More than tapering, less than full dose

Efficient use of biologics in the treatment of rheumatoid arthritis

Nathan den Broeder

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Chapter 1

General introduction

General Introduction

It was in the year 1800, that a physician named Augustin Jacob Landré-Beauvais first described what is now known as rheumatoid arthritis (RA).[1] Landré-Beauvais referred to this disease as 'primary asthenic gout' and while the name did not survive, his descriptions of the patients and the disease are still accurate. Landré-Beauvais describes a chronic disease that leads to inflamed, swollen and painful joints that eventually become deformed, that occurs more in women than men, and that can affect many different joints, predominantly those of the hand and feet, either simultaneously or at different times.

Today, RA is known to be an auto-immune disease in which the immune system attacks the synovium in our joints.[2] This leads to the pain and swelling of the joint, and in the longer term to joint damage. In addition to its effects on the joints, RA is also associated with extra-articular manifestations, a higher risk of cardiovascular events and infections and more general symptoms such as fatigue. RA is most common in women and affects around 0.25% of the population.[3] In the Netherlands, approximately 70,000 to 90,000 people have RA, as the prevalence in Western Europe is somewhat higher at 0.35%.[3,4]

Treatment of rheumatoid arthritis

For the pharmacological treatment of RA, there are several options.[5,6] Corticosteroids can rapidly relieve symptoms and retard progression of joint damage but are not ideal for long term use due to their side effects (especially in higher doses). NSAIDs (nonsteroidal anti-inflammatory drugs) can also be used to relieve symptoms, but do not affect progression of joint damage. Therefore, drugs known as disease modifying anti-rheumatic drugs (DMARDs) are the main treatment of RA. There are several classes of DMARDs: the first-line option are the conventional synthetic DMARDs (csDMARDs), consisting of small molecules that generally have a broad immuno-modulating effect. The most important drug of this class is methotrexate, which is the first choice in the treatment of RA. Other commonly used csDMARDs are leflunomide and hydroxychloroquine. If a patient does not respond to, or suffers from adverse effects of csDMARDs, the next choice is often a biologic DMARD (bDMARD) or a targeted synthetic DMARD (tsDMARD). Both bDMARDs and tsDMARDs have a more targeted effect toward a single inflammatory pathway. However, the chemical structure of tsDMARDs differs from bDMARDs. Where tsDMARDs are small molecules like csDMARDs, bDMARDs are larger molecules of biologic origin such as monoclonal antibodies and are the main focus of this thesis.

Perhaps as important as the drugs used is the way they are used. Which patients do you treat with which drug, at what time and at what dose? The current best known answer to these questions is a treatment strategy known as treat-to-target (T2T).[7] This strategy consists of 3 core principles:

1. Set a target of a desired level of disease activity
2. Measure whether this target is achieved or not
3. Change the treatment until the target is achieved

From these principles follows the need to quantify disease activity to allow for setting the target and measuring whether it has been achieved. There are several scores available for this purpose in RA. Most supported by evidence and most used are the Disease Activity Score with 28 joints (DAS28) (or DAS28-CRP), the Simple Disease activity Index (SDAI) and the Clinical Disease activity Index (CDAI).[8-11] These scores all consist of some combination of patient- and physician reported outcomes in the form of a visual analog scale (VAS) of disease activity, a measurement of how many joints are swollen and/or painful, and in most cases the level of inflammatory markers measured from a blood sample in the form of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). As a treatment target, the levels of these scores corresponding to low disease activity or remission are recommended.[5-7,12] In terms of measurement frequency, this can range from every few months with new, active RA, to yearly with RA in longstanding remission.[5-7]

Current best practice to find the right treatment to achieve the treatment target is largely a process of trial and error. While some specific nuances and exceptions exist, most b/tsDMARDs have a similar efficacy where around a third of patients responds well, a third shows moderate response and a third shows no response.[13] As it is not possible to accurately predict which patients will respond to which drug, it is important to follow the T2T principles of frequently monitoring disease activity, and switching to another drug in case of insufficient response.[7,14] This process repeats until the treatment target is achieved. The order in which drugs are tried are usually based on other considerations than efficacy, such as safety, costs, and patient preferences.

Although seemingly crude, this trial-and-error T2T process, in combination with the availability of quite a number of DMARDs of all types, does allow a large majority of patients to achieve their treatment target.[15] Therefore, this thesis is mainly about what to do once the target is achieved.

Beyond disease activity

At this point, we've seen how, through a bit of trial and error coupled with good T2T, remission or low disease activity can be reached in most patients. So why not stop here? The disease is under control, the patient is happy, so we can all just pack up and go home, right? With all the impartiality of someone who has spent the last 4 years working on RA research, I'd say that's a bridge too far![1] What we have ignored up to this point is any aspect other than disease activity. These are aspects that should not be ignored such as the high costs of many b/tsDMARDs of up to €10,000 per year, the side effects of these drugs and the burden for patients associated with their use such as injections or having to come to the hospital for infusions.[16-18] Even before RA was called RA, Landré-Beauvais already noted the need to look also at the downsides of potential treatments, noting that: "the disadvantages of topical emollients cancel or outweigh their usefulness".[19]

The most obvious way to reduce the negative aspects of RA drugs is to use as little of them as possible. Because the lowest effective dose of a drug varies between individuals and has thus far proven to be very hard to predict, the way to achieve this is again through T2T trial-and-error.[20,21] More formally, this is called disease-activity guided dose optimization. In this treatment strategy, the dose of a drug is reduced (or the interval increased) step by step while monitoring disease activity, until the drug is either stopped completely or there is a relevant increase in disease activity, at which point the lowest effective dose is reinstated.[22] The effectiveness and safety of this strategy is well-supported by trial and observational data for various drugs in RA, especially for the commonly used TNF-inhibitors, and also in other immune mediated inflammatory diseases such as spondyloarthritis, psoriasis and inflammatory bowel disease.[21,23-26]

In **Chapter 2** of this thesis, we looked at the cost-effectiveness of disease-activity guided dose optimization of TNF-inhibitors adalimumab and etanercept in the long term extension of a trial of this strategy. During the original 18-month trial, the trial's dose optimization protocol had been very cost-effective, with large reductions in drug expenses and no clear loss of effectiveness.[23,27] During the extension phase (months 18-36), the control group was also able to use dose optimization, though in a less protocolized manner.[28] Therefore, this data was used to answer the question of whether cost-effectiveness of dose optimization was maintained up to year 3, and also whether less protocolized dose optimization in usual care was cost-effective and how this compared to the results of the protocolized tapering during the trial.

1 Do not take the bridge too far, lest one end up in *Arnhem*

Other than just using less of a drug, the use of biosimilars can strongly reduce the costs of treatment, though they will not help for other downsides such as side effects. Biosimilars are generic variants of the originator drug that can be used after the original drug's patent has expired. Their effect on prices occurs through competition between multiple manufacturers of the same drug. As a result, by having the opportunity to use different equivalent options, payers have a stronger negotiation position and prices drop.[29] Research has shown that it is possible to switch from originator to biosimilar drugs without increases in disease activity or side effects.[6,30-32]

In **Chapter 3** of this thesis, we sought to do something similar, but also quite different. Instead of transitioning between identical drugs of different manufacturers, we studied the effects of switching between two different IL-6 inhibitors: from tocilizumab to sarilumab. Similarly to biosimilar switching, a goal was to increase competition to reduce prices. In addition, this specific switch has the benefit of reducing the injection burden (sarilumab is injected once every two weeks compared to the weekly tocilizumab), and providing an option in case of drug shortages. The latter proved more relevant than initially thought when the COVID-19 pandemic resulted in a worldwide shortage of tocilizumab. To investigate the effectiveness of this switch we conducted an open-label observational study of RA patients switching from tocilizumab to sarilumab.

Rituximab

Rituximab is one of the bDMARDs that is used to treat RA. Itis a bit of a special case as its recommended dosing seems to be too high. It was originally developed to treat non-Hodgkin lymphoma and works by binding to B-cell marker CD20 resulting in B-cell depletion.[33] It was initially tried in RA with the goal of working as a one-time curative treatment, with both the dosing of rituximab (varying from 1400mg/m^2 to 500mg/m^2, approximately 2100mg and 750mg respectively[2]) and the use of co-medication (most patients also received cyclophosphamide and high dose prednisolone) inspired by the treatment of lymphoma.[34,35] These initial studies showed that, although the effect of an infusion usually lasted for months, the effects did decline over time.[34-36] Notably, a lower dose than 500mg/m^2 (i.e. 750mg) was not attempted in these studies, despite the far lower B-cell load in RA compared to B-cell lymphoma.

Following clinical trials of rituximab used doses of 2x1000mg or 2x500mg per cycle and while both doses showed largely comparable efficacy, rituximab was eventually approved for the treatment of RA in a dose of 2x1000mg with an interval of at least 24

2 Mg/m^2 refers to dosing by body surface area, and the authors initial studies of rituximab appear to have used somewhat inconsistent values and fairly low values of body surface area to convert from mg to mg/m^2 hence the total doses are approximate and on the lower end.

weeks.[33] A later systematic review and meta-analysis showed that high dose (2x1000mg) and low dose (2x500mg or 1x1000mg) were comparably efficacious in many ways.[37,38] Low dose rituximab was non-inferior to high dose in most measures of disease activity, with the exception of the more stringent measures (ACR70, good EULAR response, remission). Furthermore, low dose rituximab did result in significantly higher radiographic progression, though the difference was small and appeared mainly during the first 6 months of treatment: Sharp-van der Heijde Score progression was 0.22 points higher at 6 months and 0.25 points higher at 1 year, compared to a minimum clinically import change of about 6 points per year (MCID varies based on patient characteristics).[39]

Few studies investigated doses lower than low dose (i.e. 1000mg per treatment course), but there are some indications that these 'ultra-low' doses may be effective. Firstly, a small study in healthy volunteers showed that even a dose as low as 1mg/m^2 leads to almost complete, but short-lived, B-cell depletion.[40] Secondly, several case reports have described that doses of 50 to 200mg lead to more durable B-cell depletion and even clinical effectiveness.[41-43] Finally, a small open-label cohort of RA patients treated with 100mg rituximab showed good clinical results at 24 weeks in 15 patients who all achieved good EULAR response, of whom 2 required an additional 500mg of rituximab.[44]

Based on these promising preliminary data on ultra-low doses of rituximab, and the lack of dose finding prior to its use in RA, we designed the REDO trial to assess the efficacy of continued treatment with 200mg and 500mg compared to 1000mg of rituximab in RA patients responding well to previous dose(s) of 1000mg. In this thesis, we describe both the trial design **(Chapter 4),** the original 6 month double-blind randomized controlled trial **(Chapter 5),** and the observational extension phase designed to further clarify the longer term effectiveness of ultra-low dose rituximab **(Chapter 6).**

In doing these studies, one of the outcomes of interest was radiographic joint damage caused by RA. This damage is usually assessed on conventional radiographs of the hand and feet. To measure this joint damage, several scoring systems exist. The gold standard is the Sharp-van der Heijde Score (SHS) which numerically grades the presence and severity of erosions and joint space narrowing of a set of joints of the hand and feet.[45] These joint scores are then summed to calculate the total SHS, ranging from 0 to 448. However, grading according to this method is labor-intensive and therefore expensive. This makes the Simple Erosion and Narrowing Score (SENS), an alternative, simpler scoring system attractive.[46] In this system, the same joints are assessed for erosions and joint space narrowing, but instead of grading they are

simply scored dichotomously as either 1/present or 0/absent. The sum of the joint scores is again the total score, now ranging from 0-86. Previous research showed similar measurement properties of both scores, but warned that the discriminative power may be lower as additional damage to joints with pre-existing damage is not measured.[46-51] However, the relevance of this effect with regards to the statistical power of a trial to show effects on radiographic damage has not been quantified. In **Chapter 7**, we therefore looked at the performance of the SHS and SENS in data from two randomized controlled trials to quantify the loss in power to detect differences in progression of joint damage incurred by using the SENS over the SHS.

Aims and outline of this thesis

Based on the background described above, the aims of this thesis are:

- To assess the long-term cost-effectiveness of disease activity guided dose optimization of TNF-inhibitors adalimumab and etanercept in RA patients with stable low disease activity **(Chapter 2)**
- To determine the efficacy and persistence of switching from tocilizumab to sarilumab in RA patients doing well on tocilizumab (**Chapter 3**)
- To investigate the effectiveness of continued treatment with ultra-low doses of rituximab in RA **(Chapters 4, 5 and 6)**
- To quantify the effect of using the Simple Erosion and Narrowing Score rather than the Sharp-van der Heijde Score on the power of a study to show differences in radiographic progression **(Chapter 7)**

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Chapter 2

Three-year cost-effectiveness analysis of the DRESS study: protocolized tapering is key

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The DRESS (Dose REduction Strategy of Subcutaneous TNF inhibitors) study previously showed clinical non-inferiority and superior cost-effectiveness of disease activity guided tapering of tumour necrosis factor inhibitors (TNFi) (dose reduction, DR group) over full dose continuation (usual care, UC group) in rheumatoid arthritis (RA) patients with low disease activity. [1, 2] Safety and efficacy of this strategy were maintained up to three years with a large reduction in TNFi use. [3] During the extension phase, the majority of the UC group attempted dose reduction. This prevented a valid comparison of disease activity guided tapering to full dose continuation over the entire study period but presented an opportunity to make the following comparisons:

1. Tapering long-term results (in DR group 18-36 months) vs. short-term results (in DR group 0-18 months)
2. Tapering at rheumatologist discretion (in UC group 18-36 months) compared to full dose continuation (in UC group 0-18 months)
3. Tapering at rheumatologist discretion (in UC group 18-36 months) compared to protocolized tapering (in DR group 0-18 months)

We previously reported the main results of the DRESS extension study (Dutch trial register, NTR3216, CMO region Arnhem-Nijmegen, NL37704.091.11), an open label non-inferiority randomised controlled trial in which RA patients with low disease activity on a stable TNFi dose (adalimumab or etanercept) were randomised 2:1 to disease activity guided tapering or full dose continuation. In the first 18 months in the DR group, the TNFi dose was reduced stepwise until flare or TNFi discontinuation. In the extension phase, both groups were treated according to a treat-to-target protocol: tapering was recommended in case of stable low disease activity, at discretion of the rheumatologist in both groups. [1,3] Quality adjusted life years (QALY) were determined by trapezoid method based on the EQ5D-5L measured quality of life. Since medication costs were the main cost drivers in the DRESS study, only medication costs were recorded from 18-36 months. Because comparisons within one group are paired observations, we bootstrapped within-patient differences in QALY and costs instead of group level differences for these comparisons for a more efficient analysis.

Results from 1000 bootstrapped replications concerning mean QALYs and total medication costs for the 3 comparisons are presented in Figure 1 and Table 1. As shown, for the DR group, costs are slightly but non-significantly higher after 18 months (higher in 86.3% of replications) with QALY being equal (lower in 66.2%, higher in 33.8% of replications, 0.007 (95% CI: -0.039 to 0.026) higher QALY for 0-18 months). Tapering at rheumatologist discretion is associated with lower cost (100% of replications) and slightly lower QALY (in 98.5%) compared to full dose continuation, but also with higher cost (in 99.7% of replications) and non-significantly lower QALYs

Table 1: Summary of results for each comparison

Comparison	QALY	Difference in QALY	Medication costs	Difference in medication costs	iNMB
Protocolized tapering 18-36 months vs. Protocolized tapering 0-18 months	1.230 (1.189 to 1.272)	-0.007 (-0.039 to 0.026)	12282 (10775 to 13866)	578€ (-575 to 1732)	-1104€ (-3819 to 1612)
	1.237 (1.207 to 1.268)		11704 (10648 to 12905)		
Unprotocolized tapering 18-36 months vs. Usual care 0-18 months	1.208 (1.152 to 1.272)	-0.047 (-0.092 to -0.005)	15717 (13783 to 17757)	-5941€ (-7764 to -4013)	2151€ (-1507 to 5571)
	1.255 (1.206 to 1.304)		21658 (20085 to 22979)		
Unprotocolized tapering 18-36 months vs. Protocolized tapering 0-18 months	1.208 (1.152 to 1.272)	-0.028 (-0.096 to 0.043)	15717 (13783 to 17757)	4013€ (1676 to 6199)	-6309€ (-12272 to -280)
	1.237 (1.207 to 1.268)		11704 (10648 to 12905)		

Positive QALY or iNMB and negative cost differences favour the group listed first. All figures are presented as mean (95% percentile based confidence interval); QALY: Quality adjusted life years; iNMB: incremental Net Monetary Benefit based on a willingness to pay of €80,000 per QALY. [4]

compared to protocolized tapering (in 80.2%). These results are not explained by differing disease activity at the start of tapering, as DAS28-CRP was higher and the proportion of DAS28-CRP remission was lower in those starting protocolized reduction (2.17 vs 2.01, and 67% vs 71%, respectively). Also, bias due to selective drop-out is unlikely (drop-out <5%).

Figure 1: Cost-effectiveness plane of the 3 comparisons made; QALY: Quality adjusted life years.

In conclusion, cost-effectiveness of protocolized tapering was maintained from 18 to 36 months, although medication costs rose slightly (ns), possibly because a subset of patients returned to a higher dose during follow-up. Tapering at rheumatologist discretion was less cost-saving than protocolized tapering and resulted in higher QALY loss than protocolized tapering, but is still cost-effective compared to full dose continuation.

Disclosures

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Contributors

NvH, AdB, AvdM, WK, FvdH, RvV, NdB, and JB were involved in the study design. NvH, AdB, AvdM, and FvdH were involved in the data collection. NdB and WK performed the data analyses. All authors were involved in writing, revision, and final approval of the manuscript. NdB is the study guarantor.

