFi dose optimisation is confirmed in several systematic reviews,[9] and supporting data also exist on tapering of other disease-modifying antirheumatic drugs (DMARDs)[10,11] and in other inflammatory diseases.[12-14] Consequently, for RA, a recommendation on dose optimisation was included in the current EULAR guideline, stating that in patients in sustained remission without glucocorticoid use, dose reduction of any DMARD (biological DMARDs (bDMARDs), targeted synthetic DMARDs (tsDMARDs) and/or conventional synthetic DMARDs (csDMARDs)) may be considered.[1]

Because of the chronic nature of RA, longer-term data (> 3 years) on dose optimisation are of importance. The most important outcomes of interest for dose optimisation would be disease activity, b/tsDMARD use, radiological outcomes, and the interrelation between these three key variables. Also, it is debated whether a discontinuation attempt should be part of a dose optimisation strategy,[1] and it is not clear whether repeated dose optimisation attempts over time are a sensible approach. Therefore, this study aimed to assess 10-year outcomes of TNFi dose optimisation in RA in a cohort of patients originally included in the DRESS study.

Materials & Methods

Study design and participants

This is a 10-year observational extension study of the DRESS study, a randomised controlled, open-label, non-inferiority trial which compared disease activity-guided dose optimisation of TNFi with dose continuation in patients with RA. An extensive description of the inclusion criteria and the rationale of the study are described elsewhere.[5,15] In short, RA patients treated with stable adalimumab or etanercept for ≥ 6 months with stable low disease activity on at least two consecutive visits were included.

For the current study, participants of the DRESS study were included if they had completed the 3-year extension study. We collected pseudonymised data on patient-, disease- and treatment characteristics from the electronic health records from the Sint Maartenskliniek (locations Nijmegen, Boxmeer, Geldrop and Woerden) from January 2015 to October 2022, and combined this with data from the earlier publications. The local ethics committee provided exemption for this follow-up study (METC Oost-Nederland; 2023-16202), as ethical approval for this type of study is not required under Dutch law.

Procedures

During the 18-month intervention phase, patients were treated following a standardised treat-to-target protocol with visits every three months.[5,15] Disease activity was assessed with the DAS28-CRP.(16) Patients in the dose optimisation group with DAS28-CRP ≤ 3.2 received stepwise dose reduction by increasing the interval of adalimumab or etanercept. The dose optimisation protocol contained the following steps, displayed as percentage of the current daily dose to the defined daily dose (%DDD): 100% - 66% - 50% - 0% (full discontinuation). In case of a flare, the dose was increased to the last effective dose or, in case of a flare at full dose, treatment was switched to another biological DMARD (bDMARD). Flare definition was a DAS28-CRP increase from baseline of > 1.2, or as an increase of > 0.6 with a current DAS28-CRP ≥ 3.2.[16]

During the extension phase (month 18-36), disease activity-guided dose optimisation was encouraged for all participants. After the extension phase, it became standard of care for all RA patients in the Sint Maartenskliniek with sustained low disease activity (LDA) or remission.[17] The dose optimisation protocol was slightly adjusted with an extra step (33% of DDD) before discontinuation, resulting in the following protocol: 100% - 66% - 50% - 33% - 0%. Also, since March 2015, the more stringent cut-offs validated for DAS28-CRP for remission (DAS28-CRP < 2.4) and LDA (DAS28-CRP < 2.9) have been used.[18] During the observational follow-up, patients were treated by their

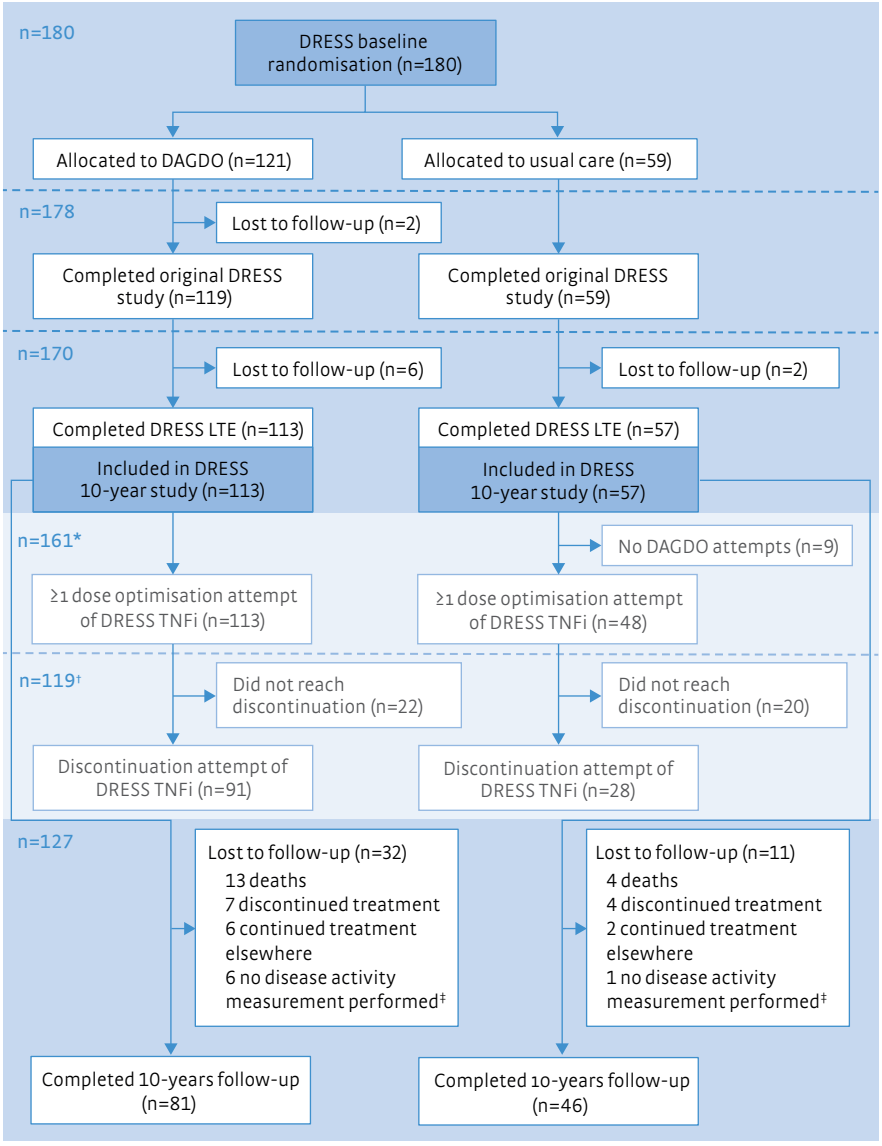


Figure 1. Study flowchart

*Represents the number of patients with 1 DAGDO attempt. †Represents the number of patients with ≥1 discontinuation attempt. At least one disease activity measurement was required to be included in the analyses. DAGDO: disease activity–guided dose optimization; DRESS: Dose REduction Strategy of Subcutaneous TNF inhibitors study; LTE: long-term extension study (3 year follow-up); TNFi: TNF inhibitor

own rheumatologist, and treatment changes were based on shared decision making between patient and rheumatologist.

Outcomes

For this extension study, we defined the following descriptive study outcomes: 1) TNFi dose, b/tsDMARD dose and disease activity over time, 2) proportions of patients with a first and second dose optimisation attempt, and the effectiveness of those attempts, 3) proportion of patients with, and duration of the first discontinuation attempt, and 4) radiographic progression between 3 and 10 years.

The TNFi and other b/tsDMARD dose over time was defined as the mean time-weighted ratio of the current dose to the DDD per subsequent year after baseline. Adalimumab 40mg/2 weeks, and etanercept 50mg/week were used as 100% of DDD (**Supplementary Table 1**). We used the trapezoid method to calculate the mean time-weighted drug use. Drug survival was defined as the use of the current b/tsDMARD until start of a new b/tsDMARD or censoring. Time after discontinuation of the current b/tsDMARD was still considered drug survival including the start of a glucocorticoid and/or a csDMARD, as long as no other b/tsDMARD was started. The disease activity over time was defined as the mean-time weighted DAS28-CRP, also calculated with the trapezoid method.

For both the dose optimisation and discontinuation attempts, only the first episode of the original DRESS TNFi use was used (until switch to another b/tsDMARD). A dose optimisation attempt was defined as the moment of initiation of the dose optimisation protocol up until the first dose increase or censoring. For example, when a patient was using full dose of TNFi (100% of the DDD) at the start of the study, the moment of starting 66% of DDD was marked as start of the dose optimisation attempt. If the same patient was using 66% of DDD after the first dose optimisation attempt (due to a persistent flare at 33%) but re-attempted 33% of DDD at a later time point, the initiation of 33% was also marked as a dose optimisation attempt. The effectiveness of dose optimisation attempts were operationalised as change in %DDD after 1.5 years (in line with the extension study). Additionally, we calculated the proportions of patients with a lower dose, full discontinuation and stable dose.

The first discontinuation attempt was defined as reaching a %DDD of 0% for the first time. The duration of a discontinuation attempt was defined as the time from reaching 0% until restart of the same or another b/tsDMARD. Use of concomitant antirheumatic drugs (csDMARDs, NSAIDs, glucocorticoids) was allowed and noted.

We assessed radiographic progression between 3 years and 10 years of the hands and feet, using the radiographs taken at the end of the DRESS extension study as 3 years,[7] and radiographs taken (in routine care) between June 2021 and January 2023 as 10-year time point. The radiographs were scored pairwise by two readers (CvdT and NvH), blinded for disease activity and medication use, but in a known sequential order, using the modified Sharp-van der Heijde score (SvdH, range 0 – 448).(19) The 3-year radiographs were re-scored for this study. We calculated the mean progression in SvdH between 3 and 10 years and per year, as well as the proportion of patients exceeding (1) the smallest detectable change (SDC), calculated with the 95% levels of agreement method(20) and (2) a score of 0.5 SvdH units representing minimal radiographic progression.[5] In addition, as we found a relationship between radiographic progression and mean time-weighted DAS28-CRP with effect modification of TNFi %DDD in the first 1.5 years of the DRESS study,[6] we studied the relationship between disease activity on progression, and b/tsDMARD dose on progression, in a multivariable logistic regression analysis containing all three variables.

Statistical analysis

We performed no formal sample size analysis, as we used all eligible DRESS study participants. The last available DAS28-CRP measurement of each patient before November 1st, 2022, was used as the censoring date. For the exploratory outcomes, descriptive statistics of mean ± standard deviation and median (interquartile range) were used depending on their distribution. For percentages, the 95% confidence interval (CI) was calculated where appropriate.

Durations of drug survival and discontinuation were analysed with Kaplan-Meier analyses. For radiographic progression, logistic regression was used for studying the relationship between radiographic progression, %DDD and disease activity. Progression exceeding the SDC was used as the cut-off point (progression yes/no) for the dependent variable with mean-time weighted DAS28-CRP and b/tsDMARD %DDD as independent variables. Results were displayed as odds ratios (OR) with 95% CI. Stata/IC version 13.1 (StataCorp, College Station, TX, USA) was used for the statistical analyses.

Table 1. Baseline characteristics

	Total (n=170)
General characteristics	
Female sex	109 (64)
Age at baseline (years)	59 ± 10
Active smoker at baseline	44 (26)
Body Mass Index at baseline (kg/m²)	26.7 ± 4.6
Disease characteristics	
Disease duration at baseline (years)	10 (6 - 16)
Rheumatoid factor positive	136 (80)
ACPA positive	124 (73)
Erosive disease at baseline	96 (61, n=158)
DAS28-CRP score at baseline	2.18 ± 0.69
Treatment characteristics	
TNFi at baseline (etanercept/adalimumab)	112/58
Duration of DRESS TNFi use (years)	3.4 ± 2.4
Concomitant csDMARD use at baseline	113 (66)
≥ 1 previous TNFi used	62 (37, n=166)
DRESS randomisation (dose optimisation/usual care)	113/57

Either displayed as mean ± standard deviation, median (interquartile range) or number (percentage).

Results

Participants

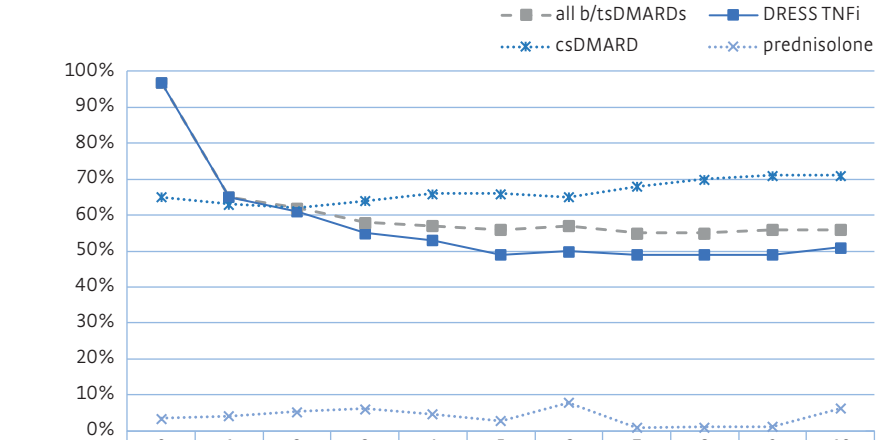
Of the 180 patients randomised in the original DRESS-study, 170 patients (94%) completed the 36 months follow-up (original randomisation: 113 disease activity-guided dose optimisation and 57 usual care). No objections against pseudonymous data use were received, thus data of all 170 patients could be included in this study (Figure 1). A total of 127 patients completed 10-year follow-up (Figure 1), and the median follow-up time was 10.0 years (interquartile range (IQR) 9.3-10.3). The patient characteristics are displayed in Table 1.

Medication use and disease activity

At DRESS-study baseline, the used TNF-inhibitor (DRESS TNFi) was etanercept for 112 patients and adalimumab for 58 patients. The median drug survival of the DRESS TNFi from study baseline was 8.9 years (min to max: 0.50 – 10.7 years) and was similar for etanercept (median 8.5 years) and adalimumab (median 9.3 years). At their last

available measurement, 55 patients (32%) were still using their DRESS TNFi, 60 patients (36%) used another b/tsDMARD and another 55 patients (32%) had discontinued their DRESS TNFi without starting a new b/tsDMARD. Of the 55 patients without b/tsDMARD at that time, 29 patients were using a csDMARD, 2 patients oral prednisolone, 4 patients both a csDMARD and prednisolone, and 20 patients were DMARD-free. Throughout the study, 60 of 170 patients changed to a different b/tsDMARD from their original DRESS TNFi.

The proportion of the mean DRESS TNFi dose in relation to the daily defined dose (%DDD) decreased from 97% at baseline (95% CI 96% - 99%, n=170) to 49% at year 5 (95% CI 42% - 56%, n=129, see Figure 2). At year 10, the %DDD remained stable: 51% (43% - 59%, n=85). The same pattern was found for all b/tsDMARDs (including the DRESS TNFi) with a decrease from 97% at baseline (96% - 99%, n=170) to 56% at year 10 (49% - 63%, n=127, see also Figure 2).



	0	1	2	3	4	5	6	7	8	9	10
all b/tsDMARDs	97%	65%	62%	58%	57%	56%	57%	55%	55%	56%	56%
n b/tsDMARD	170	170	170	170	163	157	153	146	142	132	127
DRESS TNFi	97%	65%	61%	55%	53%	49%	50%	49%	49%	49%	51%
csDMARD	65%	63%	62%	64%	66%	66%	65%	68%	70%	71%	71%
prednisolone	3,5%	4,1%	5,3%	6,1%	4,6%	2,8%	7,9%	0,9%	1,0%	1,1%	6,3%
n DRESS TNFi*	170	170	167	159	145	129	121	110	104	92	85

Follow-up time (years)

Figure 2. Mean drug dose relative to the daily defined dose per year

Represents the drug dose relative to the daily defined dose (%DDD) per subsequent year (for all b/tsDMARDs and DRESS TNFis), and the proportion of patients on DRESS TNFi using co-medication (for csDMARD and prednisolone) Number also applicable for csDMARD and prednisolone. b/ts DMARD: biologic/targeted synthetic DMARD; csDMARD: conventional synthetic DMARD; DRESS: Dose REduction Strategy of Subcutaneous TNF inhibitors study; TNFi: TNF inhibitor

The mean time-weighted disease activity measured with DAS28-CRP throughout the study was 2.13 (95% CI 2.10 – 2.16). An overview of the MTW DAS28-CRP per study year is displayed in Figure 3.

Dose optimization attempts

One hundred and sixty-one patients (161/170, 95%) had at least 1 dose optimisation attempt of their DRESS TNFi during the study. The median number of dose optimisation attempts per patient was 2 (range 0-5). 159/161 patients had at least 1.5 years of follow-up of their first dose optimisation attempt available. When comparing the DRESS TNFi dose after 1.5 years to the dose at the start of the first optimisation attempt in these patients, 70 used a lower dose (44%), 46 had reached full discontinuation (29%), and 43 used a similar dose (27%). The mean %DDD reduction was 48% ± 38%.

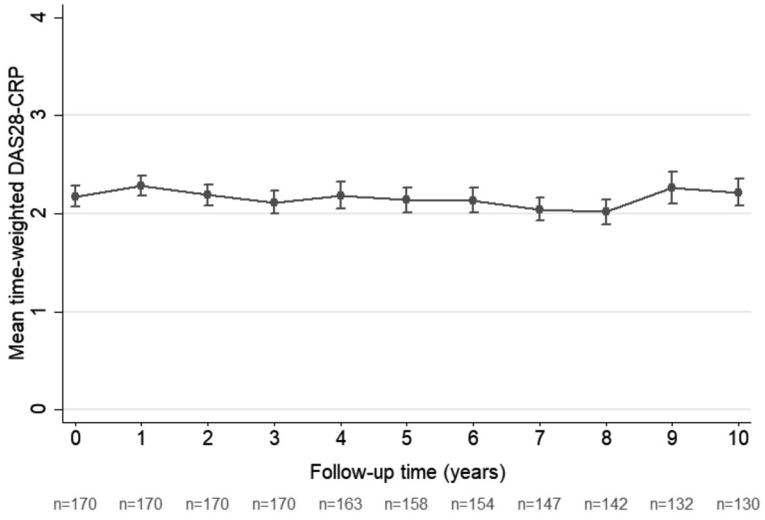


Figure 3. Mean time-weighted disease activity per year measured with DAS28-CRP

Ninety-nine patients (99/161, 61%) had a second dose optimisation attempt. The median time between the start of the first and second attempt was 2.7 years (IQR 1.7 – 4.2 years). The starting dose for the second dose optimisation attempt was full dose (%DDD = 100%) for 60 patients (61%) and a tapered dose (%DDD < 100%) for 39 (39%). The time between the first and second attempt was not associated with a successful second attempt (no restart or dose increase during study period; OR 0.92, 95% CI 0.73-1.18). 86/99 patients had at least 1.5 years of follow-up of their second dose

optimisation attempt available. When comparing the DRESS TNFi dose after 1.5 years to the dose at the start of the second optimisation attempt in these patients, 44 used a lower dose (51%), 18 had reached full discontinuation (21%), and 24 used a similar dose (28%). The mean %DDD reduction was 33% ± 37%.

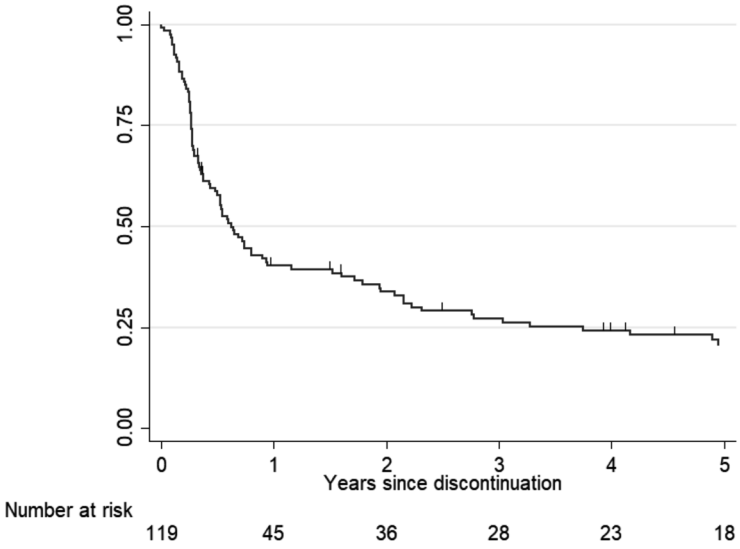


Figure 4. Survival of first discontinuation attempt of the DRESS TNFi in years.

The upticks represent censored subjects. DRESS: Dose REduction Strategy of Subcutaneous TNF inhibitors study; TNFi: TNF inhibitor

Discontinuation attempts

Of the 161 patients with a dose optimisation attempt, 119 (74%) attempted discontinuation of the DRESS TNFi at least once (Figure 1). At the time of their first discontinuation attempt, 65 patients (56%, 65/119) used a csDMARD as comedication, 3 oral glucocorticoids (3%) and 2 both a csDMARD and oral glucocorticoid (2%). The median glucocorticoid dose at that time was 5 mg daily (n=5), with one patient being on a short course of 30 mg for 7 days.

The median duration of the first discontinuation attempt was 7 months (IQR 3 – 33 months). The survival of the first discontinuation attempt is displayed in Figure 4. Thirteen patients (11%, 13/119) started extra comedication during this discontinuation period: 10 patients started a csDMARD and 3 started oral glucocorticoids.

Twenty-five patients (21%, 25/119) never had to restart their TNFi or another b/tsDMARD after their first discontinuation attempt throughout the study period. The median observed time in discontinuation of these patients was 73 months (IQR 30 – 111 months). At the end of follow-up, 12 of these patients (48%) were using a csDMARD, 1 oral prednisolone (4%), and 12 were DMARD-free (48%).