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Chapter 3

Non-medical switching from tocilizumab to sarilumab in rheumatoid arthritis patients with low disease activity, an observational study

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Abstract

Tocilizumab and sarilumab are IL6-receptor antagonists registered for rheumatoid arthritis, with equal effectiveness and safety. Switching from tocilizumab to sarilumab could be a strategy to reduce injection burden, in case of drug shortages, and to reduce costs.

This study therefore aims to investigate the effectiveness and safety of switching RA patients with well-controlled disease under tocilizumab treatment to sarilumab.

RA patients with low disease activity (DAS28-CRP<2.9 or <3.5 with clinical judgement), on stable dose tocilizumab (>6 months) were offered to switch to sarilumab. Patients who switched and consented were followed for 6 months. Sarilumab was started at 200mg and double the last tocilizumab interval.

Co-primary outcomes at 6 months were 1) the 90% confidence interval (CI) of DAS28-CRP change from baseline compared to the non-inferiority margin of 0.6 and 2) the 90% CI of the proportion of patients persisting with sarilumab, compared to a pre-specified minimum of 70%.

Of 50 invited patients, 25 agreed to switch to sarilumab, and 23 patients switched and were included. One patient was lost to follow up immediately after inclusion, therefore 22 patients are included in analyses.

At 6 months, mean change in DAS28-CRP was 0.48 (90%CI: 0.11 to 0.87), compared to the non-inferiority margin of 0.6. Sarilumab persistence was 68% (90%CI: 51% to 82%, 15 out of 22 patients), compared to the pre-specified minimum of 70%.

Non-medical switching from tocilizumab to sarilumab in patients doing well on tocilizumab failed to show non-inferiority regarding disease activity and drug persistence.

Introduction

Tocilizumab and sarilumab are IL6-receptor antagonists authorized for the treatment of rheumatoid arthritis (RA). Both drugs are anti-IL6-receptor antibodies, with similar safety and efficacy data, although tocilizumab is a humanised anti-body, while sarilumab is fully human. Regarding their safety, two head-to-head studies (ASCERTAIN and Study 1309) showed no clinically meaningful differences in adverse events.[1] Concerning their efficacy, both drugs seem equal, which is confirmed by a systematic literature review and reflected in the EULAR guideline.[2-4]

The question is whether this group-level equivalence of efficacy and safety also translates to the individual level, i.e. can patients expect the same effect after switching from one drug to the other. Data from the ASCERTAIN trial extension showed rarely a loss of response when switching from blinded intravenous (IV) tocilizumab to open label sarilumab.[5] In contrast, the PROSARA study showed that response to sarilumab was similar in patients that were tocilizumab inadequate responders compared to those previously receiving another bDMARD or JAK inhibitor.[6] This suggests that a patients' response to sarilumab may not be strongly correlated to their response to tocilizumab.

Recent shortages of tocilizumab, driven mainly by its use in the treatment of COVID-19, have made the option of non-medical switching to another drug with the same mechanism (i.e. sarilumab) increasingly relevant. Furthermore, the ability to switch to the most cost-effective treatment option within a class of drugs, and the reduced injection frequency of sarilumab (once per 2 weeks instead of weekly) are additional reasons why non-medical switching (i.e. switching for non-clinical reasons) from tocilizumab to sarilumab might be relevant.

This study therefore aims to investigate the effectiveness and safety of switching RA patients with stable well-controlled disease under tocilizumab treatment to sarilumab.

Methods

SAARTOOS (SArilumab Actively Replacing TOcilizumab, an Open label Study) is an open-label, observational single arm study prospectively registered in the Netherlands Trial Register: number NL8174.

RA patients doing well (DAS28-CRP<2.9, or <3.5 with clinical judgement of low disease activity) on a stable dose (>6 months) of tocilizumab were offered a voluntary switch

to sarilumab in clinical care in the Sint Maartenskliniek in the Netherlands between December 2020 and June 2021. Patients were identified through the electronic patient record. Patients who gave written informed consent were followed for 6 months after their switch from tocilizumab to sarilumab.

Sarilumab was prescribed at a dose of 200mg. The sarilumab dosing interval was determined by doubling each patient's last tocilizumab dosing interval, and initiated at the time the next tocilizumab dose would have been administered. All treatment decisions after the initial switch, including changes in the sarilumab interval or stopping sarilumab, were left to the treating physician.

Outcomes

Co-primary outcomes were 1) the 90% confidence interval (CI) of DAS28-CRP change from baseline to month 6 compared to the non-inferiority margin of 0.6 and 2) the 90% CI of the proportion of patients persisting with sarilumab at month 6, compared to a pre-specified minimum persistence of 70% at month 6. The DAS28-CRP is a widely used composite disease activity score consisting of the number of swollen and tender joints from a set of 28, a visual analog scale of patient reported disease activity and the serum C-reactive protein level.[7-9] The non-inferiority margin of 0.6 reflects the measurement error of the DAS28-CRP and is a widely used margin for non-inferiority studies in RA.[10-14]

Secondary outcomes included the CDAI, proportion of patients experiencing DAS28-CRP based flare (and post-hoc the proportion of patients remaining on sarilumab at month 6 without flare), changes in co-medication, baseline expectations of both patient and physician on sarilumab efficacy and tolerability and adverse events (categorized according to Common Toxicity Criteria for Adverse Events version 5.0 (CTC AE v5)).[15] Several pre-planned secondary outcomes (disability as measured by HAQ-DI, anti-drug antibodies and pharmacokinetics) were not collected due to practical issues resulting from the COVID-19 pandemic.

To confirm the attainability of our primary outcomes even in the potential presence of regression to the mean of the DAS28 to higher levels, and regular drug survival attrition, we collected a historical control cohort using the same inclusion criteria. Patients using tocilizumab in the year preceding the start of switching to sarilumab were included, and we collected data on disease activity and tocilizumab persistence after 4-8 months.

Statistical analyses

All analyses were performed in STATA/IC 13.1. Change in DAS28-CRP was analyzed using a one-sample t-test. The Wilson score procedure was used to compute the confidence interval of the proportions of sarilumab persistence at months 3 and 6.[16] Based on an expected DAS28-CRP change of 0 with a standard deviation of 1.0, and an expected SRL persistence of 85%, 55 patients are needed for a power of 80% to reject both co-primary null-hypotheses, with a one-sided alpha of 5%. To compensate for drop-out, we aimed to include at least 58 patients.

Comparisons of change in disease activity and treatment persistence with the historical control group was performed using linear and logistic regression with clustered sandwich estimator to correct standard errors for inclusion of some patients in both cohorts. The risk difference of persistence and tis CI were calculated using the *adjrr* package.[17] *Missing* disease activity measurements were imputed using multiple imputation by chained equation, see Supplementary data S1.

Ethics approval

This study was reviewed and the need for approval was waived by the medical ethics committee (CMO) region Arnhem-Nijmegen (number 2019-5828, October 10th 2019), as it outside the scope of the Medical Research Involving Human Subjects Act due to its observational nature. Informed consent was obtained from all participants prior to inclusion.

Results

Of 50 patients who were offered to switch, 25 agreed to switch to sarilumab, of whom 23 patients switched and were included. 25 patients declined the offer to switch. Reasons to decline switching were: fear of flare (n=7), not willing to switch to subcutaneous administration (n=5), no longer met inclusion criteria (n=4), not willing or able to complete follow up (n=2), currently hospitalized (n=1), and unknown (n=6). Switching (and inclusion) were halted on the advice of the Data Safety Monitoring Board at this point due to frequent flares, an observed increase in disease activity and suboptimal sarilumab persistence. One patient was lost to follow up immediately after inclusion (did not show up to appointments for >6 months), therefore 22 patients are included in analyses (Table 1).

DAS28-CRP increased from baseline to month 6: mean change 0.48 (90% CI: 0.11 to 0.87), compared to the non-inferiority margin of 0.6. 15 of 22 patients remained on sarilumab at month 6, leading to a persistence of 68% (90% CI: 51% to 82%), compared

to the pre-specified minimum of 70%. One patient discontinuing sarilumab after 6 months due to sustained remission was considered to be persistent. Both co-primary outcomes therefore failed to meet their criteria for successful switching.

In the historical control cohort, 31 patients were included. Baseline characteristics were similar, with the exception of a lower proportion of rheumatoid factor or anti-CCP positive patients, a higher proportion of IV tocilizumab use and a longer tocilizumab treatment duration in the control cohort (table 1). The control cohort met non-inferiority criteria regarding both DAS28-CRP change (0.09 (90% CI: -0.33 to 0.50)) and treatment persistence (94% (90% CI: 82%-98%)). In the switching cohort, the increase in DAS28-CRP was 0.39 points higher (90% CI: -0.17 to 0.94) and the persistence 25% lower (90% CI: 9% to 42%)

Table 1: Baseline characteristics

Baseline characteristics	Switching cohort, n=22	Control cohort, n=31
Age, mean (sd)	66 (11)	62 (14)
Female sex, n (%)	17 (77%)	25 (81%)
Rheumatoid factor positive, n (%)	18 (82%)	19 (61%)
Anti-CCP positive, n (%)	18 (82%)	18 (58%)
Erosive disease, n (%)	14 (67%)	14 (45%)
2010 ACR/EULAR classification criteria, n (%)	21 (95%)	27 (87%)
DAS28-CRP, mean (sd)	1.9 (0.6)	1.9 (0.8)
CDAI, median (IQR)	4 (2.5-5.3)	Not recorded
Disease duration, years, median (IQR)	20 (10-24)	16 (7-24)
Duration of tocilizumab use, years, median (IQR)	2.7 (2.1-7.3)	4.0 (1.5-6.0)
Tocilizumab dose, n (%) 162mg per week 162mg per 10 days 162mg per 2 weeks 162mg per 3 weeks 162mg per 4 weeks 8mg/kg per 4 weeks 8mg/kg per 6 weeks 6mg/kg per 4 weeks 4mg/kg per 4 weeks	 10 (45%) 2 (9%) 9 (41%) 1 (5%) 0 0 0 0 0	 9 (29%) 2 (6%) 4 (13%) 2 (6%) 1 (3%) 8 (26%) 2 (6%) 1 (3%) 2 (6%)
Concomittant csDMARD use, n (%)	7 (32%)	9 (29%)
Sarilumab dose, n (%) 200mg per 2 weeks 200mg per 3 weeks 200mg per 4 weeks 200mg per 6 weeks	 10 (45%) 2 (9%) 9 (41%) 1 (5%)	

The DAS28-CRP increase in the intervention group was driven both by objective and subjective components. Median (IQR) CDAI increased from 4 (2.5-5.3) at baseline to 7 (3-10) at month 6. During the study, 8 (36%) patients experienced one or more DAS28-CRP based flares, compared to 5 (16%) in the control cohort. Eleven (50%) patients remained on sarilumab for 6 months without experiencing flare.

Baseline expectations of patients and physicians were positive as neither any patients nor any physicians expected worsening of either disease activity or adverse effects prior to switching. Patient preferences after using sarilumab (n=20, 2 missing) were inconsistent, with 5 (25%) patients preferring tocilizumab, and 5 (25%) patients preferring sarilumab with the remaining 10 (50%) patients reporting no preference.

In terms of (co-)medication, 4 (18%) patients required additional corticosteroids (oral or intramuscular), 5 (23%) patients switched back to tocilizumab and 2 (9%) switched to baricitinib.

Occurrence of adverse events is described by CTC AE v5 category in table 2. Infections were the most common and occurred in 7 (32%) patients, followed by administration site reactions and leucopenia, each in 3 (14%) patients, and planned surgery in 2 (9%) of patients. No other category of adverse event occurred more than once.

Table 2: Adverse events by CTCAE v5 category

Category of adverse event	Number of patients (%)
Any adverse event	17 (77%)
Grade >=2	12 (55%)
Grade >=3	4 (18%)
Infections and infestations	7 (32%)
Administration site conditions	3 (14%)
Investigations	3 (14%)
Surgical and medical procedures	2 (9%)
Other	6 (27%)

Discussion

Non-medical switching from tocilizumab to sarilumab in patients doing well on tocilizumab failed to achieve non-inferiority and instead showed an increase in disease activity and high non-persistence. This finding was contrary to our expectations given the identical mechanism and similar overall efficacy of both drugs and previous ASCERTAIN data but it is not without precedent. The PROSARA study showed that response is similar regardless of whether a patient was a tocilizumab inadequate responder prior to starting sarilumab or had another treatment history.[6] This also suggests that the identical mechanism and group-level efficacy do not have to mean identical efficacy of both drugs for each individual patient.

Strengths of this study include the prospective and pragmatic design that mirrors clinical practice as much as possible. In addition, the co-primary effectiveness and treatment persistence outcomes allowed a stringent evaluation of these main requirements of successful switching. The main limitations of the study are the observational, single-arm design and the limited sample size. The single-arm design was addressed by the inclusion of a historical control cohort which met non-inferiority criteria for both outcomes. This shows that our results were likely caused by the switch to sarilumab, as they are not easily explained by regression to the mean or regular drug survival attrition. These different results are unlikely to be explained by baseline differences between the cohorts, as the groups were comparable with the exception of the proportion using i.v. tocilizumab, which is known to have comparable efficacy to the s.c. administration and therefore this difference is unlikely to affect our outcomes.[18] The limited sample size was the result of our decision to stop recruitment early as a higher than expected rate of flares and sarilumab discontinuation was observed. This decision is likely to bias results toward higher disease activity and sarilumab discontinuation.[19] However, the observed results of our study are different from our pre-defined criteria to such an extent that it seems very unlikely that completing inclusion would have led us to a different conclusion. The lack of blinding in this study may also be considered a limitation by some, as it may have resulted in a nocebo effect. Counter to this hypothesis, patients uniformly had either neutral or positive expectations of sarilumab and voluntarily switched from one active treatment to another, so a strong nocebo effect seems unlikely. This assumption is further strengthened by the fact that disease activity increased both for subjective and objective components of the DAS28-CRP. Furthermore, subjective effects do play an important role in how effective a switching strategy would be in clinical practice,[20] so the open label nature of the study increases its generalizability. A final point for discussion is the use of the DAS28-CRP, which can underestimate disease activity in patients treated with IL-6 inhibitors that suppress CRP production.[21] However, since both tocilizumab and sarilumab are IL-6 inhibitors, we believe this is unlikely to explain the observed increase in disease activity and this is also reflected in the increase in CDAI (which does not include CRP).

In summary, this study fails to show that non-medical switching from tocilizumab to sarilumab is non-inferior, in fact, the switch appears to result in an increase in disease activity and suboptimal sarilumab persistence. Despite the mechanistic similarity of both drugs, they therefore do not appear to be interchangeable at the individual patient level.

Contributors

N.d.B., A.d.B., F.v.d.H., A.v.d.M. and B.v.d.B. designed the research. NdB, AdB, LV, AvdM, and BvdB performed the research. NdB and LV analyzed the data. NdB wrote the manuscript.

Data sharing

The data underlying this article will be shared on reasonable request to the corresponding author.

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Patient and public involvement

A patient partner was involved in the design of this study (the choice of outcome measures, how the switch was conducted in practice, if burden for patients was acceptable) and the preparation of study documents such as the invitation and information letters. They will further be involved in disseminating the results to participants in the form of a newsletter.

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Appendix

Supplementary Data S1: Multiple imputation procedure

An overview of missing values for disease activity scores (DAS28-CRP and CDAI) at months 0 and 6 and the reasons for this are provided in the table below. The reasons for missingness appeared compatible with a missing completely at random or missing at random mechanism and therefore these values were imputed using multiple imputation to increase precision. Missing patient preferences were not imputed due to uncertainty over the mechanism of missingness.

Table S1: Overview of imputed missing values

Variable	N (%) missing	Reason for missingness
DAS28-CRP at baseline	0 (0%)	NA
DAS28-CRP at month 6	1 (5%)	Unable to measure due to COVID restrictions
CDAI at baseline	2 (9%)	VAS physician not requested by researcher
CDAI at month 6	3 (14%)	VAS physician not requested by researcher

Missing values were imputed using STATA/IC 13.1's *mi impute chained* using predictive mean matching. The imputation model included all variables to be imputed and: baseline DAS28-CRP, anti-CCP positivity, rheumatoid factor positivity, sex, and sarilumab persistence at month 6.

20 imputed datasets were generated and the primary outcome of DAS28-CRP change was derived from imputed DAS28-CRP values using *mi passive*. Estimates were pooled using *mi estimate: regress* for DAS28-CRP and *mi estimate: sqreg* for CDAI scores due to its skewed distribution. Results of imputed analyses were very similar to those of complete-case analyses.

Chapter 4

Ultra-low dose of rituximab in rheumatoid arthritis: study protocol for a randomised controlled trial

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Abstract

Background

A standard low dosing schedule of rituximab (2×500mg or 1×1000mg) is as effective for active rheumatoid arthritis (RA) as the registered dose (2×1000 mg). Moreover, several small uncontrolled studies suggest that even lower dosed treatment with rituximab (RTX) also leads to good treatment response in patients with RA. Retreatment with such an 'ultra-low' dose RTX in patients who responded well to RTX induction treatment is of special interest, as long term use of lower RTX doses may lead to shorter infusion duration, lower risk of adverse events and lower costs. However, the effect of ultra-low dose of RTX has not been investigated using a controlled trial of proper design and dimensions.

Methods/Design

REDO is an investigator driven 6-months pragmatic, double-blind, randomised controlled non-inferiority trial on the effects of ultra-low dose RTX (1×500 or 1×200 mg) compared to standard low-dose (1×1000 mg) in RA patients who are being retreated with RTX. N=140 RA patients having reached low disease activity (DAS28CRP<2.9) after the previous RTX infusion and DAS28CRP < 3.5 at moment of retreatment are randomised in a ratio of 1:2:2 to 1×1000 mg, 1×500 mg or 1×200 mg. Primary objective is testing non-inferiority of the ultra-low dose versus standard low-dose RTX, by comparing mean change in DAS28CRP from baseline to six months to the non-inferiority margin of 0.6. Secondary outcomes over the same period are: function, quality of life, safety, costs, and pharmacokinetics and dynamics as process measures.