Table 2. Radiographic outcomes between 3 and 10 years of follow-up

	Study participants (n=86)
Progression total SvdH score	5.5 (2.5 – 13)
Progression SvdH score per year	0.8 (0.4 – 1.8)
Progression erosion score	2 (0.5 – 5.5)
Progression joint space narrowing	3.5 (1.5 – 8.5)
Progression > SDC (5.7 units)	41 (48)
Progression > 0.5 units	78 (91)

Either displayed as median (IQR) or number (percentage). SvdH: Sharp-van der Heijde, SDC: smallest detectable change.

Radiographic joint damage

Eighty-six patients had radiographs at both year 3 and 10 available. The median SvdH score at 3 years was 25.8 units (IQR 10.0 - 53.5). The median progression was 5.5 units (IQR 2.5 – 13.0, see table 2). Forty-one patients (48%) had a progression exceeding the SDC (5.7 units), and 78 patients (91%) progression exceeding the minimal radiographic progression (0.5 units, supplementary figure 1).

In the regression analysis, a higher mean time-weighted DAS28-CRP was significantly associated with reaching progression equal to the SDC or more (OR 3.71 per increased point of DAS28-CRP, 95%-CI 1.31 to 10.56, p=0.014), whereas a relevant association with the b/tsDMARD %DDD could not be demonstrated (OR 0.42 for a %DDD of 100% compared to 0%, 95%-CI 0.07 to 2.49, p=0.34).

Discussion

This 10-year study on effectiveness and safety of disease activity-guided dose optimisation of TNFi in RA patients showed four key results that are reassuring but require some attention. First, we found a stable low disease activity over a 10-year period while only using half of the TNFi dose. Second, a subsequent dose reduction attempt also leads to a relevant reduction in b/tsDMARD use, albeit less reduction

compared to the first attempt. Third, the inclusion of a discontinuation attempt in the dose optimisation strategy seems sensible as it does not lead to long term disease deterioration, and because b/tsDMARD free remission for a relevant period is possible in a non-negligible number of patients. Last, there was a relevant progression of joint damage for half of the patients, although limited, which was not associated with bDMARD use or dose, but seemed partly driven by higher disease activity.

Our study has several strengths. It is the largest study on disease activity guided dose optimisation of b/tsDMARDs in RA with the longest follow-up time and with solid data quality and low attrition. Also, treat-to-target was adequately performed in this study, demonstrated by several indicators of protocol adherence. This also enabled us to analyse the effects of dose and disease activity independently.

However, our study has some limitations. First, especially for the radiographs, there is a significant proportion of data missing (49% missing). This reduces precision and might have induced bias, as radiographs possibly have been performed more often in patients with more complaints and/or more active disease who were more likely to visit the clinic, leading to an overestimation of the radiographic progression. Of note, the proportion of missing data for the clinical outcomes (disease activity and b/tsDMARD dose) was low for this retrospective design and long follow-up duration. Second, some DAS28-CRP measurements were missing at the start of dose optimisation or discontinuation. Assuming that the measurements are performed more often in presence of complaints, the disease activity may therefore be somewhat over-estimated. Last, precision was not always enough to exclude all relevant effect sizes, especially for the radiographic outcomes.

To interpret the radiographic progression seen in our study, there is no suitable direct control group available. Recent studies reporting radiographic progression in RA in cohorts with over ≥5 years of follow up without dose optimisation found a somewhat lower mean progression than our study: 1.8 - 3.1 SvdH units for 5 years follow-up and 2.5 - 3.8 SvdH units for 10 years compared to 5.5 SvdH units in our study.[21,22] However, this difference seems mainly due to the higher joint space narrowing sub-score in our study compared to other studies,[22-24] which is probably caused by a much longer disease duration at baseline in our study (10 years versus 5-8 months), resulting in more effect of primary osteoarthritis on the progression score. Of note, the median progression found of 5.5 SvdH units over 7 years was approximately the same as the previously suggested minimal clinically important difference (MCID) for one year progression.[25] Similarly to the original DRESS study, we found an association between radiographic progression and a higher DAS28-CRP, suggesting that radiographic progression is driven by disease activity.[6] Although we found no significant effect of

b/tsDMARD dose on radiographic progression in this study, a smaller effect cannot be ruled out because of the limited sample size and therefore this requires further study.

Although this is a topic of debate, our study found indications of a positive risk-benefit ratio for the inclusion of discontinuation in a dose optimisation attempt. This is demonstrated by the stable low disease activity over time, the long drug survival after restart, and the finding that one-fifth of patients can stay without TNFi for a longer time. The perception that discontinuation is a suboptimal strategy mainly stems from randomised trials in which direct discontinuation from full dose without the opportunity to restart was inferior to continuation of full dose, as well as trials with short-term flares as primary outcome.[26,27] However, a strategy of stopping and restarting when needed is different from stopping without taking effects of restarting into account, and this difference should be appreciated. Therefore, we recommend a careful stepwise dose reduction with adequate monitoring of disease activity for the selection of a subgroup of patients in whom a discontinuation attempt might be fruitful.

Another interesting finding is the additional value of a subsequent dose optimisation attempt after approximately 2.5 years. Although the mean dose reduction was lower in the follow-up attempt (33% versus 48%), the proportion of patients after 1.5 years on either a lower dose or full discontinuation was similar for both attempts (73% versus 72%). The effectiveness of the subsequent attempt suggests that the b/tsDMARD need over time may vary in a patient, possibly caused by a fluctuation in disease severity. Of note, this finding could also be explained by patient and/or physician factors, such as stricter requirements for dose escalation (not in case of subjective complaints), or more positive beliefs on dose optimisation. All in all, we suggest a follow-up dose optimisation attempt in all patients after approximately 2.5 years, as it has shown to be safe and can lead to additional dose reduction.

While we investigated several aspects of long-term effectiveness of disease activity-guided dose optimisation, some research gaps remain. A possible beneficial effect of long-term dose optimisation on adverse effects of TNFi such as infections could be of importance. Also, the long-term effectiveness of disease activity-guided dose optimisation for other drugs and diseases would be of interest, as it has been shown effective for other drugs in RA,[10,11,28] as well as in other diseases.[10,12-14]

In conclusion, over a period of 10 years, disease activity-guided dose optimisation of TNF-inhibitors in RA leads to a significant dose reduction while maintaining disease control. A discontinuation attempt seems sensible to include, and subsequent dose optimisation attempts after ~2.5 years can lead to additional dose reduction. A strict

treat-to-target seems important to limit radiographic progression. These findings are important to guide more specific dose optimisation recommendations in the future regarding how to perform dose optimisation, and how to monitor outcomes to ensure safety.

Reference list

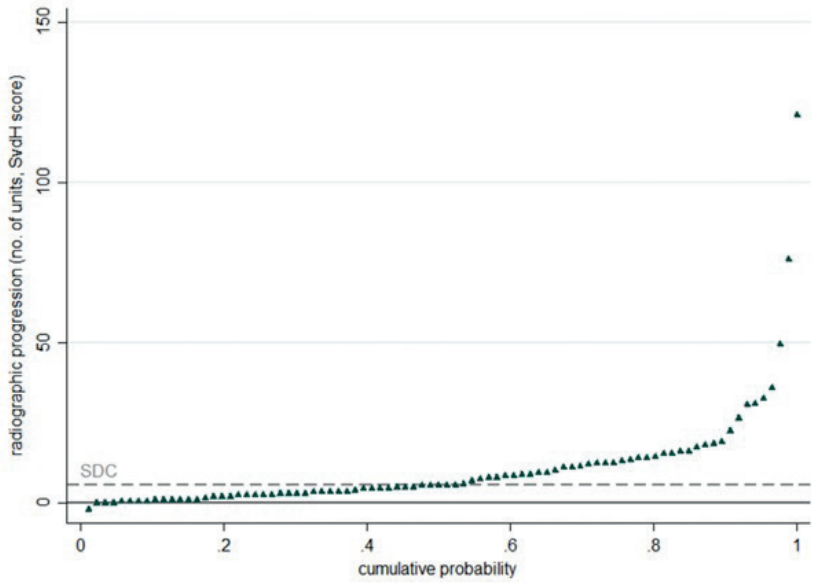
1. Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82(1):3-18.
2. Sepriano A, Kerschbaumer A, Bergstra SA, Smolen JS, van der Heijde D, Caporali R, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2023;82(1):107-18.
3. Science. JMECfCDaC. Medicines for Rheumatoid Arthritis: A Review of the Research for Adults. 2005 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK115126/table/consra2.tu2/.
4. van der Togt CJT, Van den Bemt B, Aletaha D, Alten R, Chatzidionysiou K, Galloway J, et al. Points to consider for cost-effective use of biological and targeted synthetic DMARDs in inflammatory rheumatic diseases: results from an umbrella review and international Delphi study. RMD Open. 2023;9(1).
5. van Herwaarden N, van der Maas A, Minten MJ, van den Hoogen FH, Kievit W, van Vollenhoven RF, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. Bmj. 2015; 350:h1389.
6. Bouman CA, den Broeder AA, van der Maas A, van den Hoogen FH, Landewé RB, van Herwaarden N. What causes a small increase in radiographic progression in rheumatoid arthritis patients tapering TNF inhibitors? RMD Open. 2017;3(1):e000327.
7. Bouman CA, van Herwaarden N, van den Hoogen FH, Fransen J, van Vollenhoven RF, Bijlsma JW, et al. Long-term outcomes after disease activity-guided dose reduction of TNF inhibition in rheumatoid arthritis: 3-year data of the DRESS study - a randomised controlled pragmatic non-inferiority strategy trial. Ann Rheum Dis. 2017;76(10):1716-22.
8. den Broeder N, Bouman CAM, Kievit W, van Herwaarden N, van den Hoogen FHJ, van Vollenhoven RF, et al. Three-year cost-effectiveness analysis of the DRESS study: protocolised tapering is key. Ann Rheum Dis. 2019;78(1):141-2.
9. Verhoef LM, van den Bemt BJ, van der Maas A, Vriezekolk JE, Hulscher ME, van den Hoogen FH, et al. Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. Cochrane Database Syst Rev. 2019;5(5):Cd010455.
10. Edwards CJ, Fautrel B, Schulze-Koops H, Huizinga TWJ, Kruger K. Dosing down with biologic therapies: a systematic review and clinicians' perspective. Rheumatology (Oxford). 2017;56(11):1847-56.
11. Vasconcelos LB, Silva MT, Galvao TF. Reduction of biologics in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatol Int. 2020;40(12):1949-59.
12. Michielsens CA, den Broeder N, van den Hoogen FH, Mahler EA, Teerenstra S, van der Heijde D, et al. Treat-to-target dose reduction and withdrawal strategy of TNF inhibitors in psoriatic arthritis and axial spondyloarthritis: a randomised controlled non-inferiority trial. Ann Rheum Dis. 2022;81(10):1392-9.
13. Atalay S, van den Reek J, den Broeder AA, van Vugt LJ, Otero ME, Njoo MD, et al. Comparison of Tightly Controlled Dose Reduction of Biologics With Usual Care for Patients With Psoriasis: A Randomized Clinical Trial. JAMA Dermatol. 2020;156(4):393-400.
14. van Linschoten RCA, Jansen FM, Pauwels RWM, Smits LJT, Atsma F, Kievit W, et al. Increased versus conventional adalimumab dose interval for patients with Crohn's disease in stable remission (LADI): a pragmatic, open-label, non-inferiority, randomised controlled trial. Lancet Gastroenterol Hepatol. 2023;8(4):343-55.
15. den Broeder AA, van Herwaarden N, van der Maas A, van den Hoogen FH, Bijlsma JW, van Vollenhoven RF, et al. Dose REduction strategy of subcutaneous TNF inhibitors in rheumatoid arthritis: design of a pragmatic randomised non inferiority trial, the DRESS study. BMC Musculoskelet Disord. 2013;14:299.
16. van der Maas A, Lie E, Christensen R, Choy E, de Man YA, van Riel P, et al. Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. Ann Rheum Dis. 2013;72(11):1800-5.
17. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960-77.

18. Fleischmann R, van der Heijde D, Koenig AS, Pedersen R, Szumski A, Marshall L, et al. How much does Disease Activity Score in 28 joints ESR and CRP calculations underestimate disease activity compared with the Simplified Disease Activity Index? Ann Rheum Dis. 2015;74(6):1132-7.
19. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 1999;26(3):743-5.
20. Navarro-Compán V, van der Heijde D, Ahmad HA, Miller CG, Wolterbeek R, Landewé R. Measurement error in the assessment of radiographic progression in rheumatoid arthritis (RA) clinical trials: the smallest detectable change (SDC) revisited. Ann Rheum Dis. 2014;73(6):1067-70.
21. Park YJ, Gherghe AM, van der Heijde D. Radiographic progression in clinical trials in rheumatoid arthritis: a systemic literature review of trials performed by industry. RMD Open. 2020;6(2).
22. Markusse IM, Akdemir G, Dirven L, Goekoop-Ruiterman YP, van Groenendael JH, Han KH, et al. Long-Term Outcomes of Patients With Recent-Onset Rheumatoid Arthritis After 10 Years of Tight Controlled Treatment: A Randomized Trial. Ann Intern Med. 2016;164(8):523-31.
23. Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Patra K, Sasso EH. Less radiographic progression with adalimumab plus methotrexate versus methotrexate monotherapy across the spectrum of clinical response in early rheumatoid arthritis. J Rheumatol. 2009;36(7):1429-41.
24. Genovese MC, Bathon JM, Fleischmann RM, Moreland LW, Martin RW, Whitmore JB, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. J Rheumatol. 2005;32(7):1232-42.
25. Welsing PM, Borm GF, van Riel P. Minimal clinically important difference in radiological progression of joint damage. A definition based on patient perspective. J Rheumatol. 2006;33(3):501-7.
26. Smolen JS, Nash P, Durez P, Hall S, Ilivanova E, Irazoque-Palazuelos F, et al. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. Lancet. 2013;381(9870):918-29.
27. Chatzidionysiou K, Turesson C, Teleman A, Knight A, Lindqvist E, Larsson P, et al. A multicentre, randomised, controlled, open-label pilot study on the feasibility of discontinuation of adalimumab in established patients with rheumatoid arthritis in stable clinical remission. RMD Open. 2016;2(1):e000133.
28. Takeuchi T, Genovese MC, Haraoui B, Li Z, Xie L, Klar R, et al. Dose reduction of baricitinib in patients with rheumatoid arthritis achieving sustained disease control: results of a prospective study. Ann Rheum Dis. 2019;78(2):171-8.

Supplementary data

Supplementary table 1. Daily defined dose of the included biological and targeted synthetic DMARDs

Biological DMARDs	
Abatacept	125 mg every 7 days
Adalimumab	40 mg every 14 days
Certolizumab pegol	200 mg every 14 days
Etanercept	50 mg every 7 days
Golimumab	50 mg every 30 days
Rituximab	1000 mg every 182 days
Sarilumab	200 mg every 14 days
Tocilizumab	162 mg every 7 days
Targeted synthetic DMARDs	
Baricitinib	4 mg every day
Tofacitinib	10 mg (2*5) every day



Supplementary figure 1. Probability plot

SDC: smallest detectable change, SvdH: Sharp-van der Heijde. Solid line: no progression, broken line: SDC of 5.7 points, triangle line: probability.

Chapter 6

Pharmacokinetic boosting to enable a once-daily reduced dose of tofacitinib in patients with rheumatoid arthritis and psoriatic arthritis

Céleste J.T. van der Togt
Lise M. Verhoef
Bart J.F. van den Bemt
Nathan den Broeder
Rob ter Heine
Alfons A. den Broeder

Published in Therapeutic Advances in Musculoskeletal Disease, December 2022

Abstract

Background

Tofacitinib is a Janus Kinase (JAK) inhibitor used in the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA), dosed as 5 mg twice daily. It is primarily metabolized by the cytochrome P-3A (CYP3A) enzyme, and therefore the manufacturer recommends to halve the dose when using CYP3A-inhibiting comedication. Combining half-dose tofacitinib with a registered CYP3A-inhibitor (cobicistat) could reduce costs and improve patient experience.

Objectives

Primary: bioequivalence of tofacitinib 5 mg combined with cobicistat once daily (QD; intervention) to tofacitinib 5 mg twice daily (BID; control). Secondary: safety, patient preference (7-point Likert scale at study end), and predicted differences in disease activity (DAS28-CRP and probability of ACR20-response) using a validated exposure-response model.

Design

Open-label, cross-over pharmacokinetic study

Methods

We included patients with RA or PsA, treated with tofacitinib 5mg BID for ≥ 14 days without co-medication affected by CYP3A-inhibition. Pharmacokinetic sampling was performed at baseline and after 2-6 weeks of intervention treatment. Bioequivalence was defined as 90%-CI of the average tofacitinib concentration ($C_{avg,ss;}$ intervention to control) falling between 80-125%, assessed by non-linear mixed effects modelling.

Results

Between 16 September 2019 and 15 January 2021, 30 patients were included, of whom 25 completed both PK-measurements. The tofacitinib $C_{avg,ss}$ was 85% (90% CI: 75-96%). No serious adverse events occurred. Patient preference was 56% for intervention versus 18% for control. No relevant differences in median predicted disease activity were found (DAS28-CRP: 0.03, 95% CI -0.16 to 0.22; ACR20: -0.01, -0.07 to 0.05).

Conclusion

Due to slightly lower tofacitinib concentrations during intervention treatment, pharmacokinetic bioequivalence could not formally be established. However, pharmacokinetic boosting may be an attractive strategy for cost reduction of tofacitinib, because of its safety, similar predicted pharmacodynamics and patient preference.

Introduction

Janus Kinase (JAK) inhibitors are effective and safe drugs in the treatment of both rheumatoid arthritis (RA) and psoriatic arthritis (PsA).[1] The first approved JAK-inhibitor was tofacitinib, which significantly reduces arthritis symptoms and decreases radiological progression in both conditions.[2,3] Initially, tofacitinib was only available as 5 mg twice daily (BID), but more recently once daily (QD) therapy with tofacitinib has become available by authorization of an 11 mg extended-release (XR) tablet. Interestingly, the approval of this XR tablet was entirely based on model-based prediction of the efficacy of this new formulation, using a small pharmacokinetic study and an existing exposure-response model.[4]

However, tofacitinib treatment is associated with high costs. Yearly costs per patient for tofacitinib 5 mg BID varied between 13,000 euros in the European Union and 43,000 euros in the United States in 2018.[5] Since its patent will not expire until 2028, innovative strategies are needed to provide effective but cost-effective treatment in the upcoming years.

For tofacitinib, an opportunity can be found in its metabolism, which is primarily executed by the cytochrome P450 isoenzyme 3A (CYP3A).[6] Indeed, the manufacturer advises to halve the dose of tofacitinib when co-administered with a strong CYP3A inhibiting drug, such as ketoconazole.[6] Therefore, tofacitinib treatment could be decreased to 5 mg QD if deliberately combined with such an inhibitor, a strategy called 'pharmacokinetic boosting'.

Pharmacokinetic boosting, by means of CYP3A inhibition, is a concept that is widely applied in human immunodeficiency virus (HIV)-treatment, to reduce pill burden and pharmacokinetic variability.[7] Cobicistat is an approved pharmacokinetic booster used for HIV treatment. It strongly inhibits CYP3A metabolism in the intestines as well as the liver and is otherwise pharmacologically inactive.[8] In the Netherlands, the costs for cobicistat are €1.09 per tablet, approximately one-twelfth of tofacitinib.[9,10] As cobicistat has a well-tolerated safety profile,[11] it can be a safe and efficacious drug to boost tofacitinib, and substituting tofacitinib BID for tofacitinib with cobicistat QD could lead to a significant cost reduction.

Apart from the near 50% cost reduction, boosted tofacitinib therapy could have other advantages. First, drug adherence could be improved as this is negatively associated with dose frequency.[12] Moreover, it could have a positive impact on the interpatient pharmacokinetic variability, because CYP3A significantly varies between humans[13] and the addition of a CYP3A inhibitor in combination with a reduced dose could thus

stabilize tofacitinib exposure on population level. A possible drawback includes interactions with other CYP3A substrates.

In summary, tofacitinib-cobicistat combination therapy can be an interesting strategy to reduce costs and improve patients' experience with tofacitinib. As the results of the population pharmacokinetic analysis in patients with PsA were similar to those of patients with RA, these populations can be combined in a pharmacokinetic study.[6] Therefore, the aim of our study was to investigate the bioequivalence of tofacitinib combined with cobicistat QD versus tofacitinib BID in patients with RA and PsA, and to explore effects on modelled pharmacodynamics.

Methods

Study design

This was an open-label, non-randomized, within-group crossover study with the aim to investigate the bioequivalence of tofacitinib 5 mg (Xeljanz®) with cobicistat 150 mg (Tybost®) QD (intervention) and tofacitinib 5 mg BID (control), performed in the Sint Maartenskliniek (Nijmegen, The Netherlands). In addition to the bioequivalence study, the effect of pharmacokinetic boosting on treatment outcome was predicted using a validated pharmacokinetic-pharmacodynamic model This model was previously used by the manufacturer to obtain marketing authorization for extended-release tofacitinib 11 mg, with the aim to predict efficacy based on pharmacokinetics only.[4] The reporting of this study conforms to the STROBE guideline.[14]

Participants

We recruited patients (aged ≥ 16 years) from the outpatient rheumatology clinic of the Sint Maartenskliniek. Inclusion criteria were 1) a diagnosis of either RA or PsA (according to relevant classification criteria[15-17] or a clinical diagnosis), and 2) current use of tofacitinib 5 mg BID for ≥ 2 weeks. If tofacitinib was used for > 3 months, a sufficient clinical response was also required, defined as a Disease Activity Score 28 using C-reactive protein (DAS28-CRP) of < 2.9 or a judgment of low disease activity by a rheumatologist. We excluded individuals with a known intolerance to cobicistat or with co-medication affected by the CYP3A-enzyme. Therefore, participants' co-medication (including over-the-counter medication) was checked by a pharmacist before inclusion, using a predefined list of contra-indicated medication composed for this study (**Supplementary table 1**). Some contra-indicated drugs could be replaced with a similar drug to enhance study participation, e.g. replacing simvastatin with pravastatin (**Supplementary table 1**). The use of (methyl)prednisolone, also affected by CYP3A, was accepted in a dose of ≤ 10 mg oral daily (prednisolone) or as an injection

of ≤ 120 mg intramuscular (methylprednisolone) during the study. Concomitant treatment with conventional synthetic disease modifying antirheumatic drugs (csDMARDs) such as methotrexate or leflunomide, or with non-steroidal anti-inflammatory drugs (NSAIDs) was also accepted. To exclude other CYP3A involvement, patients were asked at the start of each PK sampling day whether they had used grapefruit juice or Saint John's Wort in the week prior.

Procedures

The study consisted of an inclusion visit to obtain informed consent and to collect patient characteristics, followed by two sampling days to measure tofacitinib concentrations of both treatment regimens (figure 1). The first sampling day was planned at pharmacokinetic steady-state after ≥ 2 weeks use of tofacitinib 5 mg BID. After this sampling day, participants switched treatment to tofacitinib 5 mg and cobicistat 150 mg QD, ingested simultaneously. Then, after 2-6 weeks, another sampling day was performed. This time window was chosen to ensure that steady state of the new regimen was reached but to limit the exposure to a new medication regimen. Medication adherence was monitored throughout the study with pill count and a study medication diary. After this sampling day, the study ended for a participant.

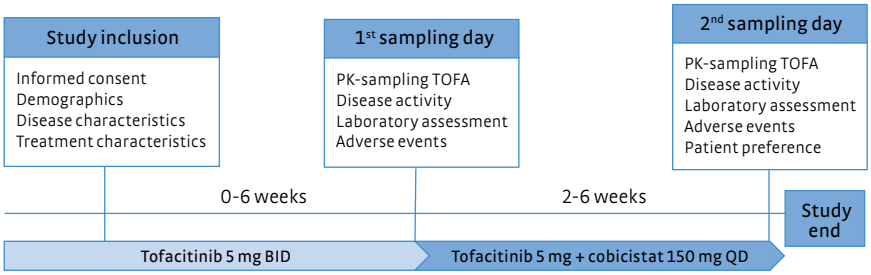


Figure 1. Study visits and measurements

PK-sampling, pharmacokinetic sampling; TOFA, tofacitinib.

At inclusion, we obtained data for demographics, disease and treatment characteristics and smoking history. On the sampling days, plasma samples were drawn pre-dose and at 0.5, 1, 2, 3, 4, 6, 9, 12, and 24-hours post-dose (24-hours intervention treatment only). We chose these time points to assess the area under the plasma concentration-time curve (AUC) of the full dosing interval on sufficient time points, in accordance with the European Medicines Agency (EMA).[18] Samples were collected in 3 mL labelled

lithium heparin tubes without gel and stored at -40°C. At the end of the study, tofacitinib concentrations were measured in batch with a validated bioanalytical assay.

Moreover, clinical and laboratory parameters, and adverse events were collected at the sampling days. Clinical assessments included height (1st sampling day only), weight, blood pressure, and DAS28-CRP and its components: swollen joint count (SJC), tender joint count (TJC), patient global assessment on disease activity (VAS), patient global assessment on pain (VAS pain), and physician global assessment on disease activity (VAS physician). Laboratory assessments included: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), alanine aminotransaminase (ALAT), total blood count, and creatinine. Adverse events were asked by a research nurse or physician and registered using the Common Terminology Criteria for Adverse Events (CTCAE) version 5 (**Supplementary table 2**).[19] Patient preference was measured at the second sampling day. Patients were asked to fill in a 7-point Likert scale for the question 'Which medication regimen do you prefer?' of which one end represented 'very strong preference for tofacitinib BID', the middle 'no preference' and the other end 'very strong preference for tofacitinib combined with cobicistat QD'.

Outcomes

The primary aim was to investigate the bioequivalence of the average tofacitinib concentration in steady state ($C_{avg,ss}$) of tofacitinib 5 mg and cobicistat 150 mg QD compared to tofacitinib 5 mg BID. The $C_{avg,ss}$, defined as the AUC divided by the dosing interval, was chosen as primary outcome for investigating bioequivalence as it best describes clinical efficacy of tofacitinib.[4] Bioequivalence was defined as the 90% confidence interval (CI) of the $C_{avg,ss}$ geometric mean ratio (GMR) falling between 80-125%.

Secondary outcomes included DAS28-CRP (measured on both sampling days), adverse events, patient preference (measured by a 7-point Likert scale on the last sampling day), and description of relevant pharmacokinetic parameters (clearance, bioavailability, and volume of distribution).
DAS28-CRP and adverse events were descriptively measured to timely assess safety and efficacy signals. Last, we predicted the effect of pharmacokinetic boosting on relevant pharmacodynamics on a population level, including the DAS28-CRP score and the American College of Rheumatology definition of 20% improvement of disease (ACR20 response).

Statistical analysis

Sample size calculation

The "Two One-Sided t-Tests (TOST) for (Bio)equivalence Studies" package version 1.4-6 in R statistics v3.4.3 was used for the sample size calculation, because of the $C_{avg,ss}$ as primary endpoint for the study. We assumed a bioequivalence ratio of 1, standard bioequivalence margins and a known 27% coefficient of variance in AUC/C_{avg}, based on the phase IIb dose ranging study of tofacitinib.[20] This led to a number of 28 patients needed to show bioequivalence with a 90% power and a significance level of 5%. To account for drop-out, we chose to include 30 patients.

Pharmacokinetic analysis

The pharmacokinetic analysis was performed by means of non-linear mixed effects modelling. In short, we fitted a one compartment pharmacokinetic model with zero order oral absorption and first order elimination previously developed by the manufacturer[21] to the obtained rich pharmacokinetic data of this study. Pharmacokinetics were allometrically scaled to a standard body weight of 70 kg.[22] Estimated glomerular filtration at baseline was investigated as a covariate for clearance. The effect of cobicistat coadministration was estimated as a binary covariate for clearance and bioavailability, as well as intra-individual variability on clearance.

From the pharmacokinetic model, the individual empirical Bayes' estimate for the $C_{avg,ss}$ of tofacitinib was obtained in absence and presence of cobicistat and used to test equivalence on the primary end point, by means of a two one-sided test (TOST) procedure.[23] The intervention regimen was considered pharmacokinetically bioequivalent to the control regimen if the 90% confidence interval of the geometric mean ratio entirely fell between 80% and 125%, in accordance with the EMA guideline.[18] Of note, we erroneously reported equivalence margins of 75% to 125% in the trial register, this was adjusted post-hoc to comply with guidelines. Only the patients who completed both sampling days were included in the primary analysis, so that both tofacitinib regimens could be compared.

Measured outcomes

Clinical efficacy in the study was evaluated with the mean difference in DAS28-CRP for both RA and PsA patients, measured on both sampling days. Safety was evaluated by descriptive analysis of the adverse events using StataIC (version 13, StataCorp LLC, TX, USA), categorized by the CTCAE v5.[19] Patient preference was evaluated by calculating the proportion of patients that preferred tofacitinib BID (Likert scale score 1-3), had no preference (score 4), and that preferred tofacitinib with cobicistat QD (score 5-7). Only the patients who actually used the combination therapy were included in these secondary analyses.

Predicted clinical outcomes

For evaluation of the effect of pharmacokinetic boosting on DAS28-CRP and probability of ACR20 response improvement on a population level, we performed a Monte Carlo simulation (n=1000 in a cross-over study) of the both outcomes at maximum efficacy, using the NONMEMV7.4 software package (ICON plc, Dublin, Ireland). In this simulation, we used the pharmacokinetic parameters from our study and the pharmacokinetic-pharmacodynamic model as described by Lamba et al, previously used for model-informed development and registration of the XR formulation of tofacitinib.[4] We predicted the median values and 95% confidence intervals (2.5th-95th percentiles of the predicted clinical outcome measure including both inter-individual variability as parameter uncertainty) of the DAS28-CRP score and the probability of ACR20 response for both study regimens. An increase of 0.6 in DAS28-CRP score and a 10% reduced probability of ACR20 were considered clinically relevant.[21,24]

Results

Inclusion

Study inclusion took place between 16 September 2019 and 15 January 2021, and study measurements were performed up until 10 March 2021. Eighty-nine patients were assessed for eligibility, and thirty patients (34%) were included (figure 2). Twenty-seven participants completed at least one sampling day and were included in the baseline and secondary analyses. Of the three excluded participants, two discontinued tofacitinib because of side effects, and the third withdrew informed consent because of fear for side effects of cobicistat. Of the 27 participants included in the baseline analyses, two could not be included in the primary analyses. One patient discontinued tofacitinib before the second sampling day could be performed due to COVID-19 lockdown. Patient preference was still collected, because combination therapy was used by this patient. The second patient was excluded due to a protocol violation (tofacitinib and cobicistat QD administered in the evening instead of the morning).

The baseline characteristics of participants are displayed in table 1. Median follow-up times were 14 days (range 14-49 days, n=26) for the intervention regimen, and 27 days (range 1-171 days, n=27) for the control regimen. Eighty-two (22/27) percent of the participants were tofacitinib starters (use ≤ 3 months).

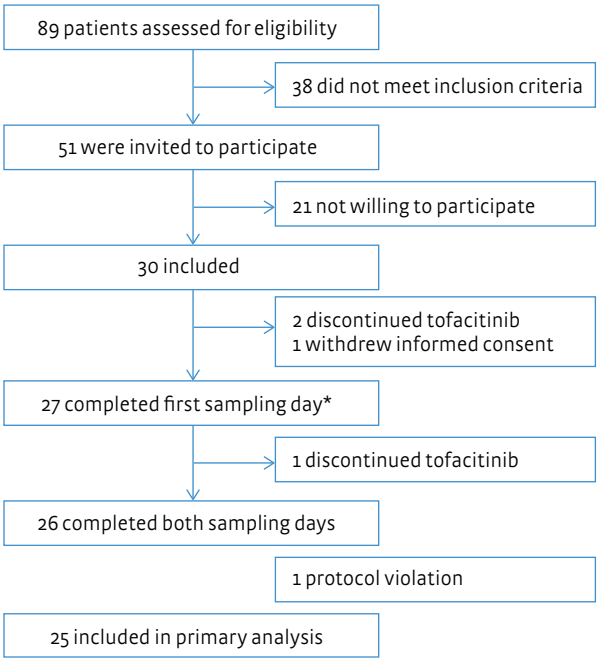


Figure 2. Study flow chart

*Included in secondary analyses

Outcomes

Pharmacokinetic bioequivalence

The median tofacitinib $C_{avg,ss}$ was 19.0 ng/ml (interquartile range (IQR) 14.1-24.3) for tofacitinib 5 mg BID, and 15.7 (14.0-19.3) for tofacitinib 5 mg with cobicistat 150 mg QD. The geometric mean ratio of tofacitinib $C_{avg,ss}$ for tofacitinib with cobicistat QD compared to tofacitinib BID was 85%, with its 90% CI being 75-96%. Thus, the bioequivalence criteria were not met (figure 3).

Measured clinical outcomes

Disease activity measured by DAS28-CRP remained stable throughout this short-term study: the change between both sampling days was 0.04 (95% CI -0.50 to 0.59, intervention to control, n=26; table 2).

No serious adverse events occurred during the study. One patient had to temporarily discontinue tofacitinib with cobicistat because of heart failure but these could be restarted without reoccurrence of symptoms after three weeks. The most frequently

Table 1. Baseline characteristics

	Participants (n=27)
Age (years)	59 (49-67)
Female gender	15 (56%)
Weight (kg)	85 ± 21
GFR calculated by CKD-epi (ml/min/1.73m²)	88 (73-90)
Disease	
· RA	17 (63%)
· RF and/or ACPA positive (RA only)	14 (82%)
· PsA	10 (37%)
Disease duration (years)	11 (4-18)
Tofacitinib use ≤ 3 months	22 (81%)
DAS28CRP at first sampling day	3·27 ± 1·41
Concomitant csDMARD use	8 (30%)
· methotrexate	4 (15%)
· leflunomide	4 (15%)
Previous biological or targeted synthetic DMARDs (n)	3 (2-4)
Adaptations made to comedication interacting with CYP3A4 prior to inclusion (multiple adaptations possible)	
· simvastatin/atorvastatin replaced by pravastatin	5 (19%)
· amlodipine replaced by hydrochlorothiazide	1 (4%)
· amlodipine replaced by enalapril	1 (4%)
· metoprolol replaced by bisoprolol	1 (4%)

Either displayed as number (percentage), mean ± standard deviation or median (interquartile range) unless indicated otherwise. Percentages were calculated over the total number of participants unless indicated otherwise. GFR = glomerular filtration rate. CKD-epi = chronic kidney disease epidemiology collaboration. RA = rheumatoid arthritis. RF = rheumatoid factor. ACPA = anti-citrullinated protein antibodies. PsA = psoriatic arthritis. DAS28-CRP = disease activity score based on 28 joints and C-reactive protein level. csDMARD = conventional synthetic disease modifying anti-rheumatic drug.

reported adverse events (AEs) during the intervention regimen were musculoskeletal, gastrointestinal, and neurological (supplementary table 2). Both gastrointestinal and neurological AEs were reported more frequently during intervention than control treatment, for which nausea (n=5) and headache (n=3) were the most reported subcategories. Except for the known and small creatinine increase during cobicistat use,[25] safety laboratory parameters did not differ between sampling days (table 2). We concluded that therefore no major efficacy and safety concerns were observed after switch.

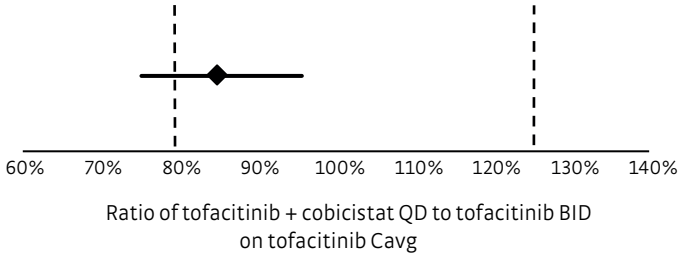


Figure 3. Assessment of bioequivalence

Geometric mean ratio with 90% confidence interval of the tofacitinib $C_{avg,ss}$ (tofacitinib 5 mg BID compared with tofacitinib 5 mg and cobicistat 150 mg QD) represented as horizontal line. Equivalence margins are represented as vertical dotted lines at 80% and 125%.

The majority of the patients (56%) preferred combination therapy of tofacitinib with cobicistat QD over tofacitinib BID, 18% preferred tofacitinib monotherapy, and 26% had no preference (figure 4).

Figure 4. Patient preference

Visual representation of the 7-point Likert scale, with the percentage represented by the length of the bar. Very strong to somewhat preference for tofacitinib BID (score 1–3), neutral (score 4) and somewhat to very strong preference for tofacitinib with cobicistat QD (score 5–7). COBI, cobicistat; TOFA, tofacitinib.

Pharmacokinetic parameters

The parameters describing the pharmacokinetics of tofacitinib and the respective relative standard errors of estimates (RSE) were as follows: baseline apparent oral clearance (in absence of renal function) was 14.6 l/h (RSE 23%), which increased by 0.0531 l/h per ml/min increase in eGFR (RSE 54%). Baseline clearance decreased with 39.1% (RSE 10%) as a result of boosting. Relative oral bioavailability increased by 23% (RSE 6%) as a result of boosting. Volume of distribution was estimated to be 91.4 l (RSE 7%). Duration of absorption could not be estimated due to very rapid absorption and limited sampling during the absorption phase, and was therefore fixed to 0.352 h, based the population pharmacokinetic parameters of the manufacturer.[21] The inter-individual variability in clearance was estimated to be 31% (RSE 29%). The inter-individual variability in relative bioavailability with and without pharmacokinetic boosting was 21% (RSE 73%) and 32.2% (RSE 30.9%), respectively.

Table 2. Efficacy and safety parameters on both sampling days

	TOFA BID (n=27)	TOFA + COBI QD (n=26)
DAS28-CRP	3.27 ± 1.41	3.18 ± 1.19
DAS28-ESR	3.27 ± 1.25 [n=25]	3.29 ± 1.36
Swollen joint count (0 - 28)	1 (0 - 2)	0 (0 - 2)
Tender joint count (0 - 28)	2 (0 - 5)	2 (0 - 3)
VAS global (mm)	40 (20 - 60)	40 (20 - 60)
VAS pain (mm)	40 (30 - 60)	40 (28 - 60) [n=24]
VAS physician (mm)	40 (25 - 50)	30 (20 - 55) [n=25]
CRP (mmol/l)	2 (1 - 10)	5 (2 - 13)
ESR (mm/h)	10 (5 - 27) [n=25]	15 (5 - 30)
Haemoglobin (mmol/l)	8.4 (7.5 – 8.8)	8.5 (7.8 – 8.9)
Leukocytes (10^9/l)	7.3 (5.7 – 8.4)	8.2 (6.2 – 9.3)
Thrombocytes (10^9/l)	241 (203 – 270)	231 (207 – 308)
Creatinine (µmol/l)	72 (59 - 87)	80 (74 – 92)
ALAT (U/l)	24 (17 – 31)	25 (17 – 30)

Either displayed as number (percentage), mean ± standard deviation or median (interquartile range). Percentages were calculated over the total number of participants unless indicated. TOFA = tofacitinib, COBI = cobicistat. DAS28 = disease activity score based on 28 joints. CRP = C-reactive protein. ESR = erythrocyte sedimentation rate. VAS global = patient's global assessment of disease activity on a visual analogue scale. VAS pain = patient's global assessment of pain. VAS physician = physician's global assessment of disease activity. ALAT = alanine aminotransferase.

Predicted clinical outcomes

The predicted median DAS28-CRP at maximum drug effect was 3.59 (95% confidence interval, reflecting both interindividual variability and variable uncertainty, 3.14-3.96) for the tofacitinib with cobicistat QD versus 3.55 (3.06-3.95) for tofacitinib BID. The median difference in predicted DAS28-CRP was 0.03 (-0.16 to 0.22, intervention-control; **Supplementary figure 1A**). The predicted ACR20 response was 64% (54%-74%) for the intervention versus 65% (54%-75%) for control, leading to a difference of -0.01 (-0.07 to 0.05; **Supplementary figure 1B**). These differences were not considered as clinically relevant differences, because our predefined clinical relevance margins (an increase of 0.6 in DAS28-CRP score and/or a 10% reduced probability of ACR20) were not met.

Discussion

We found a slightly lower tofacitinib $C_{avg,ss}$ for the tofacitinib 5mg with cobicistat 150mg QD to tofacitinib 5 mg BID, therefore pharmacokinetic bioequivalence could not be confirmed. However, because of the very comparable pharmacokinetics, no relevant differences in predicted DAS28-CRP and ACR20-response and a clear patient preference, pharmacokinetic boosting seems to be an attractive strategy for cost-effective use of tofacitinib.

This study has several strengths. As it is a multiple-dose study conducted in patients with RA and PsA instead of healthy volunteers, both tolerability and patient preference data can be optimally generalised. Also, rich pharmacokinetic sampling was performed in this study, so that the $C_{avg,ss}$ of tofacitinib could be adequately estimated. Other strengths include low drop-out and missing rates, again underscoring the high acceptability of tofacitinib with cobicistat. Lastly, the used boosting drug, cobicistat, is safe, inexpensive and also available in non-high-income countries because of its coadministration with antiretroviral drugs.
There are some limitations that should be considered. First, it should be noted that this study was designed to assess pharmacokinetic bioequivalence and that clinical outcomes (disease activity) were only measured descriptively. Although we predict the minimal changes in pharmacokinetics are of negligible clinical impact, prospective evaluation is warranted. Second, the number of participants is just below the predefined sample size calculation, perhaps also driving the failure to prove bioequivalence. Third, the majority of patients in this study only recently (< 1 month) started with tofacitinib. Combined with a short follow-up this makes it difficult to study effects on disease activity. However, the predicted clinical efficacy seemed unaffected by the slightly lower exposure, as measured with a robust and validated pharmacokinetic-pharmacodynamic model.[4] This model was previously used to obtain marketing authorisation for the extended release formulation of tofacitinib based on a pharmacokinetic study only, similar to our study.

All in all, we expect that this tofacitinib-cobicistat combination therapy can be of value in clinical practice. The phase IIb dosing study of tofacitinib showed effective response to 3 mg BID, but a dosage of 5 mg BID was chosen as standard because of a small difference in a secondary outcome (anaemia).[20] Because of the potentially serious side effects of tofacitinib, such as risk on venous thromboembolism, it may be postulated that lower tofacitinib exposure is even preferable. Moreover, we found comparable clinical efficacy and safety, and the majority of patients preferring this combination regimen. With the advantages of a once-daily regimen, but around 40-50% lower costs than the extended release formulation, we think this combination therapy is suitable to reduce costs of tofacitinib therapy.

A complicating factor of pharmacokinetic boosting may be unwanted drug-drug interactions with co-medication. During the screening phase of our study, the use of co-medication affected by CYP3A was the main reason for exclusion, especially cardiovascular drugs, used by a considerable part of patients with inflammatory arthritis. Therefore, use of cobicistat requires adequate assessment by the patient's pharmacist. During the study however, replacement of co-medication with non-CYP drugs to enable study participation was accepted by a notable proportion of patients (see table 1), and that most patients were aware that they used a drug with a higher risk of interactions. In addition, since polypharmacy and drug-drug interactions with cobicistat are frequent in HIV patients, many lessons can be learned from this field, for example by using a website designed for HIV-treatment to assess drug-drug interactions when initiating cobicistat.[26]

Future research on this strategy should include a larger study with longer follow-up with disease activity as primary outcome. Also, the safety of the combination therapy should be monitored over a longer period of time, with a specific focus on musculoskeletal, gastrointestinal and neurological adverse events. Last, costs and quality of life should be assessed throughout the study so that formal cost-effectiveness analyses can be performed.