Discussion

This study protocol shares characteristics of both early dose finding trials as well as late pragmatic clinical studies. Several choices in the design of this trial are described, and possible consequences for RA treatment and expected biosimilar introduction are discussed.

(Dutch Trial Register NTR6117, date November 15, 2016; CMO NL57520.091.16, November 8, 2016)

Background

Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody authorised for use in patients with severe active Rheumatoid Arthritis (RA) in combination with methotrexate (MTX) when patients have an inadequate response or intolerance to other DMARDs, including one or more tumour necrosis factor inhibitors (TNFi). Two large systematic reviews confirmed the effectiveness of RTX in patients with RA in combination with MTX compared to MTX alone. (1;2) In addition, long-term safety has been confirmed up to 11 years, with infection risk comparable to other bDMARDs. (3;4)

The dose finding phase of rituximab has some interesting aspects. Since RTX was originally developed as a treatment for Non-Hodgkin lymphoma, its optimal dose was initially determined for that indication. (5) The first two studies of RTX in RA indeed used treatment protocols based on experience in the treatment of lymphoma. (6;7) Both studies were open-label and consisted of a limited number of patients. It was reasoned that RA could be seen as a low grade lymphoma of synovial tissue, caused by an oligoclonal (instead of monoclonal) proliferation of B cells exhibiting malignant behaviour by destroying local tissues. Using this comparison, patients were treated with a single remission-induction treatment course, identical to that for non-Hodgkin lymphoma, combining 4 weekly rituximab infusions of 750 mg/m2 with prednisone and cyclophosphamide. The treatment goal was to achieve disease remission by eradication of pathogenic B cells. Only adriamycin was omitted as co-medication to decrease the chance on treatment related side toxicity. These two open-label case series showed that a single rituximab based treatment course could induce disease remission in a proportion of patients with RA. Although no formal dose finding efforts were done, Leandro et al. concluded in their uncontrolled study of 22 RA patients that doses below 600 mg/m^2 were less effective, but this conclusion was based on only 4 patients. The first randomised controlled trial to examine the efficacy of RTX in RA patients aimed at obtaining a treatment regimen without cyclophosphamide instead of dose finding, and used a simplified rituximab dosing regimen of 1000 mg on treatment days 1 and 15. (8) This dose is now the registered dose for treatment of RA patients.

Thereafter, dosing schedules of 2×500 mg and 1×1000 mg have been tested in several phase three and four studies, and a recent large systematic review showed that these were non-inferior to regular-dose RTX. Therefore, the current recommended RTX doses are 2×500 mg or 1×1000 mg (standard low–dose RTX) at least every 6 months. The second infusion is commonly given with an interval of 2 weeks (e.g. for 2×1000 mg). (9). Although there have been no high quality strategy studies to establish what is the best retreatment strategy, either fixed 6 month interval retreatment, or disease activity guided treat to target retreatment seem the optimal strategy.

However, even lower doses of RTX may be effective for treatment of RA. In three case studies, ultra-low doses of RTX (1×50 to 2×100mg) were surprisingly associated with deep peripheral B-cell depletion and in general adequate RA disease control. (10-12) Adding to these observations, a recent small, prospective open label study in 14 RA patients showed that a single dose of 100 mg RTX led to peripheral B-cell depletion in 11 patients (79%) after 2 weeks. (13) In that study, mean (± SEM) DAS28 score of all patients decreased from 6.2 ± 0.8 at baseline to 2.9 ± 0.8 at 24 weeks after infusion, although two patients needed additional RTX treatment.

The use of ultra-low dose RTX for retreatment could especially be effective. Firstly, B-cell depletion by RTX can persist during the entire interval between infusions (8;14). It was shown that that lower baseline B-cell counts were associated with complete B-cell depletion following a first 500 mg dose of RTX. (15) This suggests that the (partially) persisting B-cell depletion induced by an earlier infusion could reduce the dose of RTX needed for retreatment infusions.

A final argument for possible effectiveness of ultra-low dose RTX is the fact that similar monoclonal antibodies have been shown to be effective well below the authorised doses for RTX. For ocrelizumab and ofatumumab, two humanized anti-CD20 monoclonal antibodies, it was concluded that doses of 2×200 mg and 2×300 mg respectively provide optimal B-cell depletion as well as the best clinical responses. (16) Although these much lower doses compared to RTX might also be possible due to higher affinity or cytotoxic efficacy of the drug, it lends further credibility to study the efficacy of similar 'ultra-low' doses of RTX.

The use of ultra-low RTX could present several advantages over standard low-dose RTX. Firstly, infection risk should be lower, as RTX use is associated with a dose-dependent – although still low - risk of serious infection. (17;18) Also, shorter infusion duration and less administered drug could lead to less patient burden and perhaps lower risk for infusion reaction. (19) Further, RTX treatment currently is relatively expensive, with costs for low-dose 1×1000 mg every 6 months being between 4000 and 7000 euro per year. Although RTX was proven to be cost-effective in patients with an inadequate response to TNFi (20), use of ultra-low doses will further decrease costs and thereby improve cost-effectiveness. A combination of a possible effective dose of 200 mg every 6 months and expected price reductions due to upcoming availability of a rituximab biosimilar, could result in a bDMARD option availability for under 1000 euro per patient per year.

The use of an ultra-low dose of RTX might however also lead to increased disease activity in the subset of patients whose minimal effective RTX dose is 1000 mg.

Therefore, prediction of response to ultra-low dose RTX would be key to prevent patients from flaring experiencing accelerated joint damage. (21) Interesting baseline (at the moment of considering RTX retreatment) candidates for predicting the chance of good response on an ultra-low dose include higher RTX drug levels, absence of anti-rituximab-antibody levels, and low peripheral B-cell counts, as it might be hypothesised that these are all indicators for lower rituximab need. (22)

In conclusion, although the use of ultra-low doses of RTX seems promising, its' effects have never been studied in a trial of proper design and size. We therefore aim to perform a randomised controlled trial to study whether retreatment with one of two ultra-low RTX doses (1×200 mg or 1×500 mg) is non-inferior to retreatment with the standard low–dose RTX (1×1000 mg) for patients with RA who were already successfully treated with standard low–dose RTX. Also, we will analyse whether there are differences between retreatment with ultra-low dose and standard low-dose in the occurrence of serious and non-serious adverse events and cost-effectiveness, and we will analyse whether (non-)response to (ultra-)low dose of RTX at 6 months can be predicted at moment of initiating retreatment.

Patients and methods

Design

The REDO study (REtreatment with Rituximab in RhEmatoid arthritis: Disease Outcome after Dose Optimisation) is an investigator driven pragmatic, double-blind, non-inferiority randomised controlled study of 6 months duration (figure 1). The trial is funded by two health care insurance companies in the Netherlands, Centraal Ziekenfonds (CZ) and Menzis, and independent from the manufacturer of RTX (Roche). The study is expected to be performed in at least 3 departments of rheumatology of hospitals in the Netherlands: the Sint Maartenskliniek, and Radboud University Medical Centre (Radboudumc) in Nijmegen, and Reade in Amsterdam, the Netherlands. These centres together have approximately 400 RA patients being treated with RTX. Based on an earlier dose tapering trial and similar inclusion criteria, we expect an inclusion percentage of 40%.

RA patients who are scheduled for RTX retreatment with standard low-dose RTX will be randomised into three groups: standard low-dose (1×1000 mg) or one of the two ultra-low dose intervention groups (1×500 mg and 1×200 mg). Treatment response is assessed at 3 and 6 months (study end), and thereafter the allocation of patients will be revealed and treatment may be continued using any ultra-low or standard low-dose of 1x1000 mg, at the discretion of the physician and patient in shared decision making.

This report has been prepared in accordance to the SPIRIT guideline. The final report will follow the CONSORT criteria, including its' extension to non-inferiority trials. The full study protocol is available as supplementary material. There are no publication restrictions, and publication of the final study results will be performed in peer reviewed journals as well as to lay press and patient organisations.

Important protocol changes will be communicated to the Ethics committee and trial register. Privacy of patients will be protected according to Dutch law, WBP ('wet bescherming persoonsgegevens'), by using anonymised data and restricting access to patient identification logs.

Assessment	Months						Unplanned visit
	-1	-0.5	0	0*	3	6	
Patient information	X						
Patient informed consent	X						
Allocation of treatment by stratified randomisation		X					
Baseline characteristics (including radiographs of hand and feet)			X				
Disease activity			X		X	X	X
Functioning			X		X	X	X
Quality of life			X		X	X	X
Adverse events			X	X	X	X	X
Medication use			X		X	X	X
Blood sample			X	X	X	X	
Costs (questionnaire on health related work absence)			X		X	X	

0*: after infusion of study dose RTX;

Figure 1: Visits and assessments

Objectives

The primary objective of the REDO trial is to compare the difference in efficacy between two ultra-low doses (1×200 mg and 1×500 mg) and standard low-dose (1x1000 mg) of RTX retreatment on the change in DAS28-CRP, compared to a pre-specified non-inferiority margin of 0.6 DAS28 points, at 3 and 6 months. So, the study has four primary endpoints. Although we are aware that patients are sometimes treated with longer intervals than 6 months, showing non-inferiority at months six is relevant, for ultra-low RTX dose with at least with 6 months intervals is still a lower cumulative dose as standard low-dose 1000 mg every 9-12 months.

The main secondary objectives are to assess the difference in efficacy between the two ultra-low dose interventions for the same outcomes, to compare the proportion of patients with a DAS28-CRP<2.9 (low disease activity), DAS28-CRP<2.4 (remission) and remission according to Boolean ACR/EULAR criteria at 3 and 6 months follow up, to assess the between group differences in the change in functioning (HAQ-DI) and quality of life (EQ5D-5L), and to compare proportion (cumulative incidence and incidence density) of patients developing (treatment-related) adverse events in each study group over the duration of the study, with special attention to infusion-related adverse events and infections. Furthermore, the cost-effectiveness of both ultra-low RTX doses and the conventional low dose are compared for the 6 months study period. For prediction modelling, baseline factors (including RF/ACPA status, CD19+ B-cell count, serum RTX, serum anti-RTX) will be tested for associations with the outcome of DAS28-CRP low disease activity state at 6 months.

Non-inferiority margin

In non-inferiority trials, the choice for a specific non-inferiority margin (NI margin) is critical for the interpretability of the study. This choice can be based on prior art (use of NI margin in comparable studies), expert opinion, or data driven, based on association with other (un)intended effects. We have found three non-inferiority studies that have used the DAS28 as a primary outcome measure. All three studies have chosen to use a NI margin of 0.6. (23-25) Although no clear explanation is given by the authors regarding the rationale for this NI margin, a non-inferiority margin of 0.6 points in DAS28 seems a reasonable choice, as the error of measurement in DAS28 is 0.6. (26) This error of measurement is used in the EULAR response criteria to denote the difference between a non-response and a moderate response in DAS28.(27) Regarding assay sensitivity, the mean difference between placebo and RTX, added to MTX, in DAS28, is 1.2 according to a recent meta-analysis. (1) This means that the NI margin of 0.6 is sufficiently smaller than the treatment effect of RTX against placebo. We have therefore chosen to use this NI margin of 0.6, although it always remains debatable what an acceptable small NI margin is. This is especially important to

prevent a situation where multiple non-inferiority studies are performed after each other, each using the non-inferior treatment from the last study as a comparator for a new treatment. In this context, although treatment B Is non inferior to A, and C is non inferior to B, treatment C can in fact be inferior to A, the so called biocreep. (28)

Assay sensitivity

Since this is a non-inferiority trial, assay sensitivity – the ability to demonstrate inferiority with the chosen trial design - is an important issue. Assay sensitivity could be established by a placebo arm showing that not retreating with RTX is inferior to retreating with RTX. Considering it has been shown in earlier studies that the mean disease activity of patients will increase when not retreated with RTX (29), it seems unnecessary and unethical to include a placebo arm. Therefore, the comparator is a standard low-dose of RTX, while the group sizes should be large enough to gain a sufficient level of precision (see sample size calculation).

Patients

Inclusion criteria for patients in this pragmatic study are as non-restrictive as possible. This is based on the underlying principle that result of this trial should be generalizable to all RA patients who are doing well on their RTX treatment. We therefore include RA patients fulfilling either 2010 EULAR/ACR RA (30) and/or 1987 RA (31) criteria and/or having a clinical diagnosis of RA according to the treating rheumatologist, at any time point between start of the disease and inclusion.

Patients are eligible if they were treated at least once with regular low-dose RTX treatment in the last 18 months for RA, so in a dose of 1×1000 mg, 2×1000 mg or 2×500 mg, and had received no other bDMARDs after the last RTX dose. Patients treated with innovator RTX (MabThera®) as well as authorised rituximab biosimilars in similar doses as conventional RTX will also be included.

It is somewhat difficult to operationalize the criterion that patients need to be doing well enough on RTX because of the variety of retreatment strategies that are used in clinical practice. We decided on at least 6 months of stable, low disease activity after the last RTX infusion (operationalized by either DAS28-CRP<2.9 / DAS28-ESR <3.2 or judgement of low disease activity by a rheumatologist) and a current DAS28-CRP ≤3.5 / DAS28-ESR ≤3.8. The latter criterion is added, because patients are often not retreated at fixed intervals, but are retreated either based on treat to target, or on demand when disease activity increases. However, we do not want to generalise to patients being treated only when they flare severely, as it has been shown that the optimal strategy for RTX retreatment (although not completely clear yet) is either fixed interval or treat-to-target, but not treated only on demand. Also, a high SD in disease activity at study start would increase the required sample size.

Further inclusion criteria are chosen to ensure that we are able to study the subjects and to measure the outcomes (Patient informed consent, ≥18 years old and mentally competent, life expectancy > 6 months, no planned relocation out of reach of study centre, able to read and communicate well in Dutch)

For generalisability reasons, exclusion criteria are kept minimal, and only exclude patients with known (non-) response to ultra-low dose RTX (below 1×1000 mg), to prevent selection bias, and current corticosteroid dosing above 10 mg per day prednisolone equivalent, because these patients should preferably first taper there corticosteroid.

Patient recruitment

All eligible patients will be selected and approached based on information from the electronic health record according to the above-mentioned inclusion and exclusion criteria. Patients will be asked to join this study by their treating rheumatologist using a letter accompanied by the patient information (including the informed consent form). Informed consent is obtained before patients receive the study medication and baseline data are collected.

Randomization and blinding

Participants will be allocated to the treatment groups at a ratio of 1:2:2 (1×1000 mg versus 1×500 mg versus 1×200 mg). The experimental groups are larger than the control group to increase experience with the lower dosing, and with the additional benefit that a larger number of potential predictive factors for response can be studies in multivariate prediction modelling in the ultra-low dose RTX groups.

Randomisation will be performed using a computerized randomisation procedure, and stratified to ensure equal distributions of two possible effect modifiers for response to ultra-low dose RTX, concomitant conventional DMARD use and RF/ACPA status. Patients will be randomised using block randomisation in variable block sizes (multiples of 5) to more closely achieve the intended allocation ratio and to ensure that the allocation of participants will not be predictable. Patients, physicians, nurses and researchers, and data analyst/staticisian will be blinded for treatment allocation. The allocation is kept in opaque sequentially numbered envelopes, and envelopes are sequentially assigned by the pharmacist to each next patient. The infusions for the study will be prepared by the hospital pharmacy based on the randomisation number, the physical appearance of the three interventions will be indiscriminate (see below). Unblinding is expected to be rarely necessary (all patients receive RTX, and retreatment with 1000 mg is allowed when necessary), but is possible after consulting the coordinating centers pharmacist.

Interventions

Patients allocated to the standard low-dose group will receive a (blinded) single 1000 mg RTX infusion according to the standard protocol for infusion of rituximab. Patients allocated to the ultra-low dose groups will receive 500 mg or 200 mg. This dose will be diluted to the same volume as the standard low-dose infusion to ensure the blinding of the study, all premedication and procedures are identical to the standard low-dose. Of note, the possible advantage of shorter infusion times cannot be assessed in our study, because this would lead to patients and health care providers being unblinded.

It is aimed to leave all other rheumatic treatment unaltered as much as possible during the study period. However, all treatment decisions are left to the discretion of the treating physician, and (changes in) use of paracetamol (acetaminophen), tramadol, NSAIDs, oral corticosteroids, and DMARDs are all allowed during this study to ensure good care. During each visit, patients are asked about use of these medications. Suggested treatment in case of clear loss of response is escape treatment with an extra dose of 1x1000 mg RTX. This can be done without unblinding, since the authorised dose of RTX is 2x1000 mg per 6 months and no patients will exceed this dose as the maximum study dose is 1x1000 mg.

We have determined several medication changes that are defined as 'treatment failure'. These changes are: receiving an extra dose of RTX within the 6 months study period, receiving another bDMARD (thus switching to another type of bDMARD), and using corticosteroids in a dose > 10mg/day. Starting a concomitant conventional synthetic (cs)DMARD during the study period is not considered a treatment failure. Reasoning behind this is the fact that all included patients will have received these csDMARDs before with little effect on their RA, and the concomitant csDMARD is generally given as an adjuvant to increase the effectiveness of RTX.

In case of treatment failure, the patients will remain in the study, but the last measure of disease activity and other outcomes will be used as outcome employing a 'last observation carried forward' strategy.

Assessments

At baseline, several characteristics of the patients will be measured, including demographics, disease and treatment characteristics. Also, possible predictors for response to ultra-low dose RTX from peripheral blood will be collected, including (anti-)RTX drug levels and peripheral CD19 counts. Thereafter visits will be performed at 3 and 6 months, and when necessary in between (figure 1).

Several measures on disease activity will be collected during the study. The DAS28-CRP is a validated and widely accepted measure for RA disease activity and will be used as primary outcome measure. It consists of four components: 28 tender joint count, 28 swollen joint count, CRP (mg/L) and patients VAS assessment of global disease activity (0-100).(26) Remission is defined as DAS28-CRP <2.4 and low disease activity by DAS28-CRP <2.9. (32) In addition, patient VAS assessment of pain, rheumatologist VAS assessment of global disease activity, acute phase reactants (CRP and ESR), and the OMERACT patient flare questionnaire are collected. To measure functioning of patients, the HAQ-DI, a validated instrument that is widely used in rheumatology is applied. (33) Quality of life is assessed using EQ5D-5L, which is a validated instrument and comprises five questions and a visual analogue self-rating scale. (34)

Adverse events are assessed at every visit during the study period, and classified according to the Common Toxicity Criteria (CTC). (35) In addition, we focus explicitly on infusion reactions and infectious events. Patients are asked to complete a short questionnaire after the RTX infusion on the occurrence of infusion-related adverse events. Medication use is charted using data from the electronic patient records on the use of DMARDs, corticosteroids, and NSAIDs.

Costs will be calculated from a societal perspective. We will include cost of outpatients' clinic visits and telephone consultations, travel expenses for patients, costs of hospitalization due to RA, costs due to health-related work absence and costs of medication during the 6-month study period.

Sample size considerations and statistical analyses

The study has four primary endpoints, and multiplicity over the primary endpoints will be protected by a fixed testing procedure: First the non-inferiority of the 500mg versus 1000mg at 3 months will be tested at $p<0.05$ (two-sided). If this is statistically significant, then 500mg vs 1000mg will be tested at $p<0.05$ (two-sided) at 6 months. If that is statistical significant, then 200mg vs 1000mg will be tested at $p<0.05$ (two-sided) at 3 months and if that is statistically significant, the last test will be 200mg vs 1000mg at $p<0.05$ (two-sided) at 6 months. As we have 4 primary endpoints, we aim at having sufficient power for each at 95% for an NI margin of $\delta = 0.6$. Under the worst-case scenario that these four are not correlated (the expectation is that they are positively correlated, see table 1) and that the intervention is indeed non inferior to the control condition, then the overall power for rejecting the null hypothesis of inferiority on all four is at least $95\% \times 95\% \times 95\% \times 95\% = 81\%$. We calculated the sample size for one endpoint (e.g. the comparison of 500 vs 1000 mg at 6 months). For 2:1 randomization and a non-inferiority test assuming the true difference between treatments is 0, the total sample size for a t-test having a power

1-β when testing at significance level α (two-sided) and a non-inferiority margin δ is Ntot = $(4.5)^2 \times (z_{1-\alpha/2} + z_{1-\beta})^2 \times SD^2/\delta^2$, where z denotes the normal quantiles which are correct for non-small sample sizes. When correction for baseline is incorporated this sample size is reduced by $(1-r^2)$ where r is the correlation in DAS28 between baseline and follow up (formula 7 with n=1, π_0=1/3, π_1=2/3, and section 2.3 of Teerenstra S, et al. 2012). (36) Note that the two groups then have sizes Ntot/3 and 2×Ntot/3. To determine the correlation r between baseline and follow up measurement of the DAS28, the following assumptions were used. Baseline DAS28 has a SD=0.7 and the change from baseline to 3 (or 6 months) has a standard deviation of SDchange = 0.6 based on data from an earlier dose reduction trial. (37) As $SD^2change = 2 \times (1-r) \times SD^2$, it follows that r = 0.63. Then a total trial size of 80 subjects would be sufficient. Table 1 illustrates the total trial size when the correlation between endpoints is smaller than anticipated.

Table 1: Total trial sample size at various correlations between endpoints

SDchange	r	Sample size 1000 mg arm	Total trial size (5 x sample size in 1000 mg arm)
0.9	0.17	26	130
0.8	0.35	24	120
0.7	0.5	20	100
0.6	0.63	16	80

To protect for a too optimistic correlation, we therefore choose a total trial size of 130, and this is further increased to 140 patients to account for patient drop out.

Primary analyses will be done per protocol (PP), as this is the most conservative approach for a non-inferiority study. In addition, analyses will be performed on intention to treat basis (ITT). For PP analysis, we will include patients who have received the study medication and completed follow up of 6 months or until treatment failure (and last observation of disease activity carried forward).

The primary endpoints will be tested using 95% confidence intervals based on linear regression with the change in DAS28-CRP as outcome, dose group as determinant, and baseline values of DAS28-CRP as covariate (ANCOVA).

To find predictors (including age, sex, disease duration, RF/ACPA status, CD19+ B-cell count, serum RTX, serum anti-RTX), patients will be categorized into responders (DAS28-CRP < 2.9 at 6 months and no treatment failure) and non-responders (all other patients). The absolute number (and thus also proportion) of responders will determine the number of predictors that is admissible for analysis, according to the rule of 10-events-per-variable given that predictors are predetermined. Univariate logistic regression analysis will be performed for the admissible predictive factors, with a deliberately liberal p<0.20 as selection criterion. Univariately significant variables are entered in a full multivariate logistic regression model, that is step-wise reduced until all p<0.20. Internal validation and shrinkage will be performed using a bootstrapping procedure with 1000 repetitions. Performance of the multivariate predictive model will be evaluated using discrimination (area under the receiver operator curve) and calibration (calibration slope, calibration plot and Hosmer-Lemeshow test).

Costs will be calculated and quality adjusted life years (QALY) will be based on EuroQol-EQ5D-5L utility scores. Decremental cost-effectiveness analyses (CEA) will be performed using bootstrap analyses; incremental net monetary benefit (iNMB) will be used to express cost-effectiveness at different Willingness-to-Pay (WTP) values ranging from 20,000 to 80,000 euro/QALY.

Discussion

This study in summary is aimed at exploring the lower bound of effective RTX doses in RA, as there seems at least equipoise on whether ultra-low dose RTX is effective in RA. The development of the current study protocol has some interesting aspects that should be discussed.

Because proper phase I/II dose finding has not been done in RA for RTX in the development phase, and because RTX is already widely used in RA treatment, our study design shares some characteristics of both early dose finding trials (small/medium sized blinded trial, medium follow-up, multiple dosing arms), as well as late pragmatic clinical studies (non-inferiority design, wide inclusion criteria, investigator driven, treat-to-target strategy, embedded in clinical practice, cost effectiveness analyses). The lack of proper dose finding may be caused by the fact that RTX was first developed for use in lymphoma. This means that the upper limit of toxicity was already known. Also there was presumably less incentive for the pharmaceutical company to actively look for (much) lower effective RA dosing, as very different dosing schedules for between different diseases presents a problem when establishing drug prices. RTX was therefore eventually authorised in the same high dose for the treatment of RA. Indeed, due to the complex field of anti-cell or cytokine treatment - which is more pathophysiology than disease specific and might be very

different in dosing across diseases - we expect this hybrid approach of post marketing investigator driven dose finding studies to be used more often in the near future.

Of note, our trial design precludes inference of the value of long-term repeated treatment strategies with ultra-low dose RTX. For example, lower dosing might lead to shorter infusion intervals, or ultra-low dose may not be effective enough after multiple retreatments. However, we believe that showing non-inferiority at 6 months would be a valuable step forward to further study an ultra-low dose RTX retreatment strategy. Also, it will remain to be established whether inhibition of radiographic progression is not compromised using ultra-low dose RTX.

In the specific case of ultra-low RTX dosing, some interesting developments might make the results of this study perhaps even more relevant. Recently, RTX – registered only after TNFi failure – has been shown to be similar in efficacy to TNFi in bDMARD naïve patients. (27) Also, biosimilar RTX is expected to be available starting early 2017, at least in Europe. These two developments might make RTX as a first bDMARD a very realistic alternative. A promise of effective ultra-low dose retreatment would further support this more prominent position of RTX in RA treatment.

Declarations

Ethical approval and Trial registration

Dutch Trial Register, NTR 6117, date November 15, 2016. The study has received ethical review board approval (number NL57520.091.16), date November 8, 2016.

Ethical approval was obtained for all participating centres from the central Commissie Mensgebonden Onderzoek (committee of human research) CMO regio Arnhem Nijmegen, Radboud University Medical Center, PO Box 9101, 6500 HB, Nijmegen, The Netherlands.

Consent to participate

The protocol as outlined here was approved by the central medical ethical committee for all participating centres (CMO Arnhem-Nijmegen, NL57520.091.16) in 2016. The Trial is registered at NTR6117.

Availability of data and material

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

Alfons A den Broeder: congress invitations with Roche, Abbvie, Biogen, Celltrion, expert witness for Amgen and BI. Lise M Verhoef: The author declares having no competing interests. Jaap Fransen: The author declares having no competing interests Rogier Thurlings: Translational RTX research sponsored by Roche, congress invitations from Abbvie, Roche. Bart JF van den Bemt: Speakers fee from Abbvie, Pfizer, Mundipharma, Astra, MSD. Research grant from Pfizer, Abbvie. Steeven Teerenstra: The author declares having no competing interests. Nadine Boers: The author declares having no competing interests. Nathan den Broeder: The author declares having no competing interests Frank HJ van den Hoogen: advisory board member mundipharma on RTX biosimilar, congress invitation Cellgene, international advisory board Biogen etanercept biosimilar, speakers fee biosimilars Celltrion and Egis and Janssen.

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The department of rheumatology Sint Maartenskliniek takes up the role as sponsor, and is the coordinating studycenter. An independent data safety and monitoring board will be installed.

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Chapter 5

Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial

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Abstract

Background

Rituximab is an effective treatment for rheumatoid arthritis, given as either two doses of 1000 mg (2 weeks apart) every 6 months (the dose recommended by the US Food and Drug Administration and European Medicines Agency) or two doses of 500 mg (2 weeks apart) or one dose of 1000 mg (a standard low dose) every 6 months. Findings of several small uncontrolled studies suggest that doses lower than the recommended dose or standard low dose might be sufficient for maintenance treatment, potentially improving safety and reducing costs. Therefore, we aimed to compare the efficacy of ultra-low doses of rituximab (one dose of 500 mg or 200 mg) with a standard low dose of rituximab (one dose of 1000 mg) for patients with rheumatoid arthritis who respond to standard doses of rituximab.

Methods

The REDO study is a randomised, double-blind, non-inferiority trial done at five centres in the Netherlands. Adults (aged ≥18 years) with rheumatoid arthritis responding well to rituximab were randomly allocated (1:2:2) to receive intravenous rituximab as one dose of either 1000 mg, 500 mg, or 200 mg, respectively. Volumes of all doses were equal to achieve masking. Randomisation lists were computer-generated and stratified by rheumatoid factor or anti-citrullinated protein antibody status (positive or negative) and concomitant use of conventional synthetic disease modifying antirheumatic drugs (yes or no). The primary analysis was a per-protocol hierarchical testing procedure comparing ultra-low doses with a standard low dose (500 mg vs 1000 mg at 3 months, followed by 500 mg vs 1000 mg at 6 months, 200 mg vs 1000 mg at 3 months, and 200 mg vs 1000 mg at 6 months), using a non-inferiority margin of 0·60 on change from baseline in the 28-joint disease activity score based on C-reactive protein levels (DAS28-CRP). The study is registered at www.trialregister.nl, NTR6117.

Findings

Between Dec 15, 2016, and Sept 20, 2018, 142 patients were randomly allocated to either 1000 mg rituximab (n=29), 500 mg rituximab (n=58), or 200 mg rituximab (n=55). The 500 mg dose was non-inferior to 1000 mg at 3 months (mean change from baseline in DAS28-CRP, −0·07, 95% CI −0·41 to 0·27) but not at 6 months (0·29, −0·08 to 0·65). Because of the hierarchical testing procedure, non-inferiority could not be tested for the 200 mg dose. 13 patients had serious adverse events, three (10%) in the 1000 mg group, six (10%) in the 500 mg group, and four (7%) in the 200 mg group. The most frequently reported serious adverse events were cardiovascular.

No deaths occurred during the study. A significantly lower incidence of infections was seen in the ultra-low-dose groups compared with the standard dose group (1·10 infections per patient-year with the 1000 mg dose vs 0·52 per patient-year with the 500 mg dose and 0·51 per patient-year with the 200 mg dose; rate ratio 0·47, 95% CI 0·23–0·95; p=0·013 for 500 mg vs 1000 mg; 0·46, 0·23–0·95; p=0·019 for 200 mg vs 1000 mg).

Interpretation

Our study did not show non-inferiority of ultra-low doses of rituximab for continued treatment of patients with rheumatoid arthritis. Nonetheless, in clinical practice, a strategy with an ultra-low dose of rituximab might be considered after evaluation of risks and benefits, although further studies are needed to establish non-inferiority. Further analyses and a 2-year observational extension are ongoing and should provide further insight into efficacy and safety.

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Introduction

Rheumatoid arthritis is a chronic autoimmune disease affecting 0·5-1·0% of the population in Europe and North America.[1] Current guidelines for rheumatoid arthritis recommend treatment with biological disease-modifying antirheumatic drugs (DMARDs) if the response to conventional synthetic DMARDs is insufficient.[2,3] Furthermore, rheumatoid arthritis treatment should follow the treat-to-target principle (ie, setting a treatment goal, measuring disease activity, and changing treatment if the treatment target is not reached) since this approach leads to the best outcomes.[4] Because many available pharmacological treatment options for rheumatoid arthritis are costly, a major challenge is to ensure that treatment remains affordable and accessible. Several studies have shown that dose-reduction of biological DMARDs, after patients have reached their treatment goal of low disease activity or remission is effective and safe.[5] As a result, the risk of side-effects (mainly infections)[6] and the practical burden for patients can be minimised and substantial cost-savings can be realised.[7]

Rituximab, a biological DMARD targeting CD20 on B cells, improves the symptoms of patients with rheumatoid arthritis and can prevent disease progression.[8] Rituximab was originally developed as a treatment for non-Hodgkin's lymphoma, and the dose for patients with rheumatoid arthritis was derived from this indication.[9] The US Food and Drug Administration and European Medicines Agency recommend two doses of

1000 mg rituximab (2 weeks apart) every 6 months,[10] and this dosing scheme was used in the first randomised controlled trial in patients with rheumatoid arthritis.[11] However, findings of a systematic review showed that low-dose rituximab (two doses of 500 mg 2 weeks apart or one dose of 1000 mg every 6 months) was as effective as the higher dose.[12] Both doses are currently used in clinical practice.[13]

In three case reports and a small observational open label study, much lower doses of rituximab (50–200 mg) led to complete peripheral B-cell depletion and, in several cases, adequate disease control was achieved in rituximab naive patients.[14–17] In view of these results, we postulated that a lower dose of rituximab would be needed for continued treatment compared with initial rituximab doses because of a lower B-cell load.[18] Use of very low doses of rituximab for continued treatment of rheumatoid arthritis has not been studied in a well-designed randomised controlled trial of adequate size. Therefore, we aimed to assess the difference in efficacy between two ultra-low doses of rituximab (500 mg and 200 mg) and a standard low dose (1000 mg) of rituximab in patients with rheumatoid arthritis responding well to standard doses of rituximab.

Methods

Study design and participants

The REDO study is a double-blind, randomized controlled, non-inferiority trial done at five centres in the Netherlands (appendix p1). The study rationale and design have been described elsewhere[19] and are summarised here. We chose a non-inferiority design to assess whether ultra-low doses of rituximab are non-inferior to standard low-dose treatment. A placebo group to show assay sensitivity was deemed unnecessary and unethical, because data regarding on-demand treatment (in case of flare) of rituximab users, and evidence from discontinuation of anti-tumour necrosis factor agents,[5] show that not continuing treatment of patients with rheumatoid arthritis will lead to inferior outcomes.

We recruited adults (aged ≥18 years) who had a diagnosis of rheumatoid arthritis (according to 1987 or 2010 American College of Rheumatology [ACR] criteria, or by clinical diagnosis from a treating rheumatologist), who were current users of rituximab (innovator or biosimilar), and had responded to treatment with at least 6 months of stable low disease activity after the last rituximab infusion (ascertained by a 28-joint disease activity score based on C-reactive protein [DAS28-CRP] <2·90, or a judgment of low disease activity by a rheumatologist) and a DAS28-CRP of 3·50 or less at screening. Rituximab use was operationalised as at least one cycle of rituximab in the past 18 months (either one dose of 1000 mg, two doses of 500 mg, or two doses of 1000 mg, as monotherapy or combined with methotrexate or another conventional synthetic DMARD) and no other biological DMARD during this period. No maximum duration of rituximab use was defined. We excluded individuals with a known response or non-response to ultra-low-dose rituximab (<1000 mg per treatment cycle) or who were receiving corticosteroids in a dose greater than 10 mg/day prednisolone equivalent. All participants provided written informed consent.

The trial was done in accordance with Good Clinical Practice guidelines of the International Conference on Harmonization and the principles of the Declaration of Helsinki. The study was approved by the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen and the competent authority [CCMO], NL57520.091.16). A data safety monitoring board (DSMB) consisting of a rheumatologist and an internal specialist who were independent of the study looked at recruitment, efficacy (mean DAS28-CRP), number of flares, medication increases, and adverse events and serious adverse events per group; this information was provided in a report prepared by the coordinating researcher. The DSMB could decide to terminate the trial prematurely based on safety signals or new evidence resulting in the trial being redundant. Meetings of the DSMB were held once every 3 months. No interim analyses were done.

Randomisation and masking

Participants were allocated in a ratio of 1:2:2 to one intravenous dose of either 1000 mg, 500 mg, or 200 mg rituximab, using blocks of five or ten. Allocation was stratified by rheumatoid factor or anti-citrullinated protein antibody (ACPA) status (positive or negative) and concomitant conventional synth etic DMARD use (yes or no). Randomisation sequences were generated online by a senior researcher at Sint Maartenskliniek (BJFvdB). Randomisation lists were kept in pharmacies at every participating centre, at which study drugs were also prepared. The randomisation sequence was concealed before allocation and during the study; individual allocations were kept secret by the pharmacy. Patients and all people involved in treatment of patients and assessment of outcomes (researchers and care providers) were unaware of the random assignments during the study period. The physical appearance of the three interventions was identical (same volume and colour). Allocation was revealed to every patient (and relevant study staff) by the treating rheumatologist after the last study measurement (at 6 months).