In conclusion, our study shows that pharmacokinetic boosting is not pharmacokinetically equivalent but shows similar predicted efficacy. Therefore, it remains an attractive and feasible strategy to reduce costs and dosing frequency of tofacitinib in RA and PsA.

References

1. Kerschbaumer A, Smolen JS, Nash P, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a systematic literature research. RMD Open. 2020;6(3).
2. Gratacós Masmitjà J, González Fernández CM, Gómez Castro S, et al. Efficacy of Tofacitinib in the Treatment of Psoriatic Arthritis: A Systematic Review. Adv Ther. 2021;38(2):868-84.
3. Fleischmann R. A review of tofacitinib efficacy in rheumatoid arthritis patients who have had an inadequate response or intolerance to methotrexate. Expert Opin Pharmacother. 2017;18(14):1525-33.
4. Lamba M, Hutmacher MM, Furst DE, et al. Model-Informed Development and Registration of a Once-Daily Regimen of Extended-Release Tofacitinib. Clin Pharmacol Ther. 2017;101(6):745-53.
5. U.S. Government Committee on Ways and Means. A Painful Pill to Swallow : U.S. vs. International Prescription Drug Prices https://waysandmeans.house.gov/sites/democrats.waysandmeans.house.gov/files/documents/U.S.%20vs.%20International%20Prescription%20Drug%20Prices_0.pdf Accessdate: 07-02-2022.
6. Xeljanz - Summary of Product Characteristics https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf Access date: 30-11-2021.
7. Larson KB, Wang K, Delille C, et al. Pharmacokinetic enhancers in HIV therapeutics. Clin Pharmacokinet. 2014;53(10):865-72.
8. Tybost - Summary of the Product Characteristics https://www.ema.europa.eu/en/documents/product-information/tybost-epar-product-information_en.pdf Access date: 30-11-2021.
9. Nederland Z. Tybost tablet filmomhuld 150 mg - Medicijnkosten.nl https://www.medicijnkosten.nl/medicijn?artikel=TYBOST+TABLET+FILMOMHULD+150MG&id=ba17bc42307b5cae945e32abobf55813.
10. Zorginstituut Nederland. Xeljanz tablet filmomhuld 5 mg - Medicijnkosten.nl https://www.medicijnkosten.nl/medicijn?artikel=XELJANZ+TABLET+FILMOMHULD+5MG&id=a1cf93d11d448c34135e4e97ad35334e Access date: 30-11-2021.
11. Mathias AA, German P, Murray BP, et al. Pharmacokinetics and pharmacodynamics of GS-9350: a novel pharmacokinetic enhancer without anti-HIV activity. Clin Pharmacol Ther. 2010;87(3):322-9.
12. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. J Manag Care Pharm. 2012;18(7):527-39.
13. de Wildt SN, Kearns GL, Leeder JS, et al. Cytochrome P450 3A: ontogeny and drug disposition. Clin Pharmacokinet. 1999;37(6):485-505.
14. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.
15. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-24.
16. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569-81.
17. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54(8):2665-73.
18. EMA Guideline on the Investigation of Bioequivalence. 2010.
19. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf Access date: 17-12-2021.
20. Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2012;64(3):617-29.
21. Food and Drug Administration - Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review - Tofacitinib. 2011.

22. Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008;48:303-32.
23. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm. 1987;15(6):657-80.
24. van der Maas A, Lie E, Christensen R, et al. Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. Ann Rheum Dis. 2013;72(11):1800-5.
25. Sherman EM, Worley MV, Unger NR, et al. Cobicistat: Review of a Pharmacokinetic Enhancer for HIV Infection. Clin Ther. 2015;37(9):1876-93.
26. University of Liverpool. Liverpool HIV drugs interaction checker.

Supplementary data

Supplementary table 1. List of the 75 most commonly interactions with either cobicistat or tofacitinib and the action to be taken for patients on this drug when assessing eligibility

Drug name	Action to be taken
Alprazolam	Exclusion from study
Alfentanil	Exclusion from study
Alfuzosine	Exclusion from study
Amfetamines	Exclusion from study
Amiodaron	Exclusion from study
Apixaban	Exclusion from study
Atomoxetine	Exclusion from study
Atorvastatin	Replace with pravastatin
Bosentan	Exclusion from study
Budesonide	If used orally, exclusion from study, otherwise patient can be included
Calcium antagonists	Exclusion from study
Cinacalcet	Exclusion from study
Chloorpromazine	Exclusion from study
Clarythromycine	Exclusion from study
Clorazepinic acid	Exclusion from study
Colchicine	Exclusion from study if used as maintenance medication, replace with NSAIDs or prednisone if used as needed
Contraceptives with ethinylestradiol	Use alternative contraceptives
Ciclosporine	Exclusion from study
Darifenacine	Exclusion from study
Diazepam	Exclusion from study
Digoxin	Exclusion from study
Disopyramide	Exclusion from study
Dexamethason	Exclusion from study
Ergotamine	Discuss use with patient, include if possible
Erythromycine	Exclusion from study
Etoposide	Exclusion from study
Everolimus	Exclusion from study
Fentanyl	Exclusion from study

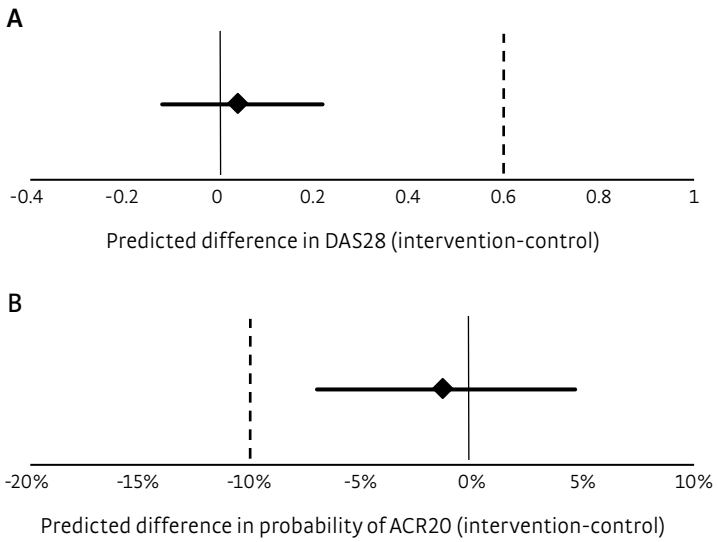
Supplementary table 1. Continued

Drug name	Action to be taken
Flecainide	Exclusion from study
Phosphodiesterase inhibitors	Exclusion from study
Guanfacine	Exclusion from study
Ketoconazol	Exclusion from study
Kinine	Exclusion from study
Irinotecan	Exclusion from study
Itraconazol	Discuss use with patient, include if possible
Ivabradine	Exclusion from study
Ivacaftor	Exclusion from study
Quinidine	Exclusion from study
Lidocaine	Exclusion from study
Lomitapide	Exclusion from study
Lurasidone	Exclusion from study
Maraviroc	Exclusion from study
Metformine	Exclusion from study
Metoprolol	Exclusion from study
Midazolam	Exclusion from study
Olaparib	Exclusion from study
Palbociclib	Exclusion from study
Panobinostat	Exclusion from study
Paroxetin	Exclusion from study
Pethidine	Exclusion from study
Piroxicam	Exclusion from study
Pimozide	Exclusion from study
Propafenon	Exclusion from study
Pyrimethamine	Exclusion from study
Quetiapine	Exclusion from study
Rivaroxaban	Exclusion from study
Rosuvastatine	Replace with pravastatin (if possible)
Saquinavir	Exclusion from study
Sertraline	Exclusion from study
Simvastatine	Replace with pravastatin
Sirolimus	Exclusion from study
Sonidegib	Exclusion from study

Supplementary table 1. Continued

Drug name	Action to be taken
Tamoxifen	Exclusion from study
Tacrolimus	Exclusion from study
Tamsulosine	Exclusion from study
Tetrabenazine	Exclusion from study
Ticagrelor	Exclusion from study
Tolvaptan	Exclusion from study
Trazodon	Exclusion from study
Trabectedin	Exclusion from study
Tyrosine kinase inhibitors	Exclusion from study
Venetoclax	Exclusion from study
Venflaxine	Exclusion from study
Vinblastine	Exclusion from study
Vincristine	Exclusion from study

(source: KNMP-kennisbank (consulted March 6th, 2018)



Supplementary figure 1. Predicted differences in disease activity (DAS28; 1A) and response (ACR20 criteria fulfilment; 1B)

Supplementary table 2. Incidence rates of adverse events classified by CTCAE

Category	TOFA + COBI QD (1.35 person-years)	TOFA BID (3.13 person-years)
Ear and labyrinth disorders	0 (0)	1 (0.32)
Eye disorders	0 (0)	2 (0.64)
Gastrointestinal disorders	8 (5.9)	3 (0.96)
General disorders and administration site conditions	3 (2.2)	3 (0.96)
Infections and infestations	0 (0)	2 (0.64)
Injury, poisoning and procedural complications	1 (0.74)	2 (0.64)
Investigations	0 (0)	1 (0.32)
Metabolism and nutrition disorders	1 (0.74)	1 (0.32)
Musculoskeletal and connective tissue disorders	14 (10)	20 (6.39)
Nervous system disorders	7 (5.2)	5 (1.60)
Psychiatric disorders	2 (1.5)	2 (0.64)
Respiratory, thoracic and mediastinal disorders	2 (1.5)	2 (0.64)
Skin and subcutaneous tissue disorders	1 (0.74)	1 (0.32)
Vascular disorders	0 (0)	3 (0.96)
Total	39 (29)	48 (15)

Displayed as number (incidence rate per person-year). CTCAE = common terminology criteria for adverse events (version 5 used in study), TOFA = tofacitinib, COBI = cobicistat.

Chapter 7

General discussion

General discussion

Optimisation of b/tsDMARD treatment in inflammatory arthritis is a fascinating but very broad topic, as demonstrated with the different subjects in the previous chapters. Therefore, I chose a few specific issues for further discussion. I will finish this chapter with conclusions, implications for clinical practice and recommendations for future research.

The following topics are further discussed in this chapter:
- The optimal use and position of rituximab treatment in rheumatoid arthritis.
- Implementation of the recommendations for cost-effective use of b/tsDMARDs.
- The future of pharmacokinetic boosting of tofacitinib in clinical care.

The optimal use and position of rituximab treatment in rheumatoid arthritis

The findings of the studies from this thesis on COVID-19 vaccination in rheumatoid arthritis (RA) patients using rituximab (**chapter 2 and 3**) include an improved humoral vaccine response when using a rituximab dose of 200 mg, and increasing time between vaccination and latest rituximab dose. In addition, the second cohort study (**chapter 3**) showed seroconversion for a relevant proportion after a third vaccination, and found persistence of response, irrespective of intercurrent rituximab treatment. The most notable finding is that vaccination response can be improved in rituximab users by timing of the vaccination relative to the rituximab infusion, but also by dose reduction and repeated vaccination. Additionally, because of the humoral impairment of rituximab, the studies supports the importance of optimizing the vaccination status before initiating therapy. This is important, since the starting dose of rituximab currently is 1000 mg, and this dosage is associated with significant impairment of humoral response. Together with new evidence emerging in the last years, I think it is important to re-evaluate the use of rituximab for RA in clinical practice, with the focus on in whom, how and when it should be used. Concerning how rituximab treatment should be given, I will focus on dosing and route of administration. Of note, different strategies also exist on retreatment of rituximab (on flare, treat to target, fixed interval) and on use of concomitant DMARDs, but are outside the scope of this thesis and discussion.

Regarding dosing, the recommended schedule in the current European Alliance of Associations for Rheumatology (EULAR) guideline is a 1x 1000/2x 500 mg infusion per cycle.[1] However, a step-down retreatment regimen inspired by the REDO study is also possible: a starting dose of 1000 mg, followed by treat-to-target based retreatment with 500 mg and 200 mg.[2] Now, the question arises whether 200 mg can

be the first retreatment dose, because of similar disease control found between 200 mg and 500 mg, the beneficial effects on humoral response as demonstrated in **chapter 2 and 3**, and a significant lower infection risk found in the REDO study.[2] The extension of the REDO study found a median yearly rituximab dose of 889 mg for the group who initiated retreatment at 200 mg, and 915 mg for the group at 500 mg.[3] This suggests that an effective retreatment scheme in most patients consist of around 500 mg every six months, but with large interindividual variation. Therefore, a step-down regimen to six-monthly 200 mg to find the lowest effective dose seems sensible. Another question is if an initial dose of 500 mg instead of 1000 mg would be sufficient to control active RA (a starting dose of 200 mg seems insufficient based on the previous discussion). Evidence in favour of initial 500 mg RTX includes a retrospective study among 166 seropositive RA patients finding low disease activity or remission at 12 weeks after an initial dose of 500 mg rituximab in the overall majority of patients.[4] Additionally, some case reports showed full B-cell depletion when initiating treatment with lower doses while maintaining sufficient response rates.[5-7] To further strengthen the hypothesis of a lower initial rituximab dose, a controlled study comparing starting with 1000 mg and 500 mg rituximab in RA would however be welcomed. Until then, starting with 1000 mg seems a solid choice, followed by treat-to-target tapering to 200 mg every 6 months.

Next, regarding the route of administration, subcutaneous administration would – if efficacy and safety is similar – be preferable over intravenous administration. Subcutaneous treatment would save infusion facility requirements (and consequently costs), reduce patient burden, and infection rates might putatively be lower as rituximab serum peak levels would be much lower. During my PhD, I was involved in setting up a study investigating bioequivalence of subcutaneous (336 mg, taking into account a bioavailability of 70%) compared to intravenous administration of 200mg rituximab in patients with RA which is currently running.[8] In summary, with the current data, I would advise a starting dose of 1000 mg rituximab for RA, followed by treat-to-target based retreatment of respectively 500 mg and 200 mg. In the future, this regimen might change to a lower starting dose of 500 mg intravenously, followed by subcutaneous injections of 336 mg.

Subsequently, I will discuss the relative position of rituximab in relation to other b/tsDMARDs for treatment of RA. Originally, rituximab was registered as second-line b/tsDMARD therapy, thus after treatment failure with TNF-inhibitors.[9] Although the EULAR guideline does no longer prefer one b/tsDMARD subclass over another to start with,[1] TNF-inhibitors are still the most commonly used as first choice b/tsDMARD,[10] probably because they were first available, have subcutaneous administration, and are registered for multiple inflammatory rheumatic diseases. As the effectiveness of

rituximab is equal to the other b/tsDMARDs,[11,12] I will argue in the next paragraphs that rituximab would be a good alternative for first choice b/tsDMARD, based on safety, patient friendliness and costs.

Regarding safety, I would like to address three related concerns: infection risk, duration of humoral impairment, and risk for hypogammaglobulinemia. In observational studies, the infection risk of authorised dose rituximab therapy (2x 1000 mg every 6 months) seems compared to other b/tsDMARDs associated with a somewhat higher overall risk for non-serious infections but not for serious infections.[13-16] However, these results may be affected with confounding by indication, as historically rituximab was used as a last resort drug. In the head-to-head studies, infection risks are similar for rituximab versus other bDMARDs or placebo, even for the authorised dose.[17,18] Specific infections associated with rituximab are severe COVID-19, hepatitis B or C reactivation, and – standing out the most - progressive multifocal leukoencephalopathy (PML).[13,19] PML, an often fatal central nervous system infection which is frequently mentioned as concern, has however a very low incidence rate of 2.56 per 100,000 RA patients.[20] Moreover, this incidence rate is found only in patients with full-dose rituximab and other PML risk factors, together with a background risk of 0.5 in 100,000 non-rituximab users. When further comparing rituximab to other b/tsDMARDs, the risk for serious infections is about 1.2 times lower compared to tocilizumab, the risk for herpes zoster about two times lower compared to JAK-inhibitors, and it has not been associated with an increased reactivation risk of tuberculosis, in contrast to TNF-inhibitors.[13,14,21] All in all, the infectious profile of rituximab is at least comparable to TNF-inhibitors, and possibly favorable for rituximab when using lower retreatment doses.

The second concern is the prolonged B-cell depletion caused by rituximab, so that it might not be stopped easily on short notice. This long depletion leads to some degree of humoral impairment, thus leading to an impaired vaccination response and possibly a high infection risk. Indeed, B-cell recovery takes up to 1 year after authorized dose rituximab (2x 1000mg every 6 months),[22] but are on average at pre-existent levels at 6 months with lower doses (200-1000 mg every 6 months).[23]
Infection risk on itself seems dose related, as demonstrated with an lower infection incidence rate for 200 mg rituximab compared to 1000 mg (rate ratio 0.44 (95% CI 0.22-0.88)).[2,24] Also, for rituximab doses ≥ 500 mg, infections seem to occur mainly early in the six monthly infusion cycle.[24,25] This suggests a dose-dependent effect for overall infection risk (area-under-the-curve), and an additional peak-level related effect for dosages ≥ 500 mg. The same applies to vaccination effectiveness, as shown with the effect of timing on humoral response in **chapter 2 and 3**. Thus, low-dose rituximab leads to fewer humoral impairment than high dose, and most probably only significant for doses ≥ 500 mg in the first three months.

The last concern is that patients on rituximab have a risk to develop hypogammaglobulinemia (HGG). The risk of HGG after long-term rituximab use is indeed increased. However, HGG itself seems not associated with an increased infection rate,[25-27] and is therefore not a clinically important issue for rituximab use in RA. Furthermore, HGG after rituximab is mostly mild and associated with a higher cumulative rituximab dose and not a longer rituximab treatment duration per se.[28,29] Therefore, I would advise to strive for the lowest possible dose, as this reduces the duration of humoral impairment and the risk for HGG.

When looking at patient friendliness, research on patient preferences regarding to DMARDs identified three important preference subgroups: based on chance of clinical effectiveness, based on route of administration, and a balanced group between the two.[30] Unfortunately, clinical effectiveness of a specific b/tsDMARD cannot (yet) be predicted for an individual patient, as explained in **chapter 4**, but route of administration can definitely be considered when selecting a drug. For patients, rituximab has the benefit of a low administration frequency compared to TNF-inhibitors, but requires infusion time in the hospital. Therefore, presenting both rituximab and TNF-inhibitors as first b/tsDMARD can increase shared decision making, letting patients choose the b/tsDMARD most suitable for them. When considering the total yearly costs, the cost of rituximab therapy is inflated by additional in-hospital infusion costs compared to subcutaneous bDMARDs.[31] This difference can decrease in the future with the availability of (equally priced) subcutaneous administration.

All in all, availability of rituximab maybe in the more earlier phase of RA can be advocated, as it is comparable in efficacy to other b/tsDMARDs, together with a good safety profile, the benefit of a low administration frequency, and low costs. For optimal use, a treat-to-target step-down treatment regimen of 1000 mg – 500 mg – 200 mg should be followed, which may be even further reduced in the future. Possible specific disadvantages of rituximab when compared to other b/tsDMARDs can be minimised by the following measures: (1) physicians should strive for the lowest possible dose, as a lower dose reduces the harms of rituximab treatment, (2) the vaccination status should be optimised before starting rituximab and during treatment vaccinations should preferably be given a few weeks before the next infusion, and (3) rituximab therapy should – just like other drugs -be timely discontinued in case of ineffectiveness or prolonged deep remission. In the future, disadvantages of rituximab may be additionally reduced with subcutaneous administration, which could further improve treatment for patients with RA.

Implementation of recommendations on cost-effective use

Although clinical guidelines are the translation of evidence to clinical practice, the process does not end with their publication. For the introduction of guidelines, three stages have been identified: development, dissemination, and implementation.[32,33] The recommendations resulting from **chapter 4** has completed the stage of development by its publication, and the stage of dissemination has been initiated with presentations on (inter)national rheumatology congresses. Consequently, I would like to focus on the implementation, to increase its use in clinical practice.

The most important question is how to implement recommendations on cost-effectiveness in general. Usually, recommendations are focused on improving diagnostics or therapy which are directly beneficial to the patient, therefore leading to incentives for patients as well as physicians to act on them. Moreover, in many cases recommendations are developed on behalf of (inter)national scientific organization(s), which improves the findability and increases their use because of the authority of these organisations towards professionals. Still, adherence to these regular recommendations is far from optimal, for example demonstrated in a study investigating rheumatologists' adherence to a RA guideline with an adherence between 21 and 72 percent.[34] In contrast to standard recommendations, our recommendations on cost-effectiveness may be even more difficult to implement, because they have more benefit for society than for the individual patient, while physicians and patients are expected to take action. Also, they currently lack endorsement from any professional association such as the EULAR or the Dutch Society for Rheumatology (NVR), possibly leading to limited findability and credibility. Therefore, I propose that two general actions should be taken to increase implementation of the recommendations on cost-effective use. First, the importance of cost-effectiveness should be propagated to (inter)national organizations within rheumatology to reach physicians and patients, preferably resulting in task forces, statements, and references to our publication in their guidelines. Second, for an update of the recommendations, endorsement of (inter)national rheumatology organizations should be sought to increase authority and findability.