Procedures

Patients received their allocated dose of rituximab (1000 mg, 500 mg, or 200 mg), along with any usual co-medication (appendix p1), by infusion at study start (baseline

visit). Apart from the study dose, treatment and measurements were the same for all participants. Follow-up visits with a nurse or a rheumatologist or clinician's assistant were planned at 3 months and 6 months after baseline. In case of an increase in disease activity, patients were encouraged to contact the hospital to plan an extra visit in which disease activity could be measured, following the treat-to-target principle. Treat ment decisions were at the discretion of the treating rheumatologist, but treatment advice was provided by the study team. We aimed to keep all antirheumatic drugs constant during the study period. In case of a disease flare, we advised to start with glucocorticoid bridging (mostly intramuscular methyl-prednisolone 120 mg). If this drug had insufficient effect, open-label rituximab (1000 mg) could be given intravenously.

Several changes to antirheumatic drug use were defined as treatment failure: receiving an extra 1000 mg dose of rituximab within the 6-month study period; switching to another type of biological DMARD; and using oral corticosteroids at a dose greater than 10 mg/day. In case of treatment failure, the participant remained in the study but the last measure of disease activity was used as the outcome, using a last-observation-carried-forward (LOCF) strategy.

At the baseline visit, we obtained data for demographics, disease and treatment characteristics, joint damage, and expectations of participants and rheumatologists about the efficacy of a low dose of rituximab. Joint damage (erosion and joint space narrowing) was assessed by radiography of hands and feet using the short erosion narrowing score (SENS),[20] which is a simplification of the Sharp/van der Heijde score (SHS). SENS was chosen as a less time-consuming scoring method, with measurement properties comparable with the SHS. SENS scores range from 0 to 86, with a higher score indicating more damage. Disease activity was measured at baseline and at the 3-month and 6-month follow-up visits by DAS28-CRP;[21] scores on DAS28-CRP range from 0·96 to 10, with higher scores indicating greater disease activity. Low disease activity was defined as DAS28-CRP of 2·90 or less, and remission as DAS28-CRP of less than 2·40. Remission was further defined by European League Against Rheumatism (EULAR) Boolean criteria,[22] which comprise a tender joint count of one or less, a swollen joint count of one or less, CRP of 1 mg/dL or lower, and a patient global assessment of 1 or lower (scores on this global assessment range from 0 to 10). Another definition for remission used index-based EULAR criteria (simplified disease activity index [SDAI] ≤3·3).[22] Function was measured at the baseline visit and at the 3-month and 6-month follow up visits using the health assessment questionnaire disability index (HAQ-DI);[23] scores range from 0 to 3, with higher scores indicating greater disability. Quality of life was measured at baseline and at 3 months and 6 months using the EuroQol five dimension scale with five levels (EQ5D-5L);[24] scores

range from 0 to 1, with higher scores indicating better quality of life. Anti rheumatic drug use and adverse events were recorded at the 3-month and 6-month follow-up visits. Adverse events and serious adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0 by the study team. We also asked participants to complete a questionnaire on infusion-related reactions 2 weeks after infusion of the assigned study drug. At baseline and 3-month and 6-month follow-up visits, we measured the number of peripheral CD19+ B cells using a flow cytometric immune-assay (appendix p1). Disease flare was assessed throughout the follow-up period and was defined as an increase from baseline in DAS28-CRP of more than 1·20, or an increase from baseline in DAS28-CRP of more than 0·60 plus DAS28-CRP at 6 months of 2·90 or higher.[25]

Outcomes

The primary outcome was change from baseline in disease activity, which was measured by DAS28-CRP at 3 months and 6 months. Secondary outcomes at 3 months and 6 months were remission (measured by DAS28-CRP and EULAR Boolean and index-based criteria), low disease activity (measured by DAS28-CRP), function (measured by HAQ-DI), quality of life (measured by EQ5D-5L), and peripheral CD19+ B-cell count. Other prespecified secondary outcomes were use of antirheumatic drugs, occurrence of disease flares, and adverse events.

Statistical analysis

Statistical analyses were done by LMV, NdB, and AAdB. The study team received advice from an independent statistician (Radboudumc, Nijmegen, Netherlands) during protocol development and data analysis. The sample size calculation for this trial has been described previously (appendix pp 1, 2).[19] We aimed to have 95% power for each of the four hierarchical primary endpoints, to maintain overall power of 81% ($0{\cdot}95^4$). We made conservative assumptions of an SD of DAS28-CRP change of 0·9, and a correlation r between baseline and follow-up measurements of 0·17; we assumed that the four endpoints were not correlated. When incorporating an extra ten patients to account for dropouts, the sample size calculation gave a total sample size of 140 patients for this trial.

To compare the 1000 mg, 500 mg, and 200 mg dosing groups at the 3-month and 6-month timepoints, we had four hierarchical primary endpoints measured as the change in DAS28-CRP from baseline. Multiplicity over the primary endpoints was protected by a fixed hierarchical testing procedure in which the next step could be taken only if the previous showed a significant result. These endpoints were tested (one-sided α=0·025) using linear regression, with the change in DAS28-CRP as outcome, dose group as determinant, and baseline values of DAS28-CRP as covariate.

Furthermore, this regression was corrected for our randomisation strata (rheumatoid factor or ACPA positivity, and concomitant DMARD use). A non-inferiority margin of 0·60 was chosen based on findings of previous trials[26,27] and because 0·60 marks the measurement error of the DAS28-CRP and the difference between EULAR non-response and moderate response.[28] The first hierarchical testing step was to test non-inferiority of the 500 mg versus 1000 mg dose at 3 months. The second step was to test 500 mg versus 1000 mg at 6 months. The third and fourth steps were to test the 200 mg dose at 3 months and 6 months, respectively, against the 1000 mg dose. Primary analyses were done per protocol. Analyses were also done by intention-to-treat principles, to assess the strategy aspect of the study. For the per-protocol analysis, we included patients who had received study medication and completed follow up of 6 months, or until treatment failure (with disease activity LOCF).

Differences in secondary outcomes between study groups were assessed by intention-to-treat principles at 3 months and 6 months, using the χ^2 test (dichotomous variables), by univariate regression analysis (continuous variables with a normal distribution), or with the Kruskal Wallis test (continuous variables without a normal distribution). Safety outcomes were compared by intention-to-treat principles between study groups by Poisson regression (incidence densities) or the χ^2 test (cumulative incidences). No correction for type I error was done.

Data were gathered using paper case report forms or by registration in the participant's electronic health record. All study data were subsequently entered in an electronic data capture database (Castor EDC, Amsterdam, Netherlands) and exported to Stata (version 13.1) for statistical analyses.

This study is registered in the Dutch trial register (trialregister.nl), NTR6117.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 15, 2016, and Sept 20, 2018, 679 individuals with rheumatoid arthritis who were using rituximab were screened for inclusion in the study. 340 (50%) people did not meet criteria for inclusion, mainly because of an insufficient response after the last rituximab infusion. A further 196 (29%) individuals did not want to participate, mostly because they feared the risk of a potential flare in disease activity. Thus, 143 patients were randomised in the REDO study and received the allocated medication. However, one participant was subsequently found not to have fulfilled inclusion criteria because of high disease activity and this participant was retrospectively excluded. Of 142 correctly randomised individuals, 29 were allocated to 1000 mg rituximab (control group), 58 were allocated to 500 mg rituximab, and 55 were allocated to 200 mg rituximab (figure 1).

Of 55 participants allocated 200 mg rituximab, one individual was lost to follow-up because of a serious adverse event (acute coronary syndrome). Treatment failure occurred in five people, of whom four (two assigned 500 mg rituximab and two assigned 200 mg rituximab) received extra rituximab because of disease flare (LOCF was applied for the primary per-protocol analysis) and one (assigned 1000 mg rituximab) received high-dose glucocorticoids for immune thrombocytopenia. This individual was excluded from the per-protocol analysis because no useful efficacy measurements were available. Thus, 142 patients were included in the intention-to-treat population and safety population and 140 individuals were included in the per-protocol population. Two cases of protocol violation occurred, in which patients received their regular infusion of rituximab a few days before the 6-month visit because of a logistical error. These patients were included in the analyses without LOCF because the early infusion was not expected to have an effect on disease activity at the 6-month measurement. Baseline demographic and disease characteristics of the per-protocol population are shown in table 1, and baseline characteristics of the intention-to-treat population are shown in the appendix (pp 3, 4).

At 3 months, 500 mg rituximab was non-inferior to 1000 mg rituximab with respect to mean change in DAS28-CRP from baseline (–0·07, 95% CI –0·41 to 0·27; figure 2). At 6 months, for 500 mg rituximab compared with 1000 mg rituximab, the 95% CI crossed the non-inferiority margin of 0·60, so non-inferiority could not be established (0·29, 95% CI –0·08 to 0·65). The per-protocol analysis suggested that 200 mg rituximab was non-inferior compared with 1000 mg rituximab at both timepoints, but because of the predefined hierarchical test procedure this conclusion cannot be formally drawn. Intention-to-treat analyses showed both 500 mg rituximab and 200 mg rituximab were non-inferior to 1000 mg rituximab after 3 months and 6 months

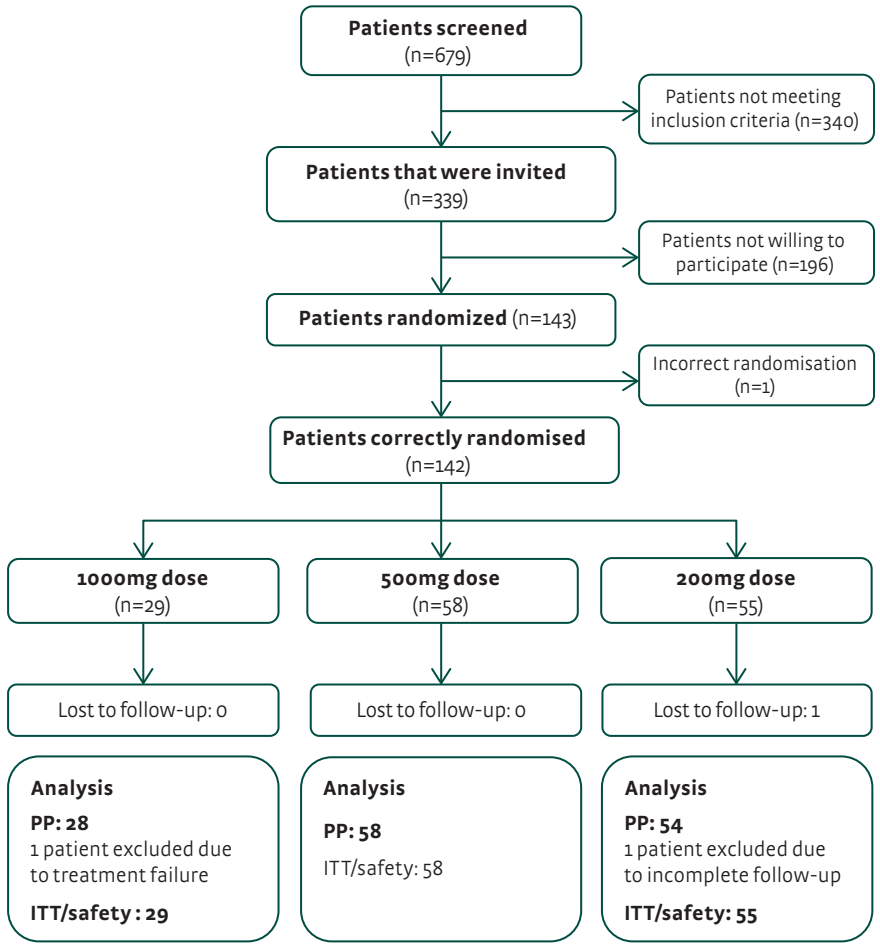

Figure 1: Trial profile

(figure 2). Findings of the primary analysis by stratification factor are shown in the appendix (p5).

Mean DAS28-CRP scores remained below the threshold for low disease activity (DAS28-CRP ≤2·90) for all groups during the study period (figure 3). Analysis of peripheral CD19+ B-cell numbers showed clear B-cell depletion for all three groups after 3 months of follow-up (table 2). No differences were seen between groups in the proportion of patients who achieved remission by EULAR Boolean or index-based criteria, or remission or low disease activity based on DAS28-CRP. Moreover, the number

Table 1: Baseline demographic and disease characteristics (per-protocol population)

	1000 mg rituximab (n=28)	500 mg rituximab (n=58)	200 mg rituximab (n=54)
Age (years)	65 (59–70)	65 (58–72)	67 (56–75)
Female sex	17 (61%)	37 (64%)	40 (74%)
Male sex	11 (39%)	21 (36%)	14 (26%)
Clinical diagnosis of rheumatoid arthritis (by ACR 1987 or ACR and EULAR 2010 criteria)	26 (93%)	57 (98%)	51 (94%)
Duration of rheumatoid arthritis (years)	16·9 (11·3)	14·9 (10·7)	13·6 (7·3)
Rheumatoid factor or ACPA positive	26 (93%)	54 (93%)	48 (89%)
Duration of rituximab use (years)	4·1 (2·8)	3·3 (2·7)	4·0 (2·4)
Concomitant use of conventional synthetic DMARDs	20 (71%)	35 (60%)	31 (57%)
Concomitant methotrexate	13 (46%)	24 (41%)	21 (39%)
Methotrexate dose (mg)	17·1 (5·6)	17·5 (6·2)	15·8 (6·6)
Previous biological DMARDs (n)	2 (1–2)	2 (1–3)	2 (1–2)
Previous conventional synthetic DMARDs (n)	2 (1–3)	2 (1–4)	3 (1–3)
Oral glucocorticoid use*	4 (14%)	9 (16%)	9 (17%)
SENS	20 (8–39)†	16 (10–39)	18 (8–31)‡
DAS28-CRP	2·45 (0·92)	2·30 (0·96)	2·56 (1·09)
DAS28-CRP remission§	15 (54%)	36 (62%)	26 (48%)
EULAR Boolean remission¶	7 (25%)	14 (24%)	11 (21%)
EULAR index-based remission (SDAI ≤3·3)	6 (25%)‖	12 (23%)**	11 (21%)‡
HAQ-DI score	1·08 (0·57)	1·21 (0·73)	1·13 (0·68)††
EQ5D-5L score	0·80 (0·11)†	0·74 (0·17)††	0·74 (0·15)‖
Recruiting centres			
Sint Maaartenskliniek	19 (68%)	41 (71%)	40 (74%)
Ziekenhuisgroep Twente	4 (14%)	7 (12%)	8 (15%)
Radboudumc	2 (7%)	4 (7%)	3 (6%)
Reade Amsterdam	1 (4%)	3 (5%)	2 (4%)
Maasstad Ziekenhuis	2 (7%)	3 (5%)	1 (2%)

Data are n (%), mean (SD), or median (IQR). ACR=American College of Rheumatology. EULAR=European League Against Rheumatism. ACPA=anti-citrullinated protein antibody. DMARD=disease-modifying antirheumatic drug. SENS=simple erosion narrowing score. DAS28-CRP=disease activity score in 28 joints based on amounts of C-reactive protein. SDAI=simplified disease activity index. EQ5D-5L=EuroQol five dimension scale with five levels. HAQ-DI=health assessment questionnaire disability index. *Maximum dose of oral glucocorticoids at baseline was 10 mg/day. †Data missing for one participant. ‡Data missing for two participants. §Defined as DAS28-CRP <2·40. ¶Defined as tender joint count ≤1, swollen joint count ≤1, CRP ≤1 mg/dL, and patient global assessment ≤1 (range 0–10). ‖Data missing for four participants. **Data missing for six participants. ††Data missing for three participants.

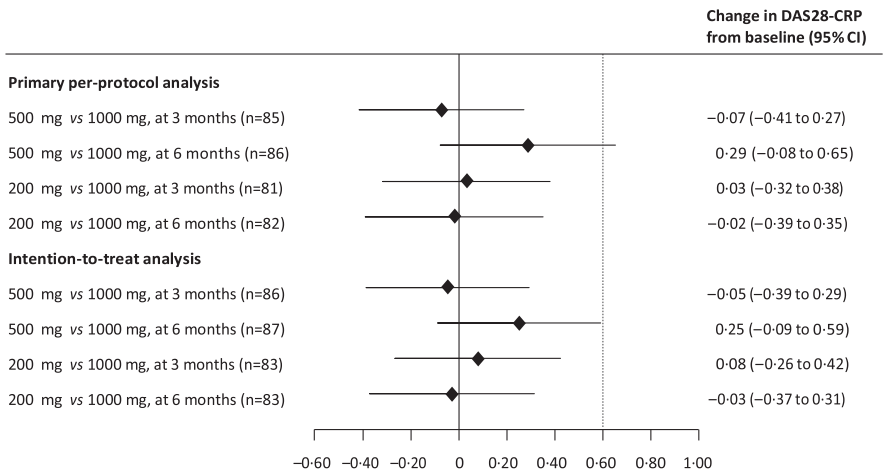

Figure 2: Change in DAS28-CRP from baseline to 3 and 6 months

Based on linear regressions corrected for baseline DAS28-CRP, rheumatoid factor or ACPA status, and concomitant conventional synthetic DMARD use. 200 mg *vs* 1000 mg per-protocol findings were not formally considered because of the hierarchical testing strategy. Vertical line at 0·60 denotes non-inferiority margin. ACPA=anti-citrullinated protein antibody. DMARD=disease-modifying antirheumatic drug. DAS28-CRP=disease activity score in 28 joints based on amounts of C-reactive protein.

of patients who had disease flares or changes in HAQ-DI and EQ5D score from baseline did not differ between groups (table 2). Use of concomitant conventional synthetic DMARDs and oral glucocorticoids remained stable during the study period (table 2). During the study period, seven (5%) of 142 patients received intra-articular injections of glucocorticoids and 27 (19%) patients received intra muscular injections of glucocorticoids. Use of glucocorticoids (particularly intra-muscular injections) was highest, but not significantly so, in patients assigned 200 mg rituximab compared with those assigned 500 mg and 1000 mg doses.