In the next paragraphs, I will explore barriers for implementation of specific recommendations from **chapter 4** and identify ways to overcome these, using a theoretical framework designed to improve guideline implementation focusing on multiple levels.[35] According to this 'Knowledge-Attitude-Behaviour Framework' of Cabana and colleagues, knowledge of the guideline influences the attitude towards the guideline which in its' turn affects the behaviour (figure 1).[36] Apart from these factors, external barriers, guideline factors and environmental factors can influence behaviour or attitudes towards a guideline. Therefore, the authors advise to assess and address

barriers across all categories so that strategies that promote guideline implementation and adherence can be developed.[36]

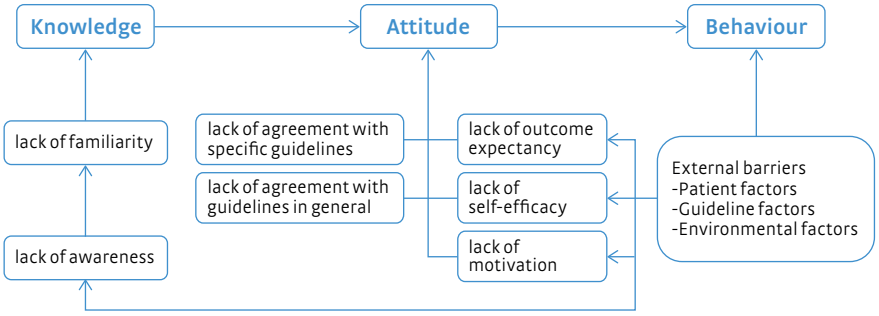


Figure 1. Sequences of potential barriers for guideline adherence of the Cabana framework (free to: Cabana et al.[36])

Concerning the strategy *disease activity-guided dose optimization*, we demonstrated in **chapter 5** long-term effectiveness and safety of dose optimization with TNF-inhibitors in RA. In addition, we showed that this strategy can include multiple tapering attempts as well as full discontinuation as final step. Regarding the attitude towards dose optimization, it was shown that patients with RA express an overall positive attitude, specifically those with controlled disease, a shorter disease duration, and without comedication.[37-39] As their main concern is the risk of a disease flare with uncontrollable symptoms, patients value shared decision making with the possibility of a dose increase when a flare occurs.[37,39] Interestingly, physicians have the same concerns as patients, but with a much lower willingness to start dose optimization (36% versus 63%),[38] and initiate conversations on dose optimization less often.[40] Lack of motivation may be an important barrier for physicians, as it might lead to a disease flare in a currently stable situation. Furthermore, dose optimization requires more effort for the physician in informing the patient, changing medication, and managing flares, which disincentives them to do so. An important benefit from dose optimization heads towards the healthcare insurers, another important stakeholder, as healthcare costs reduce. For the other strategies on lower dosing, specifically *lower dosing of rituximab*, lack of motivation also seems to be involved. For example, the comparable effectiveness of lower dosed rituximab (1* 1000 mg instead of 2* 1000mg) has been known for over a decade,[41] but has not yet been implemented in all rheumatology clinics.

A possible solution for the 'lack of motivation'-barrier is more support for the physician. For example, a pilot study investigated a combination of education, feedback, local protocol development and individualized treatment advice, and found an improved adherence to dose reduction at 1 year post-intervention.[42] However, the planned follow-up randomised trial with this combined intervention could not take place because potential hospital participants demanded financial benefit as a condition for participation, and health care payers were not included to organise such a "shared savings" model. Perhaps, physicians and healthcare insurers should therefore collaborate, with the latter creating an incentive (e.g., extra consultation time) for the first when dose optimization is adequately performed. Another solution for dose optimization and lower-dosed rituximab might be to create more awareness among patients, as they directly benefit because of lower medication use and possibly a lower risk of side effects. To do so, we need to identify patients' information needs and their preferences for channels through which to receive this information. For lower dosing of rituximab specifically, sharing preparation and infusion protocols may remove external barriers.

Two other strategies, *avoid dose loading* and *route of administration*, seem to have their specific barriers. On the strategy of avoid dose loading, the recommendation is based on one review from some of the authors of **chapter 4**. Readers could see this as a certain belief of the authors, leading to lack of credibility, although they could also consider them as the experts on a certain topic, because of their relevant publications. Nevertheless, more comparative studies on the added value of dose loading are required, specifically for the b/tsDMARDs without current evidence, as it affects the level of evidence and therefore could prevent lack of agreement. Regarding route of administration, the recommendation advises rheumatologists to use the most cost-effective form of infliximab, tocilizumab and abatacept in their hospital. However, for successful implementation, it is necessary to have insight in drug costs, other costs, and revenue related to infusion facilities. To my knowledge, physicians are often not aware of this, thus lack of insight can be an important barrier to follow this recommendation. Also, one man's costs are another man's revenue, and this can play a role for example in the relation dose reduction to drug discounts or infusion facility reimbursements. Physicians could collaborate with their hospital pharmacists and healthcare insurers to effectively compare cost-effectiveness of various routes of administration in order to make informed choices.

Last, I would like to discuss our recommendation to use a *drug formulary policy*, for which implementation could be affected by patient factors. As the discount on drug price often increases with the volume of drug bought, the use of a drug formulary policy would reduce societal drug costs through higher discounts on the preferred

drugs. However, from the physicians' and patient's perspective, a drug formulary policy limits their freedom to choose, and the possibility of shared decision making. It is difficult to completely remove these barriers, but there may be two methods to address them. The first method is carefully explaining the patient the following topics. First, the drug formulary is primarily based on medical grounds (effectiveness, tolerability, safety, experience, route of administration), leading to broad experience with the drugs early in the sequence. Only in the second place, choices are made based on economic arguments. Second, it is designed as a guidance to use in the majority of patients, thus motivated deviation is possible. Last, the why and how of cost-effective use at this point of their treatment course should explained, as involvement in treatment decisions is a positive factor towards agreement.[37] The second method for reducing the barriers may be standardisation of a drug formulary on a country instead of hospital level, such as in Norway and Denmark, thereby make treatment equal across all hospitals. In this system, physicians are strongly advised to follow the country's preference policy and use the country's registered biosimilar, but may deviate from the sequence in individual cases.[43] As a result, total b/tsDMARD costs in the period 2010-2019 in Norway have been reduced by 47%, and treatment with b/tsDMARDs has become more available at a lower cost.[43] However, standardisation also has a serious disadvantage. For b/tsDMARDs later in the preferential drug order with a lower quantity, the Dutch market would be less attractive, and therefore this system could further increase drug shortages. Because of the potential effects on availability of b/tsDMARDs of the second method, I would suggest focussing on the first method of explanation.

Overall, implementation of recommendations on cost-effective use does not automatically follow. It requires ownership from physicians and patients, and tailored solutions to overcome the barriers for the different strategies. To summarize, (inter) national scientific organizations should convey the importance of cost-effectiveness, preferably by statements, task forces or guidelines. Regarding the sequence of knowledge, physicians could collaborate with healthcare insurers and pharmacists to learn about prices of the different b/tsDMARDs and administration routes. Regarding attitude, a way to overcome barriers could be to inform patients about dose optimization and lower-dosed rituximab because of their benefits. Regarding external barriers, healthcare insurers could provide important incentives by sharing benefits of cost-effective use ("shared savings"), thus aligning incentives for all stakeholders. In addition, the recommendations on cost-effective use of b/tsDMARDs should preferably be regularly updated under the umbrella of international rheumatology organizations, to remain applicable in clinical care, because of increasing evidence on strategies and introduction of new b/tsDMARDs.

The future of pharmacokinetic boosting of tofacitinib in clinical care

In **chapter 6**, we investigated pharmacokinetic (PK) boosting of tofacitinib and concluded that it may be an effective strategy for reducing costs and dose frequency in inflammatory arthritis. In the following subsection, I will argue what (follow-up) research is needed for effective implementation for the study in **chapter 6** and boosting studies in general.

Although the current indications for tofacitinib (and other JAK-inhibitors) are more limited than during the study of **chapter 6**, PK boosting of tofacitinib may still be useful in clinical care. A surveillance study investigating the incidence of cardiovascular events and cancer between TNF-inhibitors and tofacitinib, found an increased risk for tofacitinib compared to adalimumab.[44] Therefore, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) do no longer recommend treatment with JAK-inhibitors in the following subgroups: patients aged 65 years older or above, patients with an increased risk of major cardiovascular problems or cancer, and current or past smokers.[45] Furthermore, they advise a dose reduction in patients at risk of a venous thromboembolism, cancer or major cardiovascular problems,[45] but do not further specify this. I would suggest a maximum dose of 5 mg twice daily for inflammatory arthritis, but preferably lower. Nonetheless, tofacitinib still is a safe and effective tsDMARD for patients without cardiovascular risk factors, and the lower tofacitinib levels with PK boosting could possibly reduce the risk in patients with cardiovascular risk factors. As the peak incidences of RA and cardiovascular diseases (40-60 years) overlap,[46,47] pharmacokinetic boosting may be more relevant in diseases with an onset on younger age, such as psoriatic arthritis, axial spondyloarthritis, and ulcerative colitis.[48,49]

Regarding the value of PK boosting, the study in **chapter 6** could not establish formal bioequivalence on tofacitinib serum levels due lower levels for the boosted regimen, and therefore requires further research before implementation. As no specific guideline on the design of PK boosting studies exists, the EMA drug bioequivalence guideline is mostly used, which advises a randomised, two-period, two-sequence single-dose crossover design with a wash-out period of at least five half-lives, preferably performed in healthy volunteers.[50] However, both the single-dose and the healthy volunteer aspects are not suitable for boosting studies. A single-dose study is designed for measuring peak and trough levels, whereas boosting studies mainly compare regimens with different dosing interval, leading to incomparable pharmacokinetic curves. Relevant pharmacokinetic parameters for PK boosting studies are often the area-under-the-curve (AUC) or the C_{avg} to compare the direct exposure, which require multiple dose studies with steady state. Furthermore, various factors can lead to a different exposure between healthy volunteers and patients, such as

co-medication, age (affecting renal clearance), and differences in pharmacokinetic parameters, such as a decreased absorption rate in active inflammatory bowel disease.

A recent review on PK boosting suggests a two-step trial design, including a multiple-dose, open-label bioequivalence study in patients as the first step, with the advice to perform an interim analysis to check whether dose adaptation needs to be performed.[51] The second step should be a clinical study to determine effectiveness and safety by either a double-arm randomised study or single-arm compared to a historical cohort.[51] I agree with the authors that the study design in the first step is more suitable for PK boosting studies. However, I do not agree with performing another clinical study if two regimens are pharmacokinetically equivalent, because of a lack of equipoise and therefore time consuming and costly. In this case, I would advise pharmacodynamic modelling instead, comparable to the registration of the extended release tofacitinib, in which equivalent pharmacokinetics were established, although in healthy volunteers, and equivalent pharmacodynamics were predicted.[52]

For pharmacokinetically non-equivalent regimens based on a slightly lower boosted drug level, such as the study in **chapter 6**, I agree that a second clinical study is desirable for effective implementation since such a regimen can still be clinically equivalent. First, additional pharmacodynamic modelling in the study of **chapter 6** suggested equal effectiveness. Of note, this is the same model as used for the registration of extended-release tofacitinib 11 mg daily.[52] Second, in the phase 2 study of tofacitinib, both tofacitinib 3 mg twice daily and 5 mg daily demonstrated clinical effectiveness compared to placebo, but 5 mg twice daily was chosen as standard dose because of slightly better secondary outcomes (numerically higher haemoglobin levels).[53] With the currently available safety data on tofacitinib, the lower tofacitinib dose in the boosted regimen might even be a solution instead of a problem. The study design I would propose is an open-label non-inferiority study on disease activity between tofacitinib twice daily and tofacitinib with cobicistat once daily in patients with inflammatory arthritis with a duration of at least 6 months. Preferably, this would be a multicentre study including current tofacitinib users with clinical response to reduce the chance on ineffectiveness of tofacitinib.

In conclusion, there might still be a window of opportunity for pharmacokinetic boosting of tofacitinib in patients with a low cardiovascular risk. This subgroup of patients also has fewer (cardiovascular) comedications, which will reduce the chance of drug-drug interactions. In my opinion, effectiveness of a boosting regimen would be sufficiently proven in case of 1) equivalence on a relevant pharmacokinetic outcome (AUC or C_{avg}) in a short pharmacokinetic study together with predicted

equivalent pharmacodynamics, or 2) non-equivalence on pharmacokinetics because of slightly lower drug levels, but equivalence on a relevant pharmacodynamic outcome (disease activity) using a clinical study with a follow-up of at least 6 months. Therefore, I would propose a clinical follow-up study on pharmacokinetic boosting of tofacitinib before initiating implementation.

Conclusions and implications for clinical practice

The research chapters and general discussion of this thesis result in the following conclusions and implications for clinical practice:

- Vaccination response in rituximab users can be improved with a lower dose (preferably 200 mg) and increasing time between latest rituximab dose and vaccination. In case of insufficient vaccination response, a third vaccination yields a better humoral response.
- Rituximab is a safe and effective biological DMARD for the treatment of RA, especially when vaccination status is optimised before start, and when rituximab is dosed as low as possible.
- Cost-effective use of b/tsDMARDs in inflammatory arthritis can be optimized when following the recommendations of our new "points to consider".
- Implementation of this guideline can be improved by involving (inter)national scientific organizations, involving patients and collaboration between physicians and healthcare insurers.
- Disease activity-guided dose optimization of TNF-inhibitors is long-term effective and safe, and can include discontinuation as well as multiple tapering attempts.
- Pharmacokinetic boosting of tofacitinib is potentially useful in younger patients without (cardiovascular) comedications, but a clinical study is required to confirm clinical effectiveness.

Future research

Based on the chapters of this thesis, further exploration is needed on the following topics:

- Subcutaneous administration of ultra-low dose rituximab in RA could increase opportunities for rituximab therapy and should therefore be investigated.
- A study comparing 500mg rituximab with 1000mg as initial therapy could further optimise treatment with rituximab.
- Prospective clinical studies on the (lack of) added value of dose loading could provide more real-world evidence and therefore strengthen implementation.
- The recommendations on cost-effective use of b/tsDMARDs should be regularly updated, preferably under EULAR umbrella, because of the increasing evidence for the different strategies and the introduction of new b/tsDMARDs.
- Implementation research on cost-effectiveness guidelines should be initiated, for example with a survey amongst patients and rheumatologists.
- Pharmacokinetic boosting of tofacitinib should be evaluated in a clinical study in inflammatory arthritis patients before implementation.

References

1. Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82(1):3-18.
2. Verhoef LM, den Broeder N, Thurlings RM, al. e. Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial. . Lancet Rheumatol. 2019;1:145-53.
3. den Broeder N, Verhoef L, de Man YA, Kok MR, Thurlings R, van der Weele W, et al. Long-term clinical and radiological effectiveness and safety of ultralow doses of rituximab in rheumatoid arthritis: observational extension of the REDO trial. RMD Open. 2024;10(2).
4. Chandramohan P, Jain A, Antony G, Krishnan N, Shenoy P. Low-dose rituximab protocol in rheumatoid arthritis-outcome and economic impact. Rheumatol Adv Pract. 2021;5(1):rkaa077.
5. Bruzzese V. Therapeutic effectiveness of minimal doses of rituximab in a patient with rheumatoid arthritis. Int J Immunopathol Pharmacol. 2011;24(1):265-7.
6. Bruzzese V, Marrese C, Hassan C, Andriani A, Zullo A. Prompt efficacy of very low-dose rituximab on monoclonal B lymphocytosis in a rheumatoid arthritis patient. Int J Rheum Dis. 2013;16(6):764-5.
7. Bruzzese V, Pepe J. Unexpected and persistent depletion of B lymphocytes CD20 following a minimum dose of anti-CD20 antibody (Rituximab). Reumatismo. 2009;61(4):306-8.
8. CCMO. Vergelijking van subcutane en intraveneuze herbehandeling met ultra-low dose rituximab in reumatoïde artritis: een gerandomiseerde open-label non-inferiority trial (trial register) 2024 [Available from: https://onderzoekmetmensen.nl/nl/trial/52719.
9. Agency. EM. Summary of Product Characteristics - MabThera 2023 [Available from: https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf.
10. Lauper K, Iudici M, Mongin D, Bergstra SA, Choquette D, Codreanu C, et al. Effectiveness of TNF-inhibitors, abatacept, IL6-inhibitors and JAK-inhibitors in 31 846 patients with rheumatoid arthritis in 19 registers from the 'JAK-pot' collaboration. Ann Rheum Dis. 2022;81(10):1358-66.
11. Hazlewood GS, Barnabe C, Tomlinson G, Marshall D, Devoe DJ, Bombardier C. Methotrexate monotherapy and methotrexate combination therapy with traditional and biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis: A network meta-analysis. Cochrane Database Syst Rev. 2016;2016(8):Cd010227.
12. Singh JA, Hossain A, Tanjong Ghogomu E, Mudano AS, Tugwell P, Wells GA. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA). Cochrane Database Syst Rev. 2016;11(11):Cd012437.
13. Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis. 2018;77(6):905-10.
14. Sepriano A, Kerschbaumer A, Bergstra SA, Smolen JS, van der Heijde D, Caporali R, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2023;82(1):107-18.
15. Tarp S, Eric Furst D, Boers M, Luta G, Bliddal H, Tarp U, et al. Risk of serious adverse effects of biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis. Rheumatology (Oxford). 2017;56(3):417-25.
16. Bechman K, Halai K, Yates M, Norton S, Cope AP, Hyrich KL, et al. Nonserious Infections in Patients With Rheumatoid Arthritis: Results From the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Arthritis Rheumatol. 2021;73(10):1800-9.
17. Shi Y, Wu Y, Ren Y, Jiang Y, Chen Y. Infection risks of rituximab versus non-rituximab treatment for rheumatoid arthritis: A systematic review and meta-analysis. Int J Rheum Dis. 2019;22(8):1361-70.
18. Volkmann ER, Agrawal H, Maranian P, Furst DE. Rituximab for Rheumatoid Arthritis: A Meta-Analysis and Systematic Review. Clinical Medicine Insights: Therapeutics. 2010;2:CMT.S5566.

19. Chiu YM, Chen DY. Infection risk in patients undergoing treatment for inflammatory arthritis: non-biologics versus biologics. Expert Rev Clin Immunol. 2020;16(2):207-28.
20. Berger JR, Malik V, Lacey S, Brunetta P, Lehane PB. Progressive multifocal leukoencephalopathy in rituximab-treated rheumatic diseases: a rare event. J Neurovirol. 2018;24(3):323-31.
21. Redeker I, Albrecht K, Kekow J, Burmester GR, Braun J, Schäfer M, et al. Risk of herpes zoster (shingles) in patients with rheumatoid arthritis under biologic, targeted synthetic and conventional synthetic DMARD treatment: data from the German RABBIT register. Ann Rheum Dis. 2022;81(1):41-7.
22. Pollastro S, Musters A, Balzaretti G, Niewold I, van Schaik B, Hässler S, et al. Sensitive B-cell receptor repertoire analysis shows repopulation correlates with clinical response to rituximab in rheumatoid arthritis. Arthritis Res Ther. 2024;26(1):70.
23. Wientjes MHM, Gijzen TMG, den Broeder N, Bloem K, de Vries A, van den Bemt BJF, et al. Drug levels, anti-drug antibodies and B-cell counts were not predictive of response in rheumatoid arthritis patients on (ultra-)low-dose rituximab. Rheumatology (Oxford). 2022;61(10):3974-80.
24. Veeken LD, Opdam M, Verhoef LM, Popa C, van Crevel R, den Broeder AA. Infection incidence, timing, and dose dependency in rheumatoid arthritis patients treated with rituximab: a retrospective cohort study. Rheumatology (Oxford). 2023.
25. Opdam MAA, de Leijer JH, den Broeder N, Thurlings RM, van der Weele W, Nurmohamed MT, et al. Rituximab dose-dependent infection risk in rheumatoid arthritis is not mediated through circulating immunoglobulins, neutrophils or B cells. Rheumatology (Oxford). 2022;62(1):330-4.
26. Kim SH, Park NY, Kim KH, Hyun JW, Kim HJ. Rituximab-Induced Hypogammaglobulinemia and Risk of Infection in Neuromyelitis Optica Spectrum Disorders: A 14-Year Real-Life Experience. Neurol Neuroimmunol Neuroinflamm. 2022;9(5).
27. Rempenault C, Lukas C, Tardivon L, Daien CI, Combe B, Guilpain P, et al. Risk of severe infection associated with immunoglobulin deficiency under rituximab therapy in immune-mediated inflammatory disease. RMD Open. 2024;10(1).
28. Opdam MAA, Campisi LM, de Leijer JH, Ten Cate D, den Broeder AA. Hypogammaglobulinemia in rheumatoid arthritis patients on rituximab: prevalence and risk factors. Rheumatology (Oxford). 2023.
29. Md Yusof MY, Vital EM, McElvenny DM, Hensor EMA, Das S, Dass S, et al. Predicting Severe Infection and Effects of Hypogammaglobulinemia During Therapy With Rituximab in Rheumatic and Musculoskeletal Diseases. Arthritis Rheumatol. 2019;71(11):1812-23.
30. van Heuckelum M, Mathijssen EG, Vervloet M, Boonen A, Hebing RC, Pasma A, et al. Preferences of patients with rheumatoid arthritis regarding disease-modifying antirheumatic drugs: a discrete choice experiment. Patient Prefer Adherence. 2019;13:1199-211.
31. Nederland. Z. Medicijnkosten.nl [Available from: www.medicijnkosten.nl.
32. Forrest D, Hoskins A, Hussey R. Clinical guidelines and their implementation. Postgrad Med J. 1996;72(843):19-22.
33. Brouwers MC, Kerkvliet K, Spithoff K. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. Bmj. 2016;352:i1152.
34. Lesuis N, den Broeder AA, Hulscher ME, van Vollenhoven RF. Practice what you preach? An exploratory multilevel study on rheumatoid arthritis guideline adherence by rheumatologists. RMD Open. 2016;2(1):e000195.
35. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet. 2003;362(9391):1225-30.
36. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. Jama. 1999;282(15):1458-65.
37. Verhoef LM, Selten EMH, Vriezekolk JE, de Jong AJL, van den Hoogen FHJ, den Broeder AA, et al. The patient perspective on biologic DMARD dose reduction in rheumatoid arthritis: a mixed methods study. Rheumatology (Oxford). 2018;57(11):1947-55.
38. Wiemer N, Webster P, Attur M, Yin Y, Sharma T. Patient perspectives on tapering biologic or targeted synthetic therapy in well-controlled rheumatoid arthritis and comparison with providers' perspectives. Rheumatology (Oxford). 2023;62(Suppl_4):iv3-iv7.