Serious adverse events were reported for 13 patients (table 3); three (10%) were assigned to 1000 mg rituximab, six (10%) were assigned to 500 mg rituximab, and four (7%) were assigned to 200 mg rituximab. The most frequently reported serious adverse events were cardiovascular; the appendix (p 5) lists all serious adverse events. No deaths occurred during the study period. The incidence density of infect ions at 6 months was significantly lower with ultralow doses of rituximab (rate ratio 0·47, 95% CI 0·23–0·95; p=0·013 for 500 mg *vs* 1000 mg; 0·46, 0·23–0·95; p=0·019 for 200 mg *vs* 1000 mg).

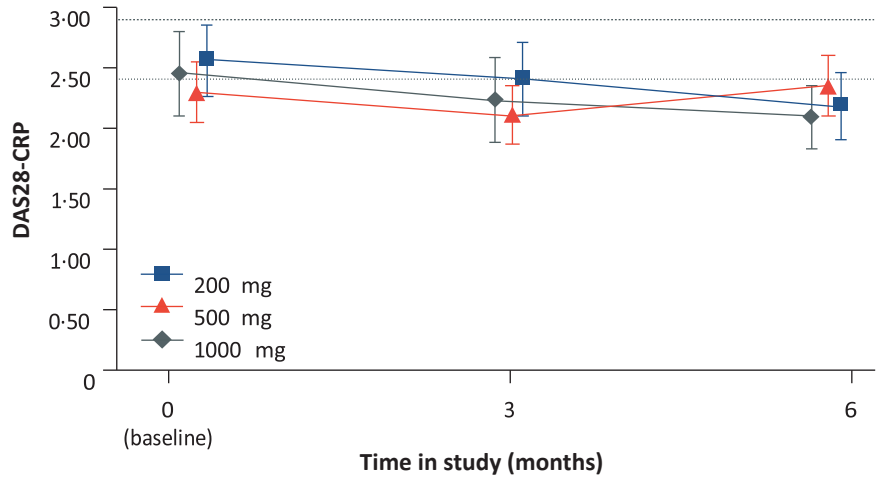

Figure 3: Disease activity during the study

Disease activity was measured by DAS28-CRP. Data are mean (95% CIs). Dashed line at DAS28-CRP 2·90 denotes threshold for low disease activity. Dotted line at DAS28-CRP 2·40 denotes threshold for remission. DAS28-CRP=disease activity score in 28 joints based on amounts of C-reactive protein.

Table 2: Primary outcome (per-protocol population) and key secondary outcomes (intention-to-treat population), at 3 months and 6 months

	At 3 months			At 6 months		
	1000 mg rituximab	500 mg rituximab	200 mg rituximab	1000 mg rituximab	500 mg rituximab	200 mg rituximab
Disease activity (per-protocol)*						
Change in DAS28-CRP from baseline	−0·22 (−0·47 to 0·04) [n=28]	−0·19 (0·43 to 0·04) [n=57]	−0·17 (−0·44 to 0·11) [n=53]	−0·35 (−0·67 to −0·04) [n=28]	0·05 (−0·21 to 0·31) [n=58]	−0·38 (−0·68 to −0·09) [n=54]
Mean DAS28-CRP score	2·23 (1·88 to 2·58) [n=28]	2·10 (1·86 to 2·35) [n=57]	2·40 (2·09 to 2·70) [n=53]	2·09 (1·83 to 2·36) [n=28]	2·35 (2·10 to 2·59) [n=58]	2·17 (1·90 to 2·45) [n=54]
Remission (intention-to-treat)						
EULAR remission by Boolean criteria†	10/29 (34%; 18 to 54)	20/56 (36%; 23 to 50)	13/54 (24%; 13 to 38)	7/29 (24%; 10 to 44)	14/58 (24%; 14 to 37)	19/54 (35%; 23 to 49)
Index-based EULAR remission (SDAI ≤3·3)	10/29 (34%; 18 to 54)	18/52 (35%; 22 to 49)	13/49 (27%; 15 to 41)	8/27 (30%; 14 to 50)	16/57 (28%; 17 to 42)	19/49 (39%; 24 to 54)
DAS28-CRP remission‡	20/29 (69%; 49 to 85)	40/57 (70%; 57 to 82)	32/54 (59%; 45 to 72)	20/29 (69%; 49 to 85)	35/58 (60%; 47 to 85)	36/54 (67%; 53 to 89)
DAS28-CRP low disease activity§	23/29 (79%; 60 to 92)	46/57 (81%; 68 to 90)	37/54 (69%; 54 to 80)	26/29 (90%; 73 to 98)	42/58 (72%; 59 to 83)	44/54 (81%; 69 to 91)
Function (intention-to-treat)¶‖						
Change in HAQ-DI score from baseline	−0·12 (−0·24 to −0·00) [n=29]	−0·05 (−0·14 to 0·04) [n=54]	−0·02 (−0·10 to 0·07) [n=50]	−0·02 (−0·12 to 0·07) [n=28]	0·02 (−0·07 to 0·11) [n=54]	0·03 (−0·05 to 0·11) [n=50]
Mean HAQ-DI score	0·96 (0·72 to 1·21) [n=29]	1·15 (0·93 to 1·36) [n=54]	1·09 (0·89 to 1·30) [n=50]	1·07 (0·83 to 1·30) [n=28]	1·21 (1·00 to 1·43) [n=54]	1·16 (0·96 to 1·37) [n=51]
Quality of life (intention-to-treat)‖‖						
Change in EQ5D-5L score from baseline	0·01 (−0·03 to 0·04) [n=27]	0·01 (−0·02 to 0·04) [n=49]	0·00 (−0·03 to 0·03) [n=45]	0·02 (−0·00 to 0·05) [n=27]	−0·02 (−0·05 to 0·01) [n=53]	−0·01 (−0·05 to 0·02) [n=48]
Mean EQ5D-5L score	0·81 (0·76 to 0·87) [n=28]	0·75 (0·69 to 0·80) [n=51]	0·73 (0·68 to 0·78) [n=46]	0·82 (0·78 to 0·87) [n=27]	0·71 (0·67 to 0·76) [n=55]	0·72 (0·67 to 0·77) [n=50]
Antirheumatic drug use during the study (intention-to-treat)						
Extra dose of rituximab (1000 mg)**	0/29 (0%; 0 to 11)	1/58 (2%; 0 to 9)	0/55 (0%; 0 to 6)	0/29 (0%; 0 to 11)	2/58 (3%; 0 to 12)	2/55 (4%; 0 to 13)
Concomitant use of conventional synthetic DMARDs	19/29 (66%; 46 to 82)	35/58 (60%; 47 to 73)	33/55 (60%; 46 to 73)	19/29 (66%; 46 to 82)	35/58 (60%; 47 to 73)	31/54 (57%; 43 to 71)
Concomitant use of glucocorticoids	4/29 (14%; 4 to 32)	9/58 (16%; 7 to 27)	8/55 (15%; 6 to 27)	4/29 (14%; 4 to 32)	9/58 (16%; 7 to 27)	9/54 (17%; 8 to 29)
Intramuscular glucocorticoid injections††	4/29 (14%; 4 to 32)	4/58 (7%; 2 to 17)	12/55 (22%; (12 to 35)	4/29 (14%; 4 to 32)	7/58 (12%; 5 to 23)	16/55 (29%; 18 to 43)
Intra-articular glucocorticoid injections††	1/29 (3%; 0 to 18)	1/58 (2%; 0 to 9)	2/55 (4%; 0 to 13)	2/29 (7%; 1 to 23)	1/58 (2%; 0 to 9)	4/55 (7%; 2 to 18)
Intramuscular or intra-articular glucocorticoid injections, or both††	5/29 (17%; 6 to 36)	5/58 (9%; 3 to 19)	13/55 (24%; 13 to 37)	6/29 (21%; 8 to 40)	8/58 (14%; 6 to 25)	18/55 (33%; 21 to 47)
Other outcomes (intention-to-treat)						
Flares during follow-up	NA	NA	NA	3/29 (10%; 2 to 27)	14/58 (24%; 14 to 37)	10/55 (18%; 9 to 31)
CD19+ B-cell number (cells per μL)‡‡	0 (0–1) [n=26]	1 (0–1) [n=47]	0 (0–1) [n=48]	4 (0–31) [n=24]	10 (1–31) [n=48]	20 (2–40) [n=47]

Data are mean (95% CI) [n] or n/N (%; 95% CI). The primary endpoint analysis was done in the per-protocol population, which included 140 participants who had received the assigned study drug and completed follow-up of 6 months (LOCF for four people who received extra rituximab after disease flare). Two DAS28-CRP measurements were missing at 3 months follow-up. Secondary endpoint and other analyses were done in the intention-to-treat population, which included 142 patients who received the assigned treatment (without LOCF). Because of missing data, several totals do not add up to 142. EULAR remission by Boolean criteria: n=139 at 3 months and n=141 at 6 months; index-based EULAR remission: n=130 at 3 months and n=133 at 6 months; DAS28-CRP remission and low disease activity: n=140 at 3 months and n=141 at 6 months; change in HAQ-DI: n=133 at 3 months and n=132 at 6 months; HAQ-DI score: n=133 at 3 months and n=133 at 6 months; change in EQ5D-5L: n=121 at 3 months and n=128 at 6 months; EQ5D-5L score: n=125 at 3 months and n=132 at 6 months; CD19+ B-cell number: n=121 at 3 months and n=119 at 6 months. Moreover, one patient in the 200 mg group was lost to follow-up just before the 6-month measurement, therefore, we could not assess concomitant conventional synthetic DMARD and glucocorticoid use (n=54). DAS28-CRP=disease activity score in 28 joints based on amounts of C-reactive protein. EULAR=European League Against Rheumatism. SDAI=simplified disease activity index. HAQ-DI=health assessment questionnaire disability index. EQ5D-5L=EuroQol five-dimension scale with five levels. DMARD=disease-modifying antirheumatic drug. NA=not applicable. LOCF=last observation carried forward. *Measured by DAS28-CRP. †Defined as tender joint count ≤1, swollen joint count ≤1, CRP ≤1 mg/dL, and patient global assessment ≤1 (range 0–10). ‡Defined as DAS28-CRP <2·40. §Defined as DAS28-CRP ≤2·90. ¶Measured by HAQ-DI. ‖Measured by EQ5D-5L. **Cumulative number of patients receiving an extra 1000 mg dose of rituximab; excluding two protocol violations whereby participants received their regular infusion with rituximab a few days before the 6-month study visit owing to a logistical error. ††Cumulative number of patients with one or more injections. ‡‡Measurements after an extra 1000 mg dose of rituximab during follow-up were excluded (n=6).

Table 3: Summary of safety events (safety population)

	Total (n=142)	1000 mg rituximab (n=29)	500 mg rituximab (n=58)	200 mg rituximab (n=55)
Adverse events and serious adverse events				
Incidence of any adverse event (new cases/patient-year)	4·51 [320/71·00]	4·12 [60/14·57]	4·63 [134/28·95]	4·58 [126/27·49]
Rate ratio (95% CI) of adverse events (comparison with 1000 mg rituximab)		..	1·12 (0·83–1·52)	1·11 (0·82–1·51)
Serious adverse events*	13 (9%; 5–15)	3 (10%; 2–27)	6 (10%; 4–21)	4 (7%; 2–18)
Deaths	0 (0%; 0–3)	0 (0%; 0–12)	0 (0%; 0–6)	0 (0%; 0–6)
Adverse events of special interest				
Incidence of infections (new cases/patient-year)†	0·63 [45/71·00]	1·10 [16/14·57]	0·52 [15/28·95]	0·51 [14/27·49]
Rate ratio (95% CI) of infections (comparison with 1000 mg rituximab)	..	..	0·47 (0·23–0·95)	0·46 (0·23–0·95)
Cumulative incidence of serious infections (grade 3 or 4)	4 (3%; 0–7)	2 (7%; 1–23)	1 (2%; 0–9)	1 (2%; 0–10)
Incidence of infusion-related complaints (new cases/ patient-year)‡	0·84 [60/71·00]	0·75 [11/14·57]	1·14 [33/28·95]	0·58 [16/27·49]
Rate ratio (95% CI) of infusion-related complaints (comparison with 1000 mg rituximab)	..	..	1·51 (0·76–2·99)	0·77 (0·36–1·66)
Cumulative incidence of serious infusion-related complaints (grade 3 or 4)	1 (<1%; 0–4)	0 (0%; 0–12)	1 (2%; 0–9)	0 (0%; 0–6)

Data are n (%; 95% CI), unless otherwise stated. Analyses were done in the safety population, which included 142 patients who received the assigned study dose. Adverse events from any cause were included in analyses. *Cumulative incidence of serious adverse events. One patient assigned to 500 mg rituximab had two serious adverse events requiring admission to hospital (acute cardiothoracic surgery and re-admission because of wound dehiscence).
†Infections were labelled as such by the study team based on the adverse event description. ‡Infusion-related complaints were labelled as such by the study team based on the adverse event description.

Discussion

To the best of our knowledge, our study is the first randomised controlled trial to investigate doses of rituximab below the standard low dose of 1000 mg for continued treatment of patients with rheumatoid arthritis. Findings of the primary per-protocol analysis did not show noninferiority of continued treatment with ultra-low doses at 6 months. Intention-to-treat analyses suggest that a strategy of ultra-low dose rituximab with treatment escalation in case of disease flare could be non-inferior for both 500 mg and 200 mg ultra-low doses, compared with the 1000 mg low dose, at up to 6 months of follow-up, although further studies are needed to conclusively show non-inferiority. Moreover, a significantly lower incidence of infections was seen with ultra-low doses. These findings confirm the results of small studies of very low doses of rituximab for rheumatoid arthritis[14–17,29] and surpass the results of other dose-reduction studies of biological DMARDs showing that approximately 60% of patients can safely reduce the dose or discontinue biological DMARD treatment.[5,30]

The results of our per-protocol analysis cannot exclude the possibility that a 500 mg dose of rituximab leads to worse outcomes compared with a 1000 mg dose. However, in view of the results with the 200 mg dose, and assuming a dose-related response, this outcome seems unlikely. Possible explanations for the inability to show noninferiority of the ultra-low doses include that the 500 mg dose results in a small deterioration in DAS28-CRP compared with the 1000 mg dose and that the true effect of 200 mg is attenuated by co-medication, or that we incorrectly did not reject the null hypothesis of inferiority for 500 mg after 6 months because of insufficient sample size. We think all explanations might be partly true because glucocorticoids were used most frequently by patients assigned to the 200 mg dose (although this was not significant) but the course of disease activity and numbers of B cells were similar for all groups with very few treatment failures. It is possible that the trial was underpowered given that not all assumptions of the sample size calculation were reached.

Strengths of our study are the randomised double-blind design, which minimises the risk of bias, and the low numbers of missing data and dropouts. Furthermore, inclusion criteria were chosen to ensure that results were generalisable to clinical practice. Limitations of our study are the recruitment of patients in one country and the potential for a carryover effect of the previous higher dose of rituximab, which cannot be ruled out in this study because of the fairly short follow-up period. Bio-creep[31] compared with two doses of 1000 mg (the authorised dose) does not seem likely in view of a study showing that the estimated difference in change in DAS28-CRP between two doses of 1000 mg and one dose of 1000 mg was 0·07 at 6 months.[12]

Thus, our study was not able to show non-inferiority of ultra-low doses of rituximab for continued treatment of patients with rheumatoid arthritis. In clinical practice, a strategy with one ultra-low dose of rituximab and extra antirheumatic drugs in case of flare might be considered, weighing the risk of flare against the benefits of improved safety, shorter infusion time, and potential cost-savings. However, additional studies are required to establish noninferiority. Additional analyses of the REDO trial with respect to cost-effectiveness and potential predictors of successful continued treatment with an ultra-low dose of rituximab will help patients and clinicians make a balanced choice. Further research on a strategy with ultra-low-dose rituximab is needed to ascertain the effects on radiographic out comes over a longer period of treatment with more than one infusion, and to confirm the safety of ultra-low dose rituximab. The ongoing 2-year observational extension of the REDO study might help to answer some of these questions. Our study provides a starting point to further investigate the potential of ultra-low doses of rituximab in rheumatoid arthritis.

Contributors

LMV, NdB, RMT, TGW, BJFvdB, FHJvdH, and AAdB contributed to study design. LMV, NdB, RMT, WHvdL, WvdW, MRK, HJBM, BJFvdB, and AAdB contributed to data collection. LMV, NdB, and AAdB contributed to data analyses. All authors contributed to data interpretation and writing of the report.

Declaration of interests

LMV reports grants from Menzis and Centraal Ziekenfonds Group, during the conduct of this study. AAdB reports grants from and congress visits on behalf of Abbvie and Biogen; expert witness for Amgen and Fresenius; and congress visits on behalf of Roche and Cellgene, outside the submitted work. RMT reports congress visits on behalf of Roche and AbbVie, outside the submitted work. BJFvdB reports grants and personal fees from UCB, Pfizer, and Abbvie; grants from Eli Lilly; and personal fees from Biogen and Novartis, outside the submitted work. FHJvdH reports speaker fees from Amgen, Boehringer Ingelheim, and Novartis; service on the advisory board for AbbVie, Biogen, Celltrion, Eli-Lilly, Mundipharma, Pfizer, and Sanofi-Genzyme; and service on the drug safety board for Corbus, outside the submitted work. WHvdL, WvdW, MRK, HJBM, TGW, and NdB declare no competing interests.