39. Hewlett S, Haig-Ferguson A, Rose-Parfitt E, Halls S, Freke S, Creamer P. Dose reduction of biologic therapy in inflammatory arthritis: A qualitative study of patients' perceptions and needs. Musculoskeletal Care. 2019;17(1):63-71.
40. Hazlewood GS, Loyola-Sanchez A, Bykerk V, Hull PM, Marshall D, Pham T, et al. Patient and rheumatologist perspectives on tapering DMARDs in rheumatoid arthritis: a qualitative study. Rheumatology (Oxford). 2022;61(2):606-16.
41. Bredemeier M, de Oliveira FK, Rocha CM. Low- versus high-dose rituximab for rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2014;66(2):228-35.
42. Lesuis N, Verhoef LM, Nieboer LM, Bruyn GA, Baudoin P, van Vollenhoven RF, et al. Implementation of protocolized tight control and biological dose optimization in daily clinical practice: results of a pilot study. Scand J Rheumatol. 2017;46(2):152-5.
43. Brkic A, Diamantopoulos AP, Haavardsholm EA, Fevang BTS, Brekke LK, Loli L, et al. Exploring drug cost and disease outcome in rheumatoid arthritis patients treated with biologic and targeted synthetic DMARDs in Norway in 2010-2019 - a country with a national tender system for prescription of costly drugs. BMC Health Serv Res. 2022;22(1):48.
44. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. N Engl J Med. 2022;386(4):316-26.
45. European Medicines Agency. EMA recommends measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders 2022 [Available from: https://www.ema.europa.eu/en/news/ema-recommends-measures-minimise-risk-serious-side-effects-janus-kinase-inhibitors-chronic.
46. Safiri S, Kolahi AA, Hoy D, Smith E, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. Ann Rheum Dis. 2019;78(11):1463-71.
47. Restivo V, Candiloro S, Daidone M, Norrito R, Cataldi M, Minutolo G, et al. Systematic review and meta-analysis of cardiovascular risk in rheumatological disease: Symptomatic and non-symptomatic events in rheumatoid arthritis and systemic lupus erythematosus. Autoimmun Rev. 2022;21(1):102925.
48. Boel A, López-Medina C, van der Heijde D, van Gaalen FA. Age at onset in axial spondyloarthritis around the world: data from the Assessment in SpondyloArthritis international Society Peripheral Involvement in Spondyloarthritis study. Rheumatology (Oxford). 2022;61(4):1468-75.
49. da Silva BC, Lyra AC, Rocha R, Santana GO. Epidemiology, demographic characteristics and prognostic predictors of ulcerative colitis. World J Gastroenterol. 2014;20(28):9458-67.
50. European Medicines Agency. Guideline on the Investigation of Bioequivalence 2010 [Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf.
51. Westra N, Touw D, Lub-de Hooge M, Kosterink J, Oude Munnink T. Pharmacokinetic Boosting of Kinase Inhibitors. Pharmaceutics. 2023;15(4).
52. Lamba M, Hutmacher MM, Furst DE, Dikranian A, Dowty ME, Conrado D, et al. Model-Informed Development and Registration of a Once-Daily Regimen of Extended-Release Tofacitinib. Clin Pharmacol Ther. 2017;101(6):745-53.
53. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2012;64(3):617-29.

Chapter 8

Summary

Summary

Biological and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) are used for the treatment of inflammatory arthritis, which in this thesis includes rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA). b/tsDMARDs have shown to be effective in reducing disease activity, slowing down radiological progression, and improving daily functioning. However, these drugs also have their disadvantages, either general (for all b/tsDMARDs) or drug-specific. Examples are high costs for the originator bDMARDs as general disadvantage, and as drug-specific disadvantage a reduced vaccination response for rituximab. Further optimisation of b/tsDMARD treatment can help decrease these disadvantages.

Regarding rituximab, optimisation of dosing and timing could increase humoral response after vaccination. Ultra-low dose rituximab for retreatment in RA (200mg or 500mg every 6 months) has shown to be effective for the majority of patients and with significant less infections compared to standard low-dose (1000mg every 6 months), but might also increase humoral response after vaccination. Moreover, the timing of vaccinations during rituximab therapy (prior to the next rituximab infusion) is merely based on expert opinion, whereas information on precise timing is important for vaccinations during clinical care and a (next) pandemic.

Regarding costs, more cost-effective use of b/tsDMARDs is warranted. So far, various strategies for cost-effective use have been investigated separately, but a comprehensive general overview was not available yet. Also, one of the most important cost-effective strategies of b/tsDMARDs is disease activity-guided dose optimisation, but long-term effects (longer than 3 years) of this strategy are unknown. An interesting new strategy for cost-effective use to explore is interference with the drug pharmacokinetics, specifically by inhibiting drug metabolism, also called 'pharmacokinetic boosting'. Tofacitinib, the most widely used tsDMARD, is known to be metabolised by the enzyme CYP3A, which would make it suitable to be boosted with a CYP3A-inhibitor, cobicistat.

Overall, this resulted in the following aims of this thesis:

- To investigate the effect of rituximab dosing and timing on humoral response against COVID-19 after two vaccinations in RA patients treated with rituximab (**chapter 2**);
- To investigate the effect of rituximab dosing on persistence of humoral response after two COVID-19 vaccinations (**chapter 3**);
- To investigate the effect of rituximab dosing and timing on seroconversion after a third COVID-19 vaccination in patients treated with rituximab (**chapter 3**).

- To provide an overview of strategies for cost-effective use of b/tsDMARDs and to formulate evidence- and consensus-based recommendations on this subject (**chapter 4**);
- To investigate the long-term (10 year) efficacy and safety of disease activity-guided dose optimisation of Tumour Necrosis Factor inhibiting drugs (TNF-inhibitors) in RA (**chapter 5**);
- To investigate the bioequivalence of pharmacokinetic boosting of tofacitinib with cobicistat in patients with RA or PsA (**chapter 6**).

Chapter 2: Humoral response to coronavirus disease-19 vaccines is dependent on dosage and timing of rituximab in patients with rheumatoid arthritis

For the prospective cohort study of **chapter 2**, we included individuals with rheumatoid arthritis who had received two vaccinations against COVID-19 and were treated with at least one dose of rituximab in the year prior to vaccination. The main objective was the presence of sufficient humoral response 2-6 weeks after the second vaccination, defined as the total immunoglobulin (IgT) against COVID-19 above the assay cut-off (> 1.1).We recorded additional patient- and treatment characteristics such as the rituximab dose, the date of latest rituximab administration, co-medication and previous COVID-19 infections. In total, we included 196 individuals, of whom 31 (16%) received 200 mg as latest rituximab dose, 67 (34%) 500 mg, and 98 (50%) 1000 mg. Fifty-five patients (28%) had a humoral response, and response was more prevalent in the 200 mg group than the 1000 mg group (45% versus 26%). In the multivariable model adjusted for dosing, timing, age, and concomitant use of csDMARDs and prednisolone, there was a likewise significant association between 200 mg rituximab and presence of response (odds ratio 3.07, 95% confidence interval 1.55-8.27). Moreover, we found an association between longer time between latest rituximab and vaccination response which was also demonstrated in the multivariable model (1.67 per month increased time, 1.39-2.01). We concluded that (COVID-19) vaccination should be preferred at least 6 months after rituximab treatment, and that rituximab should be dosed as low as possible.

Chapter 3: Seroconversion after a third COVID-19 vaccine is affected by rituximab dose but persistence is not in patients with rheumatoid arthritis

The study of **chapter 3** was a follow-up of the cohort study of **chapter 2**, and consisted of analysis of seroconversion after a third vaccine and a persistence analysis. We included participants without humoral response (IgT against COVID-19 ≤ 1.1) after two vaccinations in the third vaccine analysis, and participants with a positive response after two vaccinations in the persistence analysis. The main outcomes were (1) the proportion patients with seroconversion 2-6 weeks after a third vaccination in previous non-responders, and (2) the proportion of response persistence before the

third vaccination in previous responders. Additionally, we investigated the associations with dosing and timing in the third vaccine analysis. Of the original 196 participants in the cohort, 98 could be included in the third vaccine analysis and 23 in the persistence analysis. In the third vaccine analysis, seroconversion occurred in 19/98 participants (19%) and was higher for 200 mg versus 1000 mg rituximab users (38% versus 15%). We found non-significant trends for higher response for 200 mg versus 1000 mg (odds ratio 3.66, 95% CI 0.93-14.0) and for later timing (1.16 per month increased time, 0.97-1.35). In the persistence analysis, 96% (22/23) of all participants maintained their humoral response after three months, of whom 89% (8/9) of participants had received rituximab in between the measurements. This study showed that repeated vaccination seems useful in patients with a previous non-response, and that the response persisted irrespective of rituximab retreatment.

Chapter 4: Points to consider for cost-effective use of biological and targeted synthetic DMARDs in inflammatory rheumatic diseases: results from an umbrella review and international Delphi study

The study of **chapter 4** resulted in a clinical guideline for cost-effective use of b/tsDMARDs. For this study, we formed an international task force of 13 experts on rheumatology, epidemiology and pharmacology from seven European countries. One-to-one interviews with all of the experts led to twelve different strategies on cost-effective use of b/tsDMARDs. Systematic literature searches were performed to identify randomized controlled trials and systematic reviews for all of the strategies. Thereafter, Delphi rounds took place to formulate the recommendations (points-to-consider) with their level of evidence (LoE, 1-5) and grade of recommendation, followed by anonymous online voting for the level of agreement (LoA, range 0-10). In total, 20 points to consider were formulated for ten different strategies, with an overall mean LoA of 8.9. Ten of the twenty recommendations had a high LoE (level 1 or 2, 50%). Examples of points-to-consider with a high LoE are: (1) biosimilars are considered equal to bio-originators, and a single switch from bio-originator to biosimilar can be performed safely if contributing to cost-effectiveness; (2) the loading dose can be removed for abatacept or certolizumab in RA, and secukinumab in PsA/axSpA, as it does not lead to superior efficacy; and (3) disease activity-guided dose optimisation is strongly advised for TNF-inhibitors in RA/PsA/axSpA, as well as for other b/tsDMARDs in RA.

Chapter 5: Disease activity–guided dose optimization including discontinuation of TNF-inhibitors in rheumatoid arthritis is effective for up to 10 years: an observational follow-up of the DRESS study

The long-term extension of the randomised controlled DRESS study is described in **chapter 5**. The aim of this study was to investigate 10-year effectiveness and safety

of disease activity-guided dose optimisation, specifically by (1) TNF-inhibitor dose, b/tsDMARD dose and disease activity over time, (2) proportions of patients with a first and second dose optimization attempt, and the effectiveness of these attempts, (3) proportion of patients with, and duration of the first discontinuation attempt, and (4) radiographic progression between 3 and 10 years. We included the 170 patients who completed the 3-year extension of the DRESS study. Of these 170 patients, 127 (75%) completed 10-year follow-up. Over time, the time-weighted disease activity remained low (DAS28-CRP 2.13, 95% confidence interval 2.10-2.16), while a dose decrease was observed for both TNF-inhibitors (97% of daily defined dose at baseline to 51% at year 10) as well as all b/tsDMARDs (97% to 56%). The mean dose reduction 1.5 years after the start of the attempt was 48% (n=159) of the first attempt and 33% (n=86) for the second attempt. Full discontinuation was reached by 119 of 161 participants (74%) with a median duration of 7 months, and 25 (21%) remained in discontinuation for the rest of the observational period. Radiographic progression exceeding the smallest detectable change (5.7 Sharp-van der Heijde units) was found in 48% (41/86). We found an association between radiographic progression and a higher disease activity, but not with a lower b/tsDMARD dose. We concluded that disease activity-guided dose optimisation remains effective over 10 years, and that the inclusion of a discontinuation attempt and subsequent dose optimization attempts can be of additional value in this strategy. However, effective treat-to-target needs to be maintained to minimise radiographic progression.

Chapter 6: Pharmacokinetic boosting to enable a once-daily reduced dose of tofacitinib in patients with rheumatoid arthritis and psoriatic arthritis

Chapter 6 included a pharmacokinetic boosting study in which we compared a combination regime of tofacitinib 5 mg and cobicistat 150 mg once daily (intervention) to tofacitinib 5 mg twice daily (control). The primary objective was bioequivalence, defined as the 90% confidence interval (CI) of the average tofacitinib concentration ($C_{avg,ss}$; intervention to control) falling between 80% and 125%. Secondary objectives included safety, patient preference and modelled pharmacodynamics (disease activity, measured with DAS28-CRP and ACR20 response) with a previously validated exposure-response model. We included patients with RA and PsA currently using tofacitinib 5 mg twice daily for at least 2 weeks and without co-medication affected by CYP3A inhibition. Samples to measure tofacitinib concentration were taken at baseline and after 2-6 weeks of intervention treatment. We included 30 patients, of whom 25 completed the study. Bioequivalence was not formally met because tofacitinib levels were slightly lower in the intervention group compared to the control group ($C_{avg,ss}$ 85%, 90%-CI: 75-96%). Moreover, we found no safety concerns, a considerable patient preference for boosted therapy (56% for intervention versus 18% for control), and no relevant differences in predicted disease activity. We

concluded that although boosted tofacitinib therapy is not fully pharmacologically equivalent to tofacitinib twice daily, it may still be an attractive strategy for further research based on its safety, patient preference and predicted pharmacodynamics.

Conclusions

This thesis showed multiple strategies for optimisation of biological and targeted synthetic DMARD therapy in inflammatory arthritis. Humoral response after COVID-19 vaccination in rituximab-treated patients is generally low, but significantly improved by lower dosing and a longer time between latest rituximab and vaccination (**chapter 2 and 3**). Humoral response after COVID-19 vaccination in rituximab-treated patients, is persistent and seems unaffected by subsequent rituximab treatment (**chapter 3**). Twelve different strategies for cost-effective use of b/tsDMARD in inflammatory rheumatic diseases were identified and twenty evidence- and expert-based points to consider were formulated on ten of these strategies (**chapter 4**). Disease activity-guided dose optimisation of TNF-inhibitors in rheumatoid arthritis leads to approximately halved TNF-inhibitor dose while maintaining low disease activity over a period of 10 years (**chapter 5**). Both the inclusion of bDMARD discontinuation, as well as repeated dose optimisation attempts seem useful in disease activity-guided dose optimisation (**chapter 5**). Last, although pharmacokinetic boosting of reduced-dose tofacitinib is not fully pharmacologically bioequivalent to standard-dose tofacitinib because of slightly lower tofacitinib serum levels, it may be equally effective in clinical practice based on a exposure-response modelling. Therefore, a follow-up clinical study is advised (**chapter 6**).

Chapter 9

Nederlandse samenvatting

Zinniger en zuiniger omgaan met biologicals en JAK-remmers bij reumatische ontstekingsziekten

Reumatische ontstekingsziekten zijn ziekten waarbij de gewrichten en pezen ontstoken zijn door een eigen reactie van het lichaam. Daarom behoren deze ziekten tot de auto-immuunziekten. De ontstekingen in gewrichten en pezen hebben grote impact op patiënten door verminderde beweeglijkheid van de gewrichten, pijn en verminderd functioneren. Dit proefschrift richt zich op drie reumatische ontstekingsziekten: reumatoïde artritis (RA), artritis psoriatica en axiale spondyloartritis.

Over de tijd zijn er veel behandelingen voor deze ziekten ontwikkeld. De eerste stap in de behandeling van gewrichtsontstekingen is meestal behandeling met de klassieke reumaremmers, zoals methotrexaat en leflunomide. Wanneer deze behandeling onvoldoende werkt of teveel bijwerkingen geeft, wordt een biologische reumaremmer of JAK-remmer toegevoegd of in de plaats gegeven. Biologische reumaremmers, ook wel biologicals genoemd, beïnvloeden het afweersysteem en zijn gemaakt van eiwitten waardoor ze alleen als infuus of injectie worden gegeven. Voorbeelden van biologicals zijn TNF-remmers, zoals adalimumab, en rituximab. JAK-remmers zijn chemische stoffen die reageren op de Janus kinase (JAK) route van het immuunsysteem en worden gegeven in tabletvorm. Voorbeelden van JAK-remmers zijn tofacitinib en baricitinib. De biologicals en de JAK-remmers zijn beiden zeer effectief voor de behandeling van reumatische ontstekingsziekten: ze verlagen de ziekteactiviteit, verminderen schade aan de gewrichten en verbeteren het functioneren.

Behalve voordelen, hebben deze groepen geneesmiddelen ook nadelen. Zo zijn ze zes tot twaalf keer duurder dan klassieke reumaremmers, geven ze een verhoogde kans op infecties en kunnen er huidreacties (pijn, roodheid) ontstaan op de plek van een injectie. Het geneesmiddel rituximab heeft daarnaast nog een eigen nadeel: je kunt minder goed antistoffen opbouwen na een vaccinatie. Het is daarom belangrijk om biologicals en JAK-remmers zinnig en zuinig in te zetten. Dit proefschrift gaat over het verbeteren van de behandeling met biologicals en JAK-remmers door: 1) het verbeteren van de vaccinatierespons tijdens behandeling met rituximab en 2) zuinig omgaan met deze geneesmiddelen, welke verder toegelicht worden in de volgende alinea's.

Eerdere studies naar de werkzaamheid van vaccinaties bij mensen die rituximab gebruiken onderzochten de hoge dosering (2 infusen van 1000 mg elk halfjaar) of standaard dosering rituximab (1 infuus van 1000 mg elk halfjaar). Sinds kort weten we dat we bij een deel van de rituximab gebruikers ook verder kunnen afbouwen, naar 500 mg of zelfs 200 mg per halfjaar. Omdat deze lage doseringen het afweer-

systeem minder sterk onderdrukken, kunnen vaccins mogelijk ook beter werken. Over het beste moment van vaccineren ten opzichte van de toediening van rituximab (timing) is nog weinig bekend. Het advies is om een vaccinatie pas een halfjaar na het laatste rituximab infuus te geven, maar dit is niet uitgebreid onderzocht. De onderzoeken in **hoofdstuk 2** en **hoofdstuk 3** gaan daarom over COVID-vaccinaties bij mensen met RA die rituximab gebruiken, waarin we het effect van dosis en timing van rituximab onderzoeken.

In verschillende eerdere onderzoeken is al gekeken naar manieren om biologicals en JAK-remmers zuinig te gebruiken. Daarbij kijken we naar de werkzaamheid ten opzichte van de kosten, dit noemen we kosteneffectiviteit. Een overzicht van alle (mogelijke) strategieën met aanbevelingen hierover ontbreekt alleen nog. Het onderzoek in **hoofdstuk 4** beschrijft de eerste richtlijn naar kosteneffectief omgaan met biologicals en JAK-remmers. Een belangrijke en bekende strategie het stapsgewijs en ziekte-gestuurd afbouwen van de hoeveelheid geneesmiddel bij mensen met een rustige ziekte. Wanneer de ziekte toch actief wordt, kan de dosis van het geneesmiddel weer worden opgehoogd. Ziekte-gestuurd afbouwen van TNF-remmers bij RA is tot 3 jaar na start effectief gebleken. In **hoofdstuk 5** onderzochten we de werkzaamheid van ziekte-gestuurd afbouwen van TNF-remmers bij RA over een nog langere periode, namelijk 10 jaar. Tenslotte zou het remmen van de afbraak van JAK-remmers in het lichaam een nieuwe strategie voor kosteneffectief behandelen kunnen zijn. JAK-remmers worden namelijk afgebroken door een enzym (CYP3A) in de lever en er zijn specifieke geneesmiddelen op de markt die dit enzym remmen. Hierdoor blijven JAK-remmers langer in het lichaam aanwezig en kunnen patiënten mogelijk met een lagere dosering hetzelfde effect bereiken. **Hoofdstuk 6** beschrijft een onderzoek naar de combinatie van de JAK-remmer tofacitinib met de enzymremmer cobicistat in mensen met RA en artritis psoriatica.

Hoofdstuk 2: Werkzaamheid van de COVID-vaccinatie tijdens gebruik van rituximab

In **hoofdstuk 2** onderzochten we de werkzaamheid van de COVID-vaccinatie bij met mensen met RA die rituximab gebruikten of hadden gebruikt. Mensen met RA konden meedoen aan het onderzoek als ze twee COVID-vaccinaties hadden gekregen en het afgelopen jaar behandeld waren met rituximab. Het doel van het onderzoek was het meten van de aanwezigheid van een vaccinatierespons twee tot zes weken na de tweede vaccinatie. Hiermee bedoelen we de aanwezigheid van antistoffen tegen COVID-19 in het bloed. Daarnaast verzamelden we andere gegevens over de deelnemers, zoals de datum en dosis van het laatste rituximab infuus, het gebruik van andere reumamedicatie en eerdere COVID infecties.

In totaal deden 196 mensen mee aan het onderzoek, van wie 31 voor de vaccinatie behandeld was met 200 mg rituximab, 67 met 500 mg en 98 met 1000 mg. We vonden antistoffen tegen COVID bij 55 van de 196 mensen (28%). Deze antistoffen waren vaker aanwezig bij de groep die behandeld was met 200 mg, namelijk bij 45% van de mensen behandeld met 200 mg in tegenstelling tot 26% van de mensen behandeld met 1000 mg. We konden ook een effect van het moment van vaccineren op aanwezigheid van antistoffen aantonen. De kans op aanwezigheid van antistoffen nam toe met elke maand die langer gewacht werd met vaccineren na het rituximab infuus. Samengevat laat dit onderzoek zien dat een dosis van 200 mg ten opzichte van 1000 mg en een langere tijd tussen infuus en vaccinatie beiden een positief effect hebben op de werkzaamheid van een COVID vaccinatie.

Hoofdstuk 3: Het effect van een derde COVID-vaccinatie en het aanhouden van vaccinatierespons tijdens gebruik van rituximab

Het onderzoek van **hoofdstuk 3** is een vervolg op **hoofdstuk 2**. Het onderzoek van **hoofdstuk 3** bestond uit twee deelonderzoeken. In het eerste deelonderzoek bekeken we of een derde vaccinatie zorgt voor het ontstaan van antistoffen tegen COVID, bij mensen uit het onderzoek van **hoofdstuk 2** die na twee vaccinaties nog geen antistoffen hadden opgebouwd. Ook hierbij keken we naar het effect van dosis en timing van rituximab. In het tweede deelonderzoek keken we of de antistoffen een paar maanden later nog aanwezig waren, bij mensen die na twee vaccinaties wel antistoffen hadden opgebouwd.