Data sharing

Individual deidentified participants' data that underlie the results reported, the study protocol, statistical analysis plan, and analytical code are available with publication to researchers who provide a methodologically sound proposal to achieve aims in the approved proposal or for individual participant data meta-analysis. Proposals should be directed to l.verhoef@maartenskliniek.nl; to gain access, data requestors will need to sign a data access agreement.

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Appendix

Supplementary table 1: Participating centres

Centre	Principal investigator	No. of patients
Sint Maartenskliniek	Dr. Alfons A den Broeder	102
Ziekenhuisgroep Twente	Dr. Hein J Bernelot Moens	19
Radboudumc	Dr. Rogier M Thurlings	9
Reade Amsterdam	Prof. Mike Nurmohamed	6
Maasstad Ziekenhuis	Dr. Marc R Kok	6

Supplementary table 2: Co-medication administrated in participating centres

Centre			
Sint Maartenskliniek	cetirizine 10mg po	methylprednisolone 50mg IV	acetaminophen 1000 mg
Radboudumc	clemastine 2mg IV	methylprednisolone 100mg IV	acetaminophen 1000mg
Reade Amsterdam	clemastine 2mg IV	methylprednisolone 100mg IV	acetaminophen 1000mg
Maasstad Ziekenhuis	clemastine 2mg IV	dexamethasone 20mg IV	acetaminophen 1000mg
Ziekenhuisgroep Twente	clemastine 2mg IV	dexamethason 20mg IV	acetaminophen 1000mg

B-cell determination

Four laboratories in the Netherlands performed the B-cell analysis for the participating centres. Blood samples were drawn from patients at each visit and anticoagulated by EDTA. The amount of B-cells was determined within 24 hours after blood collection by using a combination of fluorochrome-labelled monoclonal antibodies. Cells were analysed using a fully standardised volumetric counting flow cytometer. Calibration was checked and quality control assessment was performed regularly within an (inter)national program.

Sample size calculation[1]

The study has four primary endpoints; multiplicity over the primary endpoints will be protected by a fixed testing procedure. First, the non-inferiority of the 500 mg vs. 1000 mg at three months will be tested at $p < 0.05$ (two-sided). If this is statistically significant, then 500 mg vs. 1000 mg will be tested at $p < 0.05$ (two-sided) at six months. If that is statistically significant, then 200 mg vs. 1000 mg will be tested at $p < 0.05$ (two-sided) at three months and if that is statistically significant, the last test will be 200 mg vs. 1000 mg at $p < 0.05$ (two-sided) at six months. As we have four primary endpoints, we aim to have enough power for each at 95% for an NI margin of $\delta = 0.6$. Under the worst-case scenario that these four are not correlated (the expectation is that they are positively correlated, see Table 1) and that the intervention is indeed non-inferior to the control condition, then the overall power for rejecting the null hypothesis of inferiority on all four is at least $95\% \times 95\% \times 95\% \times 95\% = 81\%$. We calculated the sample size for one endpoint (e.g. the comparison of 500 vs. 1000 mg at six months). For 2:1 randomisation and a non-inferiority test assuming the true difference between treatments is 0, the total sample size for a t-test having a power $1-\beta$ when testing at significance level α (two-sided) and a non-inferiority margin δ is $Ntot = (4.5)^2 \times (z1-\alpha/2 + z1-\beta)^2 \times SD^2/\delta^2$, where z denotes the normal quantiles which are correct for non-small sample sizes. When correction for baseline is incorporated, this sample size is reduced by $(1-r^2)$ where r is the correlation in DAS28 between baseline and follow up (formula 7 with $n = 1$, $\pi 0 = 1/3$, $\pi 1 = 2/3$, and section 2.3 of Teerenstra S, et al.[2] Note that the two groups then have sizes Ntot/3 and $2 \times$ Ntot/3. To determine the correlation r between baseline and follow-up measurement of the DAS28, the following assumptions were used. Baseline DAS28 has a SD = 0.7 and the change from baseline to three (or six months) has a standard deviation of SDchange = 0.6 based on data from an earlier dose reduction trial. As $SD^2change = 2 \times (1-r) \times SD^2$, it follows that r = 0.63. Then a total trial size of 80 participants would be enough. Table 1 illustrates the total trial size when the correlation between endpoints is smaller than anticipated. To protect for a too optimistic correlation, we therefore choose a total trial size of 130 and this is further increased to 140 patients to account for patient drop-out.

Total trial sample size at various correlations between endpoints

SD change	r	Sample size 1000mg arm	Total trial size (5 x sample size in 1000mg arm)
0.9	0.17	26	130
0.8	0.35	24	120
0.7	0.5	20	100
0.6	0.63	16	80

Supplementary table 3: Demographic and disease characteristics of the patients at baseline (intention-to-treat population)*

	1000mg (n=29)	500mg (n=58)	200mg (n=55)	Total (n=142)
Age - yr	63·8 (9·0)	64·0 (10·9)	64·2 (12·2)	64·0 (11·0)
Sex – no. of females (%)	18 (62%)	37 (64%)	40 (73%)	95 (67%)
ACR/EULAR 1987 and/or 2010 positive – no. (%)†	27 (93%)	57 (98%)	52 (95%)	136 (96%)
Duration of rheumatoid arthritis – yrs	17·1 (11·1)	14·9 (10·7)	13·5 (7·2)	14·8 (9·6)
RF/ACPA positive – no. (%)	27 (93%)	54 (93%)	49 (89%)	130 (92%)
Duration of rituximab use – yrs	4·0 (2·8)	3·3 (2·7)	4·0 (2·4)	3·7 (2·6)
Concomitant use of csDMARD – no. (%)	20 (69%)	35 (60%)	32 (58%)	87 (61%)
Of which (combination with) MTX – no.(%)	13 (45%)	24 (41%)	22 (40%)	59 (42%)
Dose of MTX in mg	17·1 (5·6)	17·5 (6·2)	15·8 (6·5)	16·8 (6·1)
No. previous bDMARDs – median (IQR)	2 (1–2)	2 (1–3)	2 (1–2)	2 (1–2)
No. previous csDMARDs – median (IQR)	2 (1–3)	2 (1–4)	3 (1–3)	2 (1–3)
Oral glucocorticoid use – no. (%) ¶‖	4 (14%)	9 (16%)	9 (16%)	22 (15%)
SENS - median (IQR) ¥	22 (8–40) [28]	16 (10–39) [58]	18 (8–31) [53]	18 (9–33) [139]
DAS28-CRP $	2·40 (0·93)	2·30 (0·96)	2·54 (1·09)	2·41 (1·00)
Proportion remission DAS28-CRP < 2·4	16 (55%)	36 (62%)	27 (49%)	79 (56%)
EULAR Boolean remission: TJC ≤1, SJC ≤1, CRP ≤1 mg/dl and PGA ≤1 (0–10)	8/29 (28%)	14/48 (24%)	11/55 (20%)	33/142 (23%)
EULAR index based remission: SDAI ≤3·3	7/25 (28%)	12/52 (23%)	12/53 (23%)	31/130 (24%)
HAQ-DI score £	1·08 (0·56) [29]	1·21 (0·73) [58]	1·11 (0·68) [52]	1·15 (0·68) [139]
EQ5D-5L score ‡	0·80 (0·11) [28]	0·74 (0·17) [55]	0·74 (0·15) [51]	0·75 (0·15) [134]
CD19+ B-cell number (cells per µL) – median (IQR)	10 (2-18) [25]	9 (1-28) [51]	9 (1-30) [53]	9 (1-30) [129]
Recruiting centres – no. (%)				
Sint Maaartenskliniek	20 (69%)	41 (71%)	41 (75%)	102 (72%)
Ziekenhuisgroep Twente	4 (14%)	7 (12%)	8 (15%)	19 (13%)
Radboudumc	2 (7%)	4 (7%)	3 (6%)	9 (6%)
Reade Amsterdam	1 (3%)	3 (5%)	2 (4%)	6 (4%)
Maasstad Ziekenhuis	2 (7%)	3 (5%)	1 (2%)	6 (4%)

*Values are means (SD) unless stated otherwise
† Proportion of patients fulfilling one or both the 1987 and 2010 criteria of ACR/EULAR for diagnosis of RA.
¶‖ Maximum dose of oral glucocorticoids at baseline was 10mg/day.
¥ Scores on the SENS (indicating the level of erosions and joint space narrowing seen on radiographs of hand and feet) range from 0–86 and higher scores indicate more damage.
$ Scores on the DAS28-CRP range from 0·96 to 10 and higher scores indicate more disease activity.
£ Scores on the HAQ-DI range from 0 to 3, with higher scores indicating greater disability.
‡ Scores on the EQ5D range from 0 to 1 and higher scores indicate better quality of life.
ACPA denotes anti-citrullinated protein antibody, ACR American College of Rheumatology, bDMARD biological disease modifying anti-rheumatic drug, CRP C-reactive protein, csDMARD conventional synthetic disease modifying anti-rheumatic drug, DAS28 disease activity score in 28 joints, EULAR European League Against Rheumatism, EQ5D EuroQol five dimension scale, HAQ-DI health assessment questionnaire disability index, IQR interquartile range, MTX methotrexate, RA rheumatoid arthritis, RF rheumatoid factor, SD standard deviation, SENS simple erosion narrowing score.

Supplementary table 4: Primary analysis by stratification factor

Comparison	Estimate
ACPA/RF negative	
500mg versus 1000mg after 3 months	-0.85 (-3.03 to 1.33) [6]
500mg versus 1000mg after 6 months	0.48 (-1.94 to 2.89) [6]
200mg versus 1000mg after 3 months	0.18 (-1.92 to 2.28) [8]
200mg versus 1000mg after 6 months	1.52 (-0.81 to 3.85) [8]
ACPA/RF positive	
500mg versus 1000mg after 3 months	-0.00 (-0.34 to 0.33) [79]
500mg versus 1000mg after 6 months	0.29 (-0.05 to 0.62) [80]
200mg versus 1000mg after 3 months	0.00 (-0.34 to 0.34) [73]
200mg versus 1000mg after 6 months	-0.17 (-0.51 to 0.18) [74]
Without concomitant csDMARD	
500mg versus 1000mg after 3 months	0.11 (-0.57 to 0.79) [30]
500mg versus 1000mg after 6 months	-0.05 (-0.67 to 0.57) [31]
200mg versus 1000mg after 3 months	-0.04 (-0.74 to 0.66) [31]
200mg versus 1000mg after 6 months	-0.50 (-1.14 to 0.14) [31]
With concomitant csDMARD	
500mg versus 1000mg after 3 months	-0.18 (-0.58 to 0.21) [55]
500mg versus 1000mg after 6 months	0.41 (-0.04 to 0.87) [55]
200mg versus 1000mg after 3 months	0.04 (-0.36 to 0.45) [50]
200mg versus 1000mg after 6 months	0.15 (-0.32 to 0.62) [51]

Supplementary table 5: Serious adverse events

SAE	Description	Patient	Study group
1	Hospitalization due to acute heart failure	SMK027	200mg
2	Hospitalization due to suspected pulmonary embolism	SMK033	500mg
3	Hospitalization due to acute heart failure	SMK024	1000mg
4	Hospitalization due to elective orthopaedic foot surgery	SMK021	500mg
5	Hospitalization due to cataract extraction	SMK048	500mg
6	Diagnosis of esophageal cancer	SMK068	500mg
7	Cardiothoracic surgery due to acute type-B aortic dissection	SMK072	500mg
8	Re-admission because of wound dehiscence (related to cardiothoracic surgery)	SMK072	500mg
9	Inguinal hernia surgery	SMK053	1000mg
10	Hospitalization for RA related coxitis	SMK077	200mg
11	Resuscitation for cardiac arrest due to myocardial infarction	SMK067	200mg
12	Hospitalization due to bronchitis	ZGT008	1000mg
13	Hospitalization due to streptococcus pneumonia	MSZ005	500mg
14	Cardioversion for to atrial fibrillation	SMK058	200mg

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Chapter 6

Long-term clinical and radiological effectiveness and safety of ultra-low doses of rituximab in rheumatoid arthritis: observational extension of the REDO trial

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Abstract

Background
The REDO trial showed similar disease activity for retreatment with ultra-low doses (200mg and 500mg per 6 months) compared to standard low dose rituximab (RTX, 1000mg per 6 months). We performed an observational extension study of the REDO trial to assess long-term effectiveness.

Methods
Patients from the REDO trial were followed from start of the trial to censoring in April 2021. RTX use was at the discretion of patient and rheumatologist using treat to target. The primary outcome was disease activity (DAS28-CRP), analyzed using a longitudinal mixed model by original randomization and time-varying RTX dose. The original DAS28-CRP non-inferiority (NI) margin of 0.6 was used. RTX dose and persistence, safety and radiological outcomes were also assessed.

Findings
Data from 126 of 142 REDO patients was collected from December 15th, 2016, up to April 30th 2021. Drop-outs continued treatment elsewhere (n=3) or did not consent (n=13).

Disease activity did not differ by original randomization group: 1000mg mean DAS28-CRP (95% CI) of 2.2 (2.0 to 2.5), 500mg 2.3 (2.1 to 2.4) and 200mg 2.4 (2.2 to 2.5). Lower time-varying RTX dose was associated with higher DAS28-CRP (0.22 (95% CI: 0.05-0.40) higher for 200mg/6 months compared to 1000mg/6 months), but remained within the NI-margin. RTX persistence was 93%. Median RTX dose was 978mg (IQR: 684 to 1413) per year, and no association was found between RTX dose and adverse events or radiological damage.

Interpretation
Long term use of ultra-low doses of rituximab is effective in RA patients responding to standard dose RTX.

Introduction

The lowest effective dose of rituximab (RTX) in the treatment of rheumatoid arthritis (RA) is unknown.[1] Dose finding studies did not thoroughly assess doses other than 2x1000mg or 2x500mg per 6 months and the authorized dose is 2x1000mg per 6 months .[2] A previous systematic review has shown 2x500mg (or 1x1000mg) to be equally effective as the authorized dose and this standard low dose is now often used in clinical practice.[3,4]

Identifying the lowest effective dose is of clear relevance for patients and society. The use of higher than necessary doses has several negative (potential) consequences. Firstly, a higher dose is likely associated with more frequent or more severe adverse effects of RTX treatment. Secondly, the costs of RTX are significant, and using a lower dose results in lower medication costs.[5] Finally, the duration of each infusion can be reduced thereby reducing the burden for patients and also lowering costs.

Inspired by case reports and a small study that reported B-cell depletion and often even good disease control with doses ranging from 50mg to 200mg, the REDO trial assessed the efficacy of ultra-low doses (200mg and 500mg) compared to standard low dose RTX (1000mg) for continued treatment of RA patients in a double-blind randomized study.[6-10] Results from the REDO trial showed similar outcomes with regards to disease activity, but did not reach statistical non-inferiority. Exploratively, non-inferiority of both doses was shown in the intention-to-treat analyses that may better reflect the trial-and-error approach to tapering that is common in clinical practice. Of note, the REDO trial also showed a reduction in the occurrence of infections: roughly half as many occurred in the 200mg and 500mg groups compared to the 1000mg group.

The two most important limitations of the REDO trial were the relatively short follow-up of one cycle of 6 months and the lack of formal non-inferiority on the group level. The limited follow-up raised some concerns regarding a possible carryover effect of previous higher dosed RTX, which could make lower doses possible, but only for a short time.[11] A longer follow-up would allow for a better estimate of the effects of ultra-low doses and also make it possible to identify patients in whom ultra-low dose RTX is ineffective through stepwise disease activity guided tapering.

We therefore performed an observational extension study of the REDO trial to describe the effectiveness of ultra-low dose RTX on a longer term in a treat-to-target context. Further objectives were to explore the use of co-medication, safety and radiographic progression in relation to the dose of RTX received.

Methods

Design and Patients

The REDO trial investigated the efficacy of ultra-low dose RTX in RA patients with stable low disease activity (at least 6 months of DAS28-CRP<2.9, or clinical judgement of low disease activity by a rheumatologist AND a DAS28-CRP ≤3.5) after previous RTX infusions of the authorized or standard low dose (2 × 1000mg, 1 × 1000mg, or 2 × 500mg). Full inclusion criteria and methods have been reported previously.[10]

The current study is an observational extension of the REDO trial using data from inclusion (Dec 15th, 2016, through Sept 20th, 2018) up to April 30th 2021. Patients were followed up in all 5 participating centers, comprising 2 university hospitals and 3 non-university hospitals. Patients and rheumatologists were unblinded after the conclusion of the original 6-month follow-up period, and rheumatologists were advised to make a shared decision with patients with a recommendation from the study team: to continue on ultra-low doses if the patient responded well to one during the trial, or to revert to 1x1000mg otherwise. Patients who had been randomized to 1000mg could continue with that dose, or in shared decision making chose to attempt a lower dose. Treatment during follow up was according to usual care based on treat-to-target principles using the DAS28-CRP or DAS28-ESR to guide treatment decisions and included the possibility of dose reduction or interval lengthening. No restrictions to medication or otherwise were placed on patients or physicians during the extension phase. The need for ethics committee approval was waived by METC Arnhem-Nijmegen (2019-5083).

All 142 patients who participated in the REDO study, except those who had previously objected to being contacted for further research (n=4) were invited to the current extension study by mail and telephone to obtain consent for data collection. Data on disease activity, medication use and adverse events were then collected from electronic patient records at the conclusion of follow up. Radiographs of hands and feet were made as part of routine care between 2 to 3 years follow up in 3 of the 5 study centers.

Randomisation and masking

In the initial randomized intervention phase of the REDO trial (months 0-6) patients were randomized 2:2:1 to a single RTX dose of 200mg, 500mg or 1000mg, stratified by rheumatoid factor or anti-citrullinated protein antibody (ACPA) status (positive or negative) and concomitant conventional synthetic DMARD use (yes or no). During this period patients, physicians and other personnel remained blinded to the RTX dose used.

At the start of the observational phase (month 6), allocation was revealed to every patient and their rheumatologist. After this point, treatment was open-label, according to usual care and without study restrictions on medication or other treatments.

Outcomes

Primary outcome of the study was disease activity over time during follow up measured by the DAS28-CRP. Secondary outcomes included the dose and interval of RTX during and at the end of the study, the proportion of patients switching to another b/tsDMARD, incidence of DAS28-CRP based flare, the use of RA co-medication (csDMARDs and oral or intramuscular/intra-articular glucocorticoids), the incidence density of adverse events (number, type and grade according to CTC AE v5).[12] Radiographs were scored according to SENS by 2 independent readers without blinding and in known chronological order to maximize sensitivity to detect progression.[13]

Statistical analyses

Mean DAS28-CRP was analyzed using a linear mixed model with a random intercept for each patient to take into account the clustering of measurements within patients and an exponential covariance model to allow for correlated residuals that are dependent on the interval between measurements. Two analyses were performed 1. Analysis by original randomization groups, corrected for stratification factors (RF/ACPA positivity and csDMARD use, both dichotomous) 2. Analysis by the time-varying dose of RTX received during the year preceding each disease activity measurement, adjusted for potential confounders csDMARD use, glucocorticoid use (both time-varying), and RF/ACPA positivity. In sensitivity analyses the time-varying dose of RTX was also calculated based on a timeframe of 6 and 9 months. In line with the REDO trial, a non-inferiority margin of 0.6 was used.[14] In disease activity analyses, patients switching to another b/tsDMARD were censored from the moment of switching onward.

RTX dose and intervals, RTX persistence and RTX treatment strategy (fixed interval or T2T retreatment as needed) were all descriptively shown either for the complete study population or per average yearly dose group as described above.

For analysis of the incidence rates of flare, use of injected or oral glucocorticoids, initiation or dose increase of csDMARDs and adverse events, 3 groups were defined based on the mean yearly RTX dose during follow up: >1500mg, 750-1500mg, and <750mg. The group >1500mg per year corresponds to a standard low dose of 1000mg per 6-8 months, 750-1500mg includes an ultra-low dose of 500mg per 6 to 8 months or 1000mg with a longer interval and <750mg is any ultra-low doses lower than 500mg per 8 months. Incidence densities were compared using unadjusted Poisson regression.

Radiographic progression scores according to SENS were compared between groups using the Kruskal-Wallis test. In addition, the smallest detectable change (SDC) was determined by ANOVA and the proportions of patients in each group with progression greater than the SDC or greater than 0.5 points (the minimum possible progression with 2 raters) were compared using Fisher's exact test.[15] SENS progression is also shown by yearly dose group in a cumulative probability plot.

Role of the funding source

This study was funded by the Sint Maartenskliniek and no external funding was involved. The original REDO trial was funded by Menzis and Centraal Ziekenfonds, two Dutch health insurance companies.

Patient and public involvement

Patient partners were involved in the design and conduct of the REDO trial (the choice of outcome measures, how the study was conducted in practice, if burden for patients was acceptable). Given this previous involvement and the limited study burden of the extended follow-up, patient partners were not involved in the extension phase.

Results

126 out of 142 REDO patients were included in current analyses (table 1) Reasons for exclusion were: continuing treatment elsewhere (n=3) and no informed consent (n=13). Of the excluded patients, 3 had been randomized to 1000mg in the original trial, 6 to 500mg, and the remaining 7 to 200mg, which is in line with the 1:2:2 allocation ratio. Data was collected for each patient from the moment of inclusion in the REDO trial (ranging December 15, 2016, through September 20, 2018) up to the last visit prior to April 30th 2021. Baseline characteristics are shown in table 1. Median follow up was 3.3 years (IQR: 2.9-3.6) resulting in a total of 404 patient-years of follow-up. 1026 DAS28-CRP measurements were available resulting in a mean of 2.54 measurements per patient per year.

Disease activity

Overall mean disease activity over the entire study duration was low (mean DAS28-CRP of 2.3, SD: 1.0).

A comparison of disease activity by original randomization group showed a mean DAS28-CRP (95% CI) during follow-up of 2.2 (2.0 to 2.5) in the 1000mg group, 2.3 (2.1 to 2.4) in the 500mg group and 2.4 (2.2 to 2.5) in the 200mg group. Compared to the 1000mg group, both the 500mg group (0.04 points higher (95% CI: -0.24-0.32)) and the 200mg group (0.12 points higher (95% CI: -0.16-0.41)) were non-inferior in terms of disease activity.

Table 1: Baseline characteristics

Original randomized dose	1000mg RTX (n=26)	500mg RTX (n=52)	200mg RTX (n=48)
Age (years)	65 (9)	64 (11)	64 (12)
Female sex	16 (62%)	31 (60%)	36 (75%)
Meeting ACR1987 or ACR/EULAR 2010 RA criteria†	24 (92%)	51 (98%)	45 (94%)
Disease duration (years)	14 (9-24)	14 (7-21)	13 (8-20)
RF and/or ACPA positive	24 (92%)	48 (92%)	42 (88%)
Duration of rituximab use (years)	3.2 (1.6-6.3)	2.4 (1.0-5.3)	3.7 (2.2-5.7)
Concomitant csDMARD	18 (69%)	33 (63%)	27 (56%)
Previous number of b/tsDMARDs used	2 (2-2)	2 (1-3)	2 (1-2)
Previous number of csDMARDs used	3 (1-3)	2 (1-4)	3 (1-3)
Oral GC use at baseline	3 (12%)	8 (15%)	6 (13%)
Baseline DAS28-CRP‡	2.4 (0.9)	2.3 (1.0)	2.6 (1.1)
Baseline radiographic damage (SENS) *	20 (8 – 41), 1 missing	17 (10-39)	17 (7-31), 1 missing

Data are n (%), mean (SD), or median (IQR).
† Proportion of patients fulfilling one or both the 1987 and 2010 criteria of ACR/EULAR for diagnosis of RA.[16,17]
‡ Scores on the DAS28-CRP range from 0·96 to 10 and higher scores indicate more disease activity.
* Scores on the SENS (indicating the level of erosions and joint space narrowing seen on radiographs of hand and feet) range from 0–86 and higher scores indicate more damage.
ACPA denotes anti-citrullinated protein antibody, ACR American College of Rheumatology, b/tsDMARD biological or targeted synthetic disease modifying anti-rheumatic drug, CRP C-reactive protein, csDMARD conventional synthetic disease modifying anti-rheumatic drug, DAS28 disease activity score in 28 joints, EULAR European League Against Rheumatism, IQR interquartile range, RA rheumatoid arthritis, RF rheumatoid factor, SD standard deviation, SENS simple erosion narrowing score.

A comparison of disease activity by time-varying RTX dose showed that a lower RTX dose in the past year was significantly associated with a higher disease activity. The DAS28-CRP was 0.14 (95% CI: 0.03-0.25) points higher per 1000mg less RTX in the past year. The upper limit of this confidence interval excludes the non-inferiority margin of 0.6 for relevant dose differences: the DAS28-CRP is estimated to be 0.22 (95% CI: 0.05-0.40) higher for the lowest (200mg per six months) compared to the highest (1000mg per six months) RTX dose. Sensitivity analyses restricting the calculations of RTX dose to infusions within a 6- or 9-month window gave similar outcomes of 0.27 (95% CI: 0.14-0.40) and 0.25 (95% CI: 0.11-0.40) points higher for the 200mg per 6 months dosing compared to 1000mg per 6 months, respectively.

The latest DAS28-CRP measurement prior to study conclusion is described in table 2 below and shows that the majority of patients are in low disease activity or remission.

Table 2: Latest DAS28-CRP at study end

Original randomized dose	1000mg RTX (n=26)	500mg RTX (n=52)	200mg RTX (n=48)
DAS28-CRP, mean (sd)	2. 47 (1.1)	2.1 (0.9)	2.6 (1.0)
Low disease activity, n (%)*	22 (85%)	46 (88%)	32 (67%)
Remission activity, n (%)	18 (69%)	37 (71%)	22 (46%)

Low disease activity defined as a DAS28-CRP below 2.9, remission defined as DAS28-CRP below 2.4. *includes patients who are in remission

Rituximab use

Rituximab persistence was 93%: 9 patients switched to another b/tsDMARD during follow up. Their last RTX dose was 1000mg in 6 patients and 500mg in 3 patients, with the final interval between RTX doses ranging from 6 to 9 months (median (IQR): 6.2 (6.0-6.4) months). Reasons for switching were side effects (n=5) and loss of response (n=4).

The median yearly RTX dose in all patients was 978mg (IQR: 684 to 1414): 1374mg (IQR: 973 to 1777) in the original 1000mg/cycle group, 915mg (IQR: 704 to 1241) in the 500mg/cycle group and 889mg (IQR: 565 to 1212) in the 200mg/cycle group. The vast majority of infusions was given following a fixed interval strategy (528 infusions, 91%), the remainder following on-demand retreatment (53 infusions, 9%). The latest RTX dose and interval at study conclusion are shown in table 3.

Table 3: Latest dose and interval of rituximab treatment at study end

Final dose	Number of participants	Final interval, months, median (IQR)
1000mg	37 (29%)*	6.4 (6.0 to 9.7)
500mg	51 (40%)*	6.2 (6.0 to 7.8)
200mg	38 (30%)*	6.0 (5.7 to 6.9)

IQR denotes interquartile range *percentages do not sum to 100% because of rounding

Flares, co-medication and adverse events

The incidence of flares, start or dose increases of csDMARDs, oral or injected glucocorticoids and adverse events is shown in table 4. The incidence rate of flare and glucocorticoid injections was significantly higher in the group receiving the highest RTX doses, potentially indicating confounding by indication.

Table 4: Incidence of flares, start or dose increases of csDMARDs, oral or injected glucocorticoids and adverse events.

Group	>1500mg RTX per year (n=28)		750-1500mg RTX per year (n=61)		<750mg RTX per year (n=37)	
Outcome	Incidence rate (per 100py)		Incidence rate (per 100py)	IRR	Incidence rate (per 100py)	IRR
Flare DAS28-CRP	38		33	0.86 (0.57 to 1.3)	17	0.46 (0.27 to 0.79)
IM/IA glucocorticoids	55		40	0.73 (0.51 to 1.0)	18	0.33 (0.20 to 0.55)
Oral glucocorticoids*	4.2		9.6	2.3 (0.77 to 6.7)	9.5	2.3 (0.72 to 7.1)
csDMARDs*	5.3		5.1	0.96 (0.33 to 2.8)	1.7	0.33 (0.06 to 1.7)
AE any†	42		48	1.1 (0.78 to 1.6)	49	1.2 (0.77 to 1.7)
AE grade≥3†	16		14	0.87 (0.46 to 1.6)	19	1.2 (0.63 to 2.3)
AE any infection†	19		18	0.96 (0.55 to 1.7)	19	1.0 (0.54 to 1.9)
AE infection grade≥3†	3.2		2.5	0.8 (0.19 to 3.4)	5.2	1.6 (0.41 to 6.6)

*start or dose increase; † adverse events categorized and graded according to the Common Toxicity Criteria Adverse Events v5[12]
AE denotes adverse event, csDMARD conventional synthetic disease modifying anti-rheumatic drug, DAS28-CRP disease activity score in 28 joints using CRP, IA intra-articular, IM intramuscular, IRR denotes incidence rate ratio, py patient-years, RTX rituximab.

Radiographic progression

Radiographs were available for 78 patients after a mean follow up of 2.4 years. Radiographic progression measured by SENS was similar in all dose groups (table 5, figure 1).

Table 5: Radiographic outcomes as measured by the Simple Erosion and Narrowing Score.

Yearly RTX dose	<750mg (n=22)	750-1500mg (n=37)	>1500mg (n=19)	p-value
Progression >0.5 points, n (%)	10 (45%)	20 (54%)	5 (26%)	0.16
Progression >2.3 (SDC), n (%)	3 (14%)	5 (14%)	0 (0%)	0.27
Median progression (IQR)	0 (-0.5 to 1.5)	1 (0 to 2)	0 (-0.5 to 1)	0.20
Median follow up, years (IQR)	2.3 (2.0 to 2.7)	2.2 (2.0 to 2.6)	2.1 (2.0 to 2.3)	NA
Mean follow up, years (sd)	2.4 (0.4)	2.3 (0.4)	2.4 (0.8)	NA

Scores on the SENS (indicating the level of erosions and joint space narrowing seen on radiographs of hand and feet) range from 0–86 and higher scores indicate more damage.
IQR denotes interquartile range, SDC smallest detectable change, RTX rituximab, sd standard deviation.

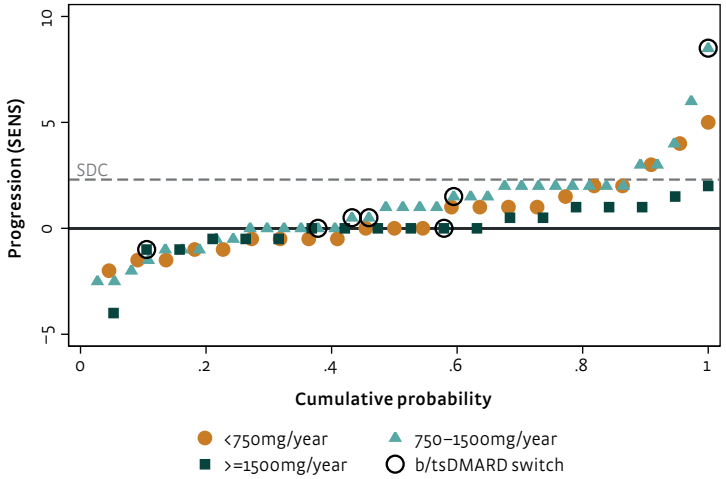

Figure 1: cumulative probability plot of radiographic progression

Progression was scored using the Simple Erosion and Narrowing Score (SENS), split by average yearly RTX dose from study start until b/tsDMARD switch or censoring. Scores on the SENS (indicating the level of erosions and joint space narrowing seen on radiographs of hand and feet) range from 0–86 and higher scores indicate more damage. SDC denotes smallest detectable change.

Discussion

This study shows that long term treat-to-target use of ultra-low doses of RTX is effective in a majority of RA patients responding well to standard dose RTX. Disease activity remained low and non-inferior to standard low-dose RTX (1000mg/6months), either according to original randomization or by received dose. Switching to other b/tsDMARDS or use of GC was rarely required and no clear differences in adverse events or radiographic progression could be shown.

These results confirm the results of the REDO trial and earlier smaller studies regarding the efficacy of ultra-low dose RTX: that RTX can be tapered to a much lower proportion of the authorized dose than other bDMARDs such as TNFi.[6-10,18] In TNFi, tapering strategies are able to reach, at a group level, about 50% of the authorized dose, while the mean yearly RTX dose of about 1000mg per year in this study is only a quarter of the authorized yearly dose.[2,19] This may be explained by the lack of dose-finding studies for RTX in RA, which may have resulted in an authorized dose too high on the dose response curve.

The use of ultra-low dose RTX has several clear benefits: primarily, it reduces medication costs and infusion duration. Another potential benefit is a reduction in adverse effects, specifically infections were seen to be lower in the ultra-low dose groups of the original REDO trial.[10] This is of additional relevance given the increased risk of severe COVID19 for patients using RTX.[20] Contrary to our earlier results, we were unable to confirm a lower rate of infections with ultra-low doses of RTX. This may be explained by less strict assessment of adverse events in the extension phase. In the original trial patients were actively asked three monthly if they experienced any adverse effects, while all data for the extension study was collected retrospectively from electronic patient records. This is reflected in the fairly low rate of recorded infections. Besides adverse events, evidence from other studies suggest an additional potential benefit of ultra-low doses: a better response to covid-vaccinations.[21,22]

Strengths of this study include the long follow-up, the setting as part of regular T2T care in multiple centers which ensures good generalizability, and the limited drop-out. The long-term follow-up alleviates concerns that the results of the REDO trial may be influenced by a carry-over effect of previous higher doses. It also allowed patients and clinicians to find the optimal dose for each patient through stepwise tapering.

This study has several potential limitations. Firstly, there was no standardized measurement frequency for disease activity. Combined with the influence of the COVID19 pandemic, this may have meant that disease activity was selectively measured more frequently in patients that had higher disease activity, while patients in remission predominantly stayed home. This may have resulted in an overestimation of disease activity, though not differentially so between RTX dose groups. However, overall, the number of disease activity measurements remained adequate to perform T2T with a mean of 2.54 per patient per year. Secondly, several outcomes (flares and glucocorticoid injections) appeared more favourable in the lower dose groups, which may be indicative of confounding by indication, i.e. that the patients doing best are more likely to reduce their dose. This would mean we both *overestimate* the efficacy of ultra-low doses, and *underestimate* the proportion of patients able to use these doses. However, tapering in those who do well is also an intended part of a dose reduction strategy and these results reassure that tapering does not appear to lead to increased rates of flare of glucocorticoid injections. Thirdly, as no systematic attempts to discontinue treatment were made, it is possible that in some patients even ultra-low dose treatment was unnecessary. While using ultra-low dose RTX in patients potentially able to stop RTX altogether is still a better option that treating the same patients with higher doses, it may result in some lack of assay sensitivity. However, the fact that a small difference in disease activity between doses was shown contradicts this possible lack of assay sensitivity. Furthermore, the fact that the original 200mg group ends up at an average yearly dose of 889mg shows that returning to higher doses was required in a sizeable proportion of patients, further supporting assay sensitivity. Also, there is vast experience that stopping of rituximab leads to flare in the large majority of patients, because on flare retreatment is still used widely. Finally, we were unable to obtain radiographs for all participants to assess radiographic progression. While no significant differences were found, a trend towards slightly higher progression in patients on lower doses of RTX was observed. Overall progression, however, was limited especially considering the long follow-up duration.

The effectiveness of ultra-low dose RTX seen in the current study raises questions on how to further improve RTX use in RA. In particular, two attractive possibilities are to start treatment with an ultra-low dose, or to replace ultra-low dose infusions with a subcutaneous injection. With regards to the optimal