Van de 196 mensen uit het onderzoek van **hoofdstuk 2**, deden er 121 mee aan dit onderzoek: 98 aan het eerste deelonderzoek en 23 aan het tweede. Het eerste deelonderzoek liet zien dat 19 van de 98 mensen (19%) antistoffen tegen COVID ontwikkelde na de derde vaccinatie. Ook in dit onderzoek hadden een lagere rituximab dosis en een langere tijd tussen infuus en vaccinatie een positief effect op het krijgen van antistoffen. Het tweede onderzoek liet zien dat de antistoffen bij 22 van de 23 mensen aanwezig bleven. Negen van de 23 mensen hadden tussen de twee antistofmetingen een infuus met rituximab gehad, van wie acht hun antistoffen behielden. Dit onderzoek liet zien dat voor mensen die rituximab krijgen vervolgvaccinaties tegen COVID zinvol zijn, omdat bij elke vaccinatie weer een deel van de mensen antistoffen krijgt. Daarnaast laat dit onderzoek zien dat ook bij mensen die rituximab krijgen, de antistoffen tenminste enkele maanden in het bloed aanwezig blijven.

Hoofdstuk 4: Richtlijn over kosteneffectief gebruik van biologicals en JAK-remmers

Hoofdstuk 4 beschrijft verschillende aanbevelingen over kosteneffectief gebruik van biologicals en JAK-remmers. Voor dit onderzoek verzamelden we een groep

experts op het gebied van reumatologie, epidemiologie en farmacologie uit zeven verschillende Europese landen. Als eerste hebben we een-op-een interviews gehouden met alle experts om de strategieën te vinden. De strategieën werden daarna gebruikt voor het literatuuronderzoek, waarbij we zochten naar literatuurstudies en gerandomiseerde studies. Het laatste deel bestond uit het opstellen van de aanbevelingen op basis van de gevonden literatuur. Voor elke strategie werd er gekeken of er een of meerdere aanbevelingen te maken waren. Daarna bepaalden we voor elke aanbeveling de sterkte van het wetenschappelijk bewijs (*level of evidence*, 1A tot 5) en de sterkte van de aanbeveling (*grade of recommendation*, A tot D). Hierna werd er anoniem gestemd over de aanbevelingen, waarbij elke expert zijn of haar mate van overeenstemming aangaf (*level of agreement*, 0 tot 10).

Er werden twaalf verschillende strategieën gevonden, waarbij we over tien strategieën in totaal twintig aanbevelingen konden opstellen. De gemiddelde overeenstemming van de aanbevelingen was 8,9. Tien van de twintig aanbevelingen hadden hierbij een hoge sterkte van wetenschappelijk bewijs (sterkte 1 of 2). Voorbeelden van aanbevelingen met een hoge sterkte van bewijs zijn: i. Het gebruiken van biosimilars, generieke varianten van biologicals; ii. Het weglaten van de oplaaddosis van de geneesmiddelen abatacept, certolizumab en secukinumab; en iii. Het ziekte-gestuurd afbouwen van TNF-remmers voor alle drie ontstekingsziekten en van alle biologicals bij RA.

Hoofdstuk 5: Ziekte-gestuurd afbouwen van TNF-remmers in RA gedurende tien jaar

De DRESS studie is het eerste onderzoek naar ziekte-gestuurd afbouwen van TNF-remmers. Dit was een gerandomiseerd onderzoek van 1,5 jaar waarin mensen met RA via loting verdeeld werden tussen ziekte-gestuurd afbouwen van de TNF-remmer en doorgaan met de huidige dosering. De deelnemers van de DRESS studie zijn hierna nog 1,5 jaar gevolgd. In deze periode was ziekte-gestuurd afbouwen toegestaan bij alle deelnemers. Beide onderzoeken van de DRESS studie lieten zien dat ziekte-gestuurd afbouwen effectief en veilig is.

Hoofdstuk 5 beschrijft een studie, waarin we de deelnemers aan het DRESS onderzoek volgden tot tien jaar vanaf het begin van het onderzoek. Hiervoor gebruikten we informatie over ziekteactiviteit en medicatie uit het patiëntendossier en beschikbare röntgenfoto's. We hadden verschillende doelen met dit onderzoek. Als eerste onderzochten we de ziekteactiviteit en de gebruikte dosis van de TNF-remmer en andere biologicals over de tijd. Als tweede onderzochten we of een tweede poging tot afbouwen van de medicatie mogelijk was, wanneer de eerste afbouwpoging niet lukte. Als derde onderzochten we of het uiteindelijk stoppen van de biological

mogelijk was. Als laatste bekeken we het ontstaan van schade aan de gewrichten door afbouwen, waarvoor we röntgenfoto's van de handen en voeten na 10 jaar hebben vergeleken met de foto's na drie jaar. De deelnemers van het onderzoek waren de 170 mensen die het vervolgonderzoek van de DRESS studie tot drie jaar hadden afgerond.

Het onderzoek liet zien dat de ziekteactiviteit laag over de periode van tien jaar, ondanks dat de dosering van de TNF-remmers gemiddeld met de helft werd afgebouwd. Van de 161 mensen die een afbouwpoging deden, kon 119 afbouwen tot stop (74%). De gemiddelde duur van de medicatiestop was zeven maanden, en 25 patiënten (21%) konden zelfs de rest van het onderzoek gestopt blijven. De gemiddelde röntgenschade die we vonden was laag. We vonden daarnaast een verband tussen hoge ziekteactiviteit en röntgenschade, maar niet tussen een lage dosis biological en röntgenschade. Op basis van dit onderzoek concluderen we dat ziekte-gestuurd afbouwen van TNF-remmers en andere biologicals veilig en effectief blijft gedurende tien jaar. Wel is het belangrijk om de ziekteactiviteit laag te houden, omdat een hoge ziekteactiviteit kan leiden tot röntgenschade van de handen en voeten.

Hoofdstuk 6: Remmen van de afbraak van tofacitinib met de enzymremmer cobicistat

In **hoofdstuk 6** onderzochten we het gebruik van een enzymremmer (cobicistat) in de behandeling met het geneesmiddel tofacitinib. De standaard dosering van tofacitinib is twee keer per dag een tablet van 5 mg . Omdat cobicistat de afbraak van tofacitinib remt, vergeleken we tofacitinib en cobicistat één keer per dag (interventie) met tofacitinib twee keer per dag (controle). We vergeleken de gemiddelde hoeveelheid tofacitinib in het bloed voor beide behandelingen. Daarnaast keken we naar bijwerkingen, voorkeur van de deelnemers en hebben we de ziekteactiviteit voor beide behandelingen berekend met een model.

Aan het onderzoek hebben dertig mensen deelgenomen, die ten minste twee weken tofacitinib 5 mg twee keer per dag gebruikten voor de behandeling van hun RA of artritis psoriatica. Aan het begin van de studie werd met een aantal bloedafnames op één dag de hoeveelheid tofacitinib in het bloed bepaald. Na de bloedafnames gingen de deelnemers tofacitinib met cobicistat één keer per dag gebruiken. Na 2-6 weken werden opnieuw bloedafnames gedaan, zodat we de hoeveelheid tofacitinib in het bloed konden vergelijken.

In totaal hebben 25 mensen het onderzoek afgemaakt. De gemiddelde hoeveelheid tofacitinib in het bloed was iets lager voor de combinatiebehandeling van tofacitinib met cobicistat. We vonden geen ernstige bijwerkingen tijdens het onderzoek. De

meerderheid van de deelnemers gaf de voorkeur aan de combinatiebehandeling. Ook de voorspelde ziekteactiviteit was niet verschillend voor de twee behandelingen. Onze conclusie was dat de behandeling van tofacitinib met cobicistat mogelijk de behandeling goedkoper en patiëntvriendelijker kan maken, ondanks de iets lagere bloedwaarden. Eerder onderzoek met tofacitinib liet namelijk zien dat een lagere dosis (3 mg twee keer per dag) mogelijk ook effectief is voor de behandeling van RA en artritis psoriatica. Uitgebreider onderzoek met de combinatie van tofacitinib en cobicistat is nodig om een verschil in werkzaamheid uit te sluiten.

Conclusies

In dit proefschrift onderzochten we verschillende manieren om de behandeling met biologicals en JAK-remmers bij reumatische ontstekingsziekten te verbeteren. De werkzaamheid van een COVID-vaccinatie bij mensen die rituximab gebruiken, kan worden verbeterd door een lagere dosering rituximab of een langere tijd tussen infuus en vaccinatie (**hoofdstuk 2 en 3**). De vaccinatierespons blijft aanwezig bij mensen die rituximab gebruiken, zelfs als er tussendoor een behandeling met rituximab is geweest (**hoofdstuk 3**). Twaalf verschillende strategieën voor kosten-effectief omgaan met biologicals en JAK-remmers werden gevonden, waarbij literatuur-onderzoek leidde tot twintig aanbevelingen over tien van deze strategieën voor de praktijk (**hoofdstuk 4**). Ziekte-gestuurd afbouwen van TNF-remmers bij mensen met RA leidt tot een halvering van de hoeveelheid geneesmiddel met een aanhoudend lage ziekteactiviteit (**hoofdstuk 5**). Tijdens het ziekte-gestuurd afbouwen zijn zowel afbouwen tot stop als herhaaldelijke afbouwpogingen van toegevoegde waarde (**hoofdstuk 5**). Tenslotte leidt de combinatietherapie van tofacitinib met cobicistat één keer daags tot een iets lagere hoeveelheid geneesmiddel in het bloed dan tofacitinib twee keer daags. Vervolgonderzoek is nodig om een verschil in werkzaamheid tussen beide behandelingen uit te sluiten (**hoofdstuk 6**).

Dankwoord

Dankwoord

Dit proefschrift is met de hulp van heel veel mensen tot stand gekomen, waarvoor ik iedereen die een bijdrage heeft geleverd hartelijk wil bedanken. In 2019 kwam ik in de Sint Maartenskliniek met het plan om een promotieonderzoek te doen, waarbij alleen het uitvoeren van de PRACTICAL-studie (hoofdstuk 6) al vast stond. Het schrijven van een proefschrift vanuit het oogpunt 'medicatie' in plaats van 'een reumatologische aandoening' waarbij ik zelf mocht meedenken over de projecten, is een hele leerzame en gave reis geweest. In het bijzonder wil ik een aantal mensen bedanken die bij hebben gedragen aan dit proefschrift.

Allereerst dank aan alle patiënten die hebben deelgenomen aan de onderzoeken in dit proefschrift. Voor jullie interesse in groten getale voor het COVID-vaccinatie onderzoek, en jullie intensieve bijdrage met meerdere opnamedagen voor het PRACTICAL onderzoek.

Beste **Alfons**, van promovendi elders hoor ik vaak dat de eerste promotor afstandelijk en amper beschikbaar is, maar jij was juist het tegenovergestelde! Ik heb je ervaren als een betrokken begeleider die vaak het beste wist hoe mijn projecten ervoor stonden, die het beste en het hardst kon trekken aan inclusies die niet hard genoeg liepen en er was altijd tijd om te overleggen als ik dat nodig had. Bedankt ook voor je geduld met sommige epidemiologische principes waarbij ik de bocht wat te kort wilde nemen: het schaap dat aan een kant zwart is, is me inmiddels echt duidelijk geworden. Naast algemene onderzoeksvaardigheden waardeer ik het ook dat je me tijdens mijn PhD veel meer hebt bijgebracht, zoals het maken van begrotingen, het beoordelen van juridische contracten, gesprekken met subsidiegevers en het schrijven van een richtlijn met een internationale onderzoeksgroep. Als laatste waardeer ik dat het niet altijd inhoudelijk hoefde te zijn: ons overleg kon ook simpelweg even bijpraten in de binnentuin zijn of een rondje wandelen om de Maartenskliniek.

Beste **Bart**, ik waardeer het erg dat het in overleg met jou altijd de vraag was hoe het met mij ging en of de werklast nog te doen was. Met name in het begin van mijn promotie hebben we uitgebreid samengewerkt om het INDIGO-project uit te denken, wat door de COVID helaas geen invulling meer heeft gekregen. Ik kijk met een positief gevoel terug op onze tekeningen van dosis-respons curves en excels met berekende farmacologische parameters. Ik ben erg blij dat jij mijn begeleider wilde zijn om zo wat klinisch farmacologische diepgang te geven aan mijn PhD-traject. Ook waardeer ik je betrokkenheid bij het Delphi-project met het vinden van Delphi members en het leiden van de digitale meetings. Ik hoop je in de toekomst weer tegen te komen bij mijn opleiding tot klinisch farmacoloog.

Beste **Lise**, bedankt voor je laagdrempelige betrokkenheid tijdens mijn PhD-traject. Met name aan het begin van het traject heb je me op gang getrokken, maar ook in het laatste stuk kon ik altijd even videobellen als ik ergens vastliep. Ik waardeer dat ik zorgvuldig onderzoek doen van je heb mogen leren, zoals het voorwerk bij de ethische commissie en lokale toetsing, maar ook juist documenteren en archiveren, wat mijn traject zeker makkelijker heeft gemaakt. Buiten het onderzoek om waren de diners en borrels op congressen altijd gezellig met jou!

Beste **David**, midden in de coronaperiode kreeg ik een nieuw project naar me toegeschoven wat jouw idee was, en wat voor een project! Bedankt voor je uitgebreide hulp hierbij, je gaf me altijd het idee dat we het samen deden in plaats van dat je mijn begeleider was. Door jouw inzet hebben we het razendsnel door de ethische toetsing gekregen, hierdoor tweehonderd patiënten kunnen includeren en heb ik ermee kunnen shinen op de NVR! Bedankt ook voor je regelmatige appjes om te vragen hoe het met me is en je enthousiasme over (kleine) mijlpalen, ook nu ik allang weg ben op de SMK.

Beste **Noortje**, bedankt voor je enthousiasme en inzet bij het DRESS-project. Zeker de dataverwerking en analyses heb ik als erg pittig ervaren, maar jouw laagdrempelige en fijne begeleiding hielp mij om het licht aan het eind van de tunnel te blijven zien. Ook het beoordelen van röntgenfoto's werd zo minder saai. Ik hoop later net als jou de reumatologie en klinische farmacologie te kunnen combineren en kijk er erg naar uit om onder jouw begeleiding de opleiding klinische farmacologie te volgen!

Beste **Rob**, ook jij voelde echt als een begeleider voor mij tijdens het PRACTICAL-project. Ik wil je bedanken voor je inzet bij de opnamedagen in het Radboud, het verwerken en analyseren van de monsters en mij een kijkje geven in farmacokinetisch modelleren.

Beste leden van de manuscriptcommissie, **prof. Reinout van Crevel, prof. Sjoerd Repping en prof. Angelique Weel-Koenders**, hartelijk dank voor het beoordelen van mijn proefschrift en het deelnemen aan de oppositie.

My sincere thanks for all members of the Delphi study: **Daniel Aletaha, Rieke Alten, Katerina Chatzidionysiou, James Galloway, John Isaacs, Denis Mulleman, Patrick Verschueren and Paco Welsing**. Thank you for participating in all the online meetings for this new project in the midst of the COVID crisis, for which we could never meet in person. Thanks to your efforts, we wrote an excellent article with smooth publication.

Bedankt ook aan alle mede-promovendi van de reumatologie SMK tijdens (een deel van) mijn promotie: **Celia, Iris Rose, Merel, Michelle, Tamara, Evy, Thomas, Nathan en Pauline**. De altijd aanwezige support, gedeelde smart en dinsdagmiddag-wandelingen van de kamer heeft zeker positief bijgedragen aan dit proefschrift. Bedankt ook voor de gezelligheid op de tripjes naar de NVR Najaarsdagen en de EULAR in Kopenhagen. **Nathan**, bedankt voor je hulp bij de analyses van het COVID- en DRESS-project. Alle mooie figuren in mijn proefschrift zijn aan jou te danken! **Thomas**, bedankt voor het delen van Stata-trucjes, EndNote irritaties en onze schrijfmarathon voor de inleiding van het proefschrift. Ik hoop ook snel bij jouw promotie te kunnen zijn!

Maike, door ons gedeelde promotieteam trokken we vanaf het begin al veel samen op. Je hebt me op zoveel manieren op weg geholpen tijdens mijn PhD: inhoudelijk door je uitstekende epidemiologie en statistiekkennis, sociaal door het managen van de samenwerking met Amsterdam en het managen van ons eigen promotieteam, en natuurlijk de gezellige kletsmomenten. Ik wens je heel veel succes met jouw laatste loodjes en kijk ernaar uit om bij jouw verdediging te zijn!

Iris Rose, ik had me geen beter maatje kunnen wensen om samen een eilandje mee te zijn op de arts-onderzoekerskamer! We hebben lief en leed gedeeld over onderzoek, over poli, over supervisoren en de ethische commissie. Ook zou de arts-assistenten-vereniging van de SMK niet bestaan hebben zonder ons.. Je bent de hardste werker die ik ken, je enorme trial is een hele mooie basis voor een proefschrift. Ik ben heel blij dat jij mijn paranimf wilt zijn.

Evy, ik ontmoette jou toen ik net een paar maanden bezig was op de SMK en jij bijkluste als onderzoeksassistent voordat je aan je co-schappen begon, bedankt voor die gezellige zomer! Ondertussen had je me bijna ingehaald met het afronden van je proefschrift en vond ik het super gezellig dat je er aan het einde van mijn SMK-tijd weer was. Nog steeds kijk ik met veel verbazing en respect hoe je zo snel dat proefschrift afgerond hebt. Ik vind het super gezellig dat je me wilt ondersteunen als paranimf!

Ik wil alle reumatologen van de Sint Maartenskliniek bedanken voor de fijne 3,5 jaar tijd die ik op de SMK heb gehad. Bedankt voor de laagdrempelige supervisie en het gevoel dat wij ANIOS echt bij het team horen. Wanneer ik tijdens mijn opleiding nog eens langskwam in de SMK, voelde het weer als een warm bad. Daarnaast wil ik nog een paar reumatologen specifiek bedanken: **Aatke**, bedankt voor je hulp bij het DRESS-artikel en **Sabien en Calin**, jullie wil ik specifiek bedanken voor de inclusies van de PRACTICAL-studie!

Ook de andere medewerkers op de Sint Maartenskliniek hebben bijgedragen aan de fijne tijd die ik heb gehad. **Victor en Karin**, bedankt voor jullie hulp bij de inclusiegesprekken van de PRACTICAL. Daarnaast is het digitaal onderwijs geven met Victor aan apothekersassistenten me altijd in positieve zin bijgebleven. **Angelique, Bianca en collega's van het secretariaat farmacie**: bedankt voor jullie geduld in het plannen van afspraken en ook voor de gezelligheid als ik eens voor een praatje kwam. **Collega's van de poli reumatologie: Bert-Jan, Margo en Isabelle**: bedankt voor het praktisch en werkbaar maken van mijn studies en het helpen bij de planning op de poli. **Reumaverpleegkundigen**, bedankt voor jullie hulp bij de COVID-studies en ook de subcutane rituximab-studie die nog in de afrondende fase is. Bedankt ook aan alle **collega's van research** voor de ondersteuning, de verdiepende cursussen/ onderwijsdagen en de gezelligheid op congressen.

Ank en Ben, ik wil jullie bedanken voor de bijdrage als patiëntpartners aan mijn onderzoeken. Door jullie kritische vragen en scherpe blik zijn mijn onderzoeken relevanter en is de communicatie met patiënten beter geworden.

Marleen, bedankt dat ik bij jouw bachelorscriptie mocht leren hoe het is om zelf begeleider te zijn. Jouw harde werk heeft een goede basis gelegd voor de uiteindelijke publicatie van de DRESS-studie. **Kasper**, bedankt voor je harde werk als student-assistent bij de PRACTICAL-studie, zonder jouw hulp op de thuisprikdagen was de studie nooit vol gekomen! Ook **alle andere student-assistenten** die geholpen hebben bij mijn projecten, waaronder **Stijn**, heel erg bedankt.

Beste collega's van de interne Rijnstate: **Daan, Maarten, Manon, Nienke, Aline, Luuk en vele anderen**: dank dat ik tegen jullie aan mocht klagen over de laatste loodjes van mijn promotieonderzoek en dat jullie door jullie promoties en onderzoek mij weer inspiratie gaven om verder te werken. Lieve mede reuma-AIOS: **Freek, Michelle, Viola en Xyrian**, ook bedankt voor het verdere motiveren voor het afmaken van mijn proefschrift en de oprechte interesse ervoor. Ik kijk er naar uit om de rest van mijn opleiding met jullie te vervolgen!

Bedankt ook aan alle lieve vrienden die oprechte interesse bleven tonen in mijn PhD-traject: **Kristina en Jordi**, **Mieke**, **Danielle** en de vrienden van 'groepje 6': **Annemieke, Florentine, Lisette en Tim**.

Lieve **papa en mama**, bedankt voor jullie oneindige support en interesse in mijn proefschrift. **Pap**, jouw handige bibliotheektrucjes hebben me zeker geholpen en voor jou heb ik me hard gemaakt om al mijn artikelen open access te publiceren. **Mam**, jouw subtiele vragen hoe het met onderzoek ging in de laatste loodjes hebben

me het duwtje in de rug gegeven om het af te ronden. Lieve **Aurora en Isaure**, bedankt voor jullie support en de gezellige activiteiten ter afleidingen: lunchen, shoppen, relaxen in papa en mama's tuin of een dagje Efteling.

Curriculum vitae

Curriculum vitae

Céleste Jeanne Theodora van der Togt werd geboren op 26 februari 1994 te Wageningen. Na de basisschool in Wageningen, vertrok ze naar het Marnix College te Ede voor haar middelbare schooltijd, waar ze in 2011 haar gymnasiumdiploma behaalde. In datzelfde jaar begon zij aan de opleiding Geneeskunde aan de Radboud Universiteit te Nijmegen. Na het tweede jaar van haar studie volgde Céleste een verdiepende Summer School aan het UMC St. Radboud, waarbij ze ook meeliep op de polikliniek reumatologie. In de laatste fase van haar opleiding had ze haar onderzoeksstage bij de afdeling klinische farmacologie/apotheek van het Canisius Wilhelmina Ziekenhuis in Nijmegen en volgde ze een keuze-coschap bij de reumatologie in het Rijnstate te Arnhem. Eind 2017 behaalde Céleste haar artsdiploma en wist zij dat ze zich verder wilde specialiseren binnen de reumatologie.

Na haar studie heeft ze een ruim jaar als basisarts (ANIOS) interne geneeskunde in Gelre Ziekenhuizen Apeldoorn gewerkt. Hierna wilde zij zich verder verdiepen binnen de reumatologie en startte zij met een promotietraject naar medicamenteuze behandeling van reumatoïde artritis en spondyloartritis bij de afdeling reumatologie van de Sint Maartenskliniek. Haar onderzoek verrichte zij onder supervisie van dr. Alfons den Broeder, prof. Bart van den Bemt, dr. Lise Verhoef en dr. David ten Cate. De resultaten van haar promotieonderzoek staan beschreven in dit proefschrift.

In 2023 is Céleste begonnen aan de opleiding tot reumatoloog in de regio Arnhem/Nijmegen. Momenteel is zij bezig aan de vooropleiding interne geneeskunde in het Rijnstate te Arnhem. In 2026 zal zij tevens starten met de opleiding klinische farmacologie aan het Radboudumc onder begeleiding van dr. Noortje van Herwaarden, met als doel reumatoloog-klinisch farmacoloog te worden.

List of publications

List of publications

van der Togt CJT, den Broeder N, Boonstra MS, van der Maas A, den Broeder AA, van Herwaarden N. Disease activity-guided dose optimisation including discontinuation of TNF-inhibitors in rheumatoid arthritis is effective for up to 10 years: an observational follow-up of the DRESS study. Rheumatology (Oxford). 2024 Feb 12.

van der Togt CJT, Van den Bemt B, Aletaha D, Alten R, Chatzidionysiou K, Galloway J, Isaacs J, Mulleman D, Verschueren P, Vulto AG, Welsing PMJ, Verhoef L, den Broeder AA. Points to consider for cost-effective use of biological and targeted synthetic DMARDs in inflammatory rheumatic diseases: results from an umbrella review and international Delphi study. RMD Open. 2023 Mar;9(1).

van der Togt CJT, Verhoef LM, van den Bemt BJF, den Broeder N, Ter Heine R, den Broeder AA. Pharmacokinetic boosting to enable a once-daily reduced dose of tofacitinib in patients with rheumatoid arthritis and psoriatic arthritis (the PRACTICAL study). Ther Adv Musculoskelet Dis. 2022 Dec 12;14.

van der Togt CJT, Ten Cate DF, van den Bemt BJF, Rahamat-Langendoen J, den Broeder N, den Broeder AA. Seroconversion after a third COVID-19 vaccine is affected by rituximab dose but persistence is not in patients with rheumatoid arthritis. Rheumatology (Oxford). 2023 Apr 3;62(4):1627-1630.

van der Togt CJT, Ten Cate DF, den Broeder N, Rahamat-Langendoen J, van den Bemt BJF, den Broeder AA. Humoral response to coronavirus disease-19 vaccines is dependent on dosage and timing of rituximab in patients with rheumatoid arthritis. Rheumatology (Oxford). 2022 Jun 28;61(SI2):SI175-SI179.

Research data management

Research data management

Ethics and privacy

Medical-scientific research with human participants was performed to answer the research questions in this thesis. The studies described in chapter 2, 3, and 6 were subject to the Medical Research Involving Human Subjects Act (WMO) and were conducted in accordance with the ICH-GCP guidelines (Good Clinical Practice). The medical ethical review committee 'METC Oost-Nederland' has given approval to conduct these studies (file numbers: NL76709.091.21; NL65634.091.18). Informed consent was obtained from research participants. For the study of chapter 5, the medical ethical review committee provided exemption, as ethical approval for this type of study is not required under Dutch law (file number: 2023-16202). The studies described in chapter 2, 3, and 6 were also reviewed and accepted by the local committee of the Sint Maartenskliniek to warrant they comply with the local protocols and policies.

Technical and organizational measures were followed to safeguard the availability, integrity and confidentiality of the data (these measures include the use of independent monitoring, pseudonymization, access authorization and secure data storage).

Data collection and storage

Data for chapter 2, 3 and 6 was collected through electronic Case Report Forms (eCRF) using CASTOR EDC. From Castor EDC data were exported to STATA/IC (StataCorp, College Station, TX, USA) and R-statistics (chapter 6 only; R Foundation, Vienna, Austria). For the study of chapter 5, data was collected from the electronic health records of the Sint Maartenskliniek and exported to STATA/IC. Pseudonymized data were stored and analysed on the department server and in Castor EDC and are only accessible by project members of the rheumatology department of the Sint Maartenskliniek. Paper (hardcopy) data is stored in cabinets on the department, which can only be accessed by staff with authorisation to enter the department. Serum samples collected in the studies of chapter 2, 3 and 6 will be stored for 10 years after the end of the study in the CWZ laboratory (location SMK; chapter 2 and 3) or the Radboudumc biobank (chapter 6).

Availability of data

All studies are published open access. The data will be archived for 25 years after termination of the study. Reusing the data for future research is only possible after a renewed permission by the participants. The anonymous datasets that were used for analysis are available from the corresponding author upon reasonable request.

PhD portfolio

PhD portfolio of Céleste Jeanne Theodora van der Togt

Department: **department of rheumatology**
PhD period: **01/04/2019 - 30/01/2025**
PhD Supervisor(s): **Dr. A.A. den Broeder, Prof. Dr. B.J.F. van den Bemt**
PhD Co-supervisor(s): **Dr. L.M. Verhoef, Dr. D.F. Ten Cate**

Training activities	Hours
Courses	
- Basiscursus regelgeving en organisatie voor klinisch onderzoekers (BROK) (2019)	42.00
- Sanquin Masterclass Biologics (2019)	7.00
- Epidemiologisch onderzoek: basisprincipes (V10) (2020)	112.00
- RIHS - Introduction course for PhD candidates (2020)	15.00
- Radboudumc - Scientific integrity (2020)	20.00
- RU - Open Science for PhD candidates (2020)	28.00
- RU - Scientific Writing for PhD candidates (2021)	84.00
- English Boost Camp: Pronunciation (2021)	5.00
- V30: Regression analysis (2021)	36.00
- V81: Missing data (2022)	18.00
- Zorgstelsel en Zorgverzekering (2022)	28.00
- Hercertificering 'Basiscursus Regelgeving en Organisatie voor Klinische onderzoekers (BROK)' (2023)	28.00
Seminars	
- How to write a peer review (2021)	2.00
Conferences	
- NVR Najaarsdagen 2019 (2019)	14.00
- NVR Najaarsdagen (including oral presentation) (2021)	8.00
- ACR e-congress (including poster presentation) (2021)	12.00
- RIHS PhD Retreat (2022)	16.00
- EULAR congress (including poster presentations) (2022)	28.00
- NVR Najaarsdagen (including oral presentations) (2022)	14.00
- NVR Najaarsdagen (including oral presentation) (2023)	14.00
Other	
- Journal Club (2021)	28.00
Teaching activities	
Lecturing	
- Rheumatology lecture for pharmacy assistants (2021)	8.00
Supervision of internships / other	
- Supervision of bachelor thesis student (M. Boonstra) (2022)	28.00
Total	**595.00**

Theses Sint Maartenskliniek

Theses Sint Maartenskliniek

Ensink, C. (2025) Sensing the path to mobility - advancing gait rehabilitation with sensor technology. Radboud University Nijmegen, Nijmegen. The Netherlands.

Zwijgers, E. (2025) Improving walking capacity after spinal cord injury. Radboud University Nijmegen, Nijmegen. The Netherlands.

Boekesteijn, R. (2024) Evaluating walking in lower-extremity osteoarthritis: Beyond the lab, towards the real world. Radboud University Nijmegen, Nijmegen. The Netherlands.

Den Broeder, N. (2024) More than tapering, less than full dose - Efficient use of biologics in the treatment of rheumatoid arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Kuijpers, R. (2024) Adapt your step: Clinical assessment and training of walking adaptability in children with mild motor disorders. Radboud University Nijmegen, Nijmegen. The Netherlands.

Te Molder, M. (2024) The unhappy patient after TKA. A paradigm shift in assessing outcome. Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Hal, T. (2024) A rheumatologist undercover: research of psoriatic arthritis at the dermatology clinic. Radboud University Nijmegen, Nijmegen. The Netherlands.

Veenstra, F. (2024). About gout. Studying potential targets for improvement of care. Radboud University Nijmegen, Nijmegen. The Netherlands.

De Jong, L.A.F. (2023). Effects of lower limb orthotic devices in people with neurological disorders. Radboud University Nijmegen, Nijmegen. The Netherlands.

Michielsens, C. (2023). Tapering strategies of biologics in inflammatory disorders. Radboud University Nijmegen, Nijmegen. The Netherlands.

Pouls, B. (2023). Supporting patients'medication management using eHealth. Test cases in rheumatology. Radboud University Nijmegen, Nijmegen. The Netherlands.

Stöcker, J. (2023). Accessible and effective non-pharmacological care for persons with systemic sclerosis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Huiskes, V. (2022). The synergistic role of patients and healthcare providers in reducing drug-related problems. Radboud University Nijmegen, Nijmegen. The Netherlands.

Marsman, D. (2022). Polymyalgia rheumatica. Clinical characteristics and new treatment opportunities. Radboud University Nijmegen, Nijmegen. The Netherlands.

Mulder, M. (2022). Going off-road. Exploring and mapping psoriatic arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Alingh, J. (2021). Effect of robotic gait training on the post-stroke gait pattern. Evaluation of LOPES II. Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Dijsseldonk, R. (2021). Step into the future: mobility after spinal cord injury. Radboud University Nijmegen, Nijmegen. The Netherlands.

Pelle, T. (2021). Beating osteoarthritis by e-self management in knee or hip osteoarthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Van Heuckelum, M (2020). Novel approaches to improve medication adherence in rheumatoid arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Mathijssen, E. (2020). The voice of patients with rheumatoid arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Bakker, S. (2019). Regional anesthesia and total knee arthroplasty. Anesthetic and pharmacological considerations. Radboud University Nijmegen, Nijmegen. The Netherlands.

Claassen, A. (2019). Strategies for patient education in rheumatic diseases. Radboud University Nijmegen, Nijmegen. The Netherlands.

Fenten, M. (2019). Optimizing locoregional anesthesia in fast track orthopaedic surgery. Radboud University Nijmegen, Nijmegen. The Netherlands.

Minten, M. (2019). On the role of inflammation and the value of low dose radiation therapy in osteoarthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Verhoef, L. (2019). Effective and efficient use of bDMARDs in rheumatoid arthritis. Radboud University Nijmegen, Nijmegen. The Netherlands.

Bekker, C. (2018). Sustainable use of medication. Medication waste and feasibility of redispensing, Utrecht University, Utrecht. The Netherlands.
Bikker, I.(2018). Organizing timely treatment in multi-disciplinary care. University of Twente, The Netherlands.
Bouman, C. (2018). Dose optimisation of biologic DMARDs in rheumatoid arthritis: long-term effects and possible predictors. Radboud University Nijmegen, The Netherlands.
Mahler, E. (2018). Contributors to the management of osteoarthritis. Utrecht University, The Netherlands.
Tweehuysen, L. (2018). Optimising biological treatment in inflammatory rheumatic diseases. Predicting, tapering and transitioning. Radboud University Nijmegen, Nijmegen, The Netherlands.
Geerdink, Y. (2017). Getting a grip on hand use in unilateral cerebral palsy. Radboud University, Nijmegen, The Netherlands.
Remijn, L. (2017). Mastication in children with cerebral palsy. Radboud University, Nijmegen, The Netherlands.
Selten, E. (2017). Beliefs underlying treatment choices in osteoarthritis. Radboud University, Nijmegen, The Netherlands.
Van Hooff, M. (2017). Towards a paradigm shift in chronic low back pain? Identification of patient profiles to guide treatment. VU University Amsterdam, Amsterdam, The Netherlands.
Lesuis, N. (2016). Quality of care in rheumatology. Translating evidence into practice. Radboud University, Nijmegen, The Netherlands.
Luites, J. (2016). Innovations in femoral tunnel positioning for anatomical ACL reconstruction. Radboud University, Nijmegen, The Netherlands.
Pakvis, D. (2016). Survival, primary stability and bone remodeling assessment of cementless sockets. An appraisal of Wolff's law in the acetabulum. Radboud University, Nijmegen, The Netherlands.
Schoenmakers, K. (2016). Prolongation of regional anesthesia. Determinants of peripheral nerve block duration. Radboud University, Nijmegen, The Netherlands.
Altmann, V. (2015). Impact of trunk impairment on activity limitation with a focus on wheelchair rugby. Leuven University, Leuven, Belgium.
Bevers, K. (2015). Pathophysiologic and prognostic value of ultrasonography in knee osteoarthritis. Utrecht University, Utrecht, The Netherlands.
Cuperus, N. (2015). Strategies to improve non-pharmacological care in generalized osteoarthritis. Radboud University, Nijmegen, The Netherlands.
Kilkens, A. (2015). De ontwikkeling en evaluatie van het Communicatie Assessment & Interventie Systeem (CAIS) voor het aanleren van (proto-)imperatief gedrag aan kinderen met complexe ontwikkelingsproblemen. Radboud University, Nijmegen, The Netherlands.
Penning, L. (2015). The effectiveness of injections in cuffdisorders and improvement of diagnostics. Maastricht University, Maastricht, The Netherlands.
Stegeman, M. (2015). Fusion of the tarsal joints: outcome, diagnostics and management of patient expectations. Utrecht University, Utrecht, The Netherlands.
Van Herwaarden, N. (2015). Individualised biological treatment in rheumatoid arthritis. Utrecht University, Utrecht, The Netherlands.
Wiegant, K. (2015). Uitstel kunstknie door kniedistractie. Utrecht University, Utrecht, The Netherlands.
Willems, L. (2015). Non-pharmacological care for patients with systemic sclerosis. Radboud University, Nijmegen, The Netherlands.
Witteveen, A. (2015). The conservative treatment of ankle osteoarthritis. University of Amsterdam, Amsterdam, The Netherlands.
Zwikker, H. (2015). All about beliefs. Exploring and intervening on beliefs about medication to improve adherence in patients with rheumatoid arthritis. Radboud University, Nijmegen, The Netherlands.
Koenraadt, K. (2014). Shedding light on cortical control of movement. Radboud University, Nijmegen, The Netherlands.
Smink, A. (2014). Beating Osteoarthritis. Implementation of a stepped care strategy to manage hip or knee osteoarthritis in clinical practice. VU University Amsterdam, Amsterdam, The Netherlands.
Stolwijk, N. (2014). Feet 4 feet. Plantar pressure and kinematics of the healthy and painful foot. Radboud University, Nijmegen, The Netherlands.
Van Kessel, M. (2014). Nothing left? How to keep on the right track. Spatial and non-spatial attention processes in neglect after stroke. Radboud University, Nijmegen, The Netherlands.

Brinkman, M. (2013). Fixation stability and new surgical concepts of osteotomies around the knee. Utrecht University, Utrecht, The Netherlands.
Kwakkenbos, L. (2013). Psychological well-being in systemic sclerosis: Moving forward in assessment and treatment. Radboud University, Nijmegen, The Netherlands.
Severens, M. (2013). Towards clinical BCI applications: assistive technology and gait rehabilitation. Radboud University, Nijmegen, The Netherlands.
Stukstette, M. (2013). Understanding and treating hand osteoarthritis: a challenge. Utrecht University, Utrecht, The Netherlands.
Van der Maas, A. (2013). Dose reduction of TNF blockers in Rheumatoid Arthritis: clinical and pharmacological aspects. Radboud University, Nijmegen, The Netherlands.
Zedlitz, A. (2013). Brittle brain power. Post-stroke fatigue, explorations into assessment and treatment. Radboud University, Nijmegen, The Netherlands.
Beijer, L. (2012). E-learning based speech therapy (EST). Exploring the potentials of E-health for dysarthric speakers. Radboud University, Nijmegen, The Netherlands.
Hoogeboom, T. (2012). Tailoring conservative care in osteoarthritis. Maastricht University, Maastricht, The Netherlands.
Boelen, D. (2011). Order out of chaos? Assessment and treatment of executive disorders in brain-injured patients. Radboud University, Nijmegen, The Netherlands.
Heesterbeek, P. (2011). Mind the gaps! Clinical and technical aspects of PCL-retaining total knee replacement with the balanced gap technique. Radboud University, Nijmegen, The Netherlands.
Hegeman, J. (2011). Fall risk and medication. New methods for the assessment of risk factors in commonly used medicines. Radboud University, Nijmegen, The Netherlands.
Smulders, E. (2011). Falls in rheumatic diseases. Risk factors and preventive strategies in osteoporosis and rheumatoid arthritis. Radboud University, Nijmegen, The Netherlands.
Snijders, G. (2011). Improving conservative treatment of knee and hip osteoarthritis. Radboud University, Nijmegen, The Netherlands.
Vriezekolk, J. (2011). Targeting distress in rheumatic diseases. Utrecht University, Utrecht, The Netherlands.
Willems, P. (2011). Decision making in surgical treatment of chronic low back pain. The performance of prognostic tests to select patients for lumbar spinal fusion. Maastricht University, Maastricht, The Netherlands.
Aarts, P. (2010). Modified constraint-induced movement therapy for children with unilateral spastic cerebral palsy: the Pirate group intervention. Radboud University, Nijmegen, The Netherlands.
Groen, B. (2010). Martial arts techniques to reduce fall severity. Radboud University, Nijmegen, The Netherlands.
Van Koulil, S. (2010). Tailored cognitive behavioral therapy in fibromyalgia. Radboud University, Nijmegen, The Netherlands.
Van den Bemt, B. (2009). Optimizing pharmacotherapy in patients with rheumatoid arthritis: an individualized approach. Radboud University, Nijmegen, The Netherlands.
Van Nes, I. (2009). Balance recovery after supratentorial stroke. Influence of hemineglect and the effects of somatosensory stimulation. Radboud University, Nijmegen, The Netherlands.
Ruiter, M. (2008). Speaking in ellipses. The effect of a compensatory style of speech on functional communication in chronic agrammatism. Radboud University, Nijmegen, The Netherlands.
Baken, B. (2007). Reflexion on reflexes. Modulation during gait. Radboud University, Nijmegen, The Netherlands.
Gaasbeek, R. (2007). High tibial osteotomy. Treatment of varus osteoarthritis of the knee. Radboud University, Nijmegen, The Netherlands.
Koëter, S. (2007). Patellar instability. Diagnosis and treatment. Radboud University, Nijmegen, The Netherlands.
Langeloo, D. (2007). Monitoring the spinal cord during corrective spinal surgery: a clinical study of TES-MEP. Radboud University, Nijmegen, The Netherlands.
De Haart, M. (2005). Recovery of standing balance in patients with a supratentorial stroke. Radboud University, Nijmegen, The Netherlands.
Den Otter, R. (2005). The control of gait after stroke: an electromyographic approach to functional recovery. Groningen University, Groningen, The Netherlands.

Spruit, M. (2005). Surgical treatment of degenerative disc conditions of the lumbar spine. Biomechanical, clinical and radiological aspects. University Utrecht, Utrecht, The Netherlands.
Weerdesteyn, V. (2005). From the mechanisms of obstacle avoidance towards the prevention of falls. Radboud University, Nijmegen, The Netherlands.
Jongerius, P. (2004). Botulinum toxin type-A to treat drooling. A study in children with cerebral palsy. Radboud University, Nijmegen, The Netherlands.
Van de Crommert, H. (2004). Sensory control of gait and its relation to locomotion after a spinal cord injury. Radboud University, Nijmegen, The Netherlands.
Van der Linde, H. (2004). Prosthetic prescription in lower limb amputation. Development of a clinical guideline in the Netherlands. Groningen University, Groningen, The Netherlands.
Hendricks, H. (2003). Motor evoked potentials in predicting motor and functional outcome after stroke. University of Nijmegen, Nijmegen, The Netherlands.
Hosman, A. J. F. (2003). Idiopathic thoracic spinal deformities and compensatory mechanisms. University of Nijmegen, Nijmegen, The Netherlands.
Donker, S. (2002). Flexibility of human walking: a study on interlimb coordination. Groningen University, Groningen, The Netherlands.
Hochstenbach, J. (1999). The cognitive, emotional, and behavioural consequences of stroke. University of Nijmegen, The Netherlands.
De Kleuver, M. (1998). Triple osteotomy of the pelvis. An anatomical, biomechanical and clinical study. University of Nijmegen, Nijmegen, The Netherlands.
Van Balen, H. (1997). A disability-oriented approach to long-term sequelae following traumatic brain injury. Neuropsychological assessment for post-acute rehabilitation. University of Nijmegen, Nijmegen, The Netherlands.
Tromp, E. (1995). Neglect in action: a neuropsychological exploration of some behavioural aspects of neglect. University of Nijmegen, Nijmegen, The Netherlands.
Van Lankveld, W. (1993). Coping with chronic stressors of rheumatoid arthritis. University of Nijmegen, Nijmegen, The Netherlands.
Geurts, A. (1992). Central adaptation of postural organization to peripheral sensorimotor impairments. University of Nijmegen, Nijmegen, The Netherlands.
De Rooij, D. (1988). Clinical and serological studies in the connective tissue diseases. University of Nijmegen, Nijmegen, The Netherlands.

Sint Maartenskliniek

Radboudumc
university medical center

Radboud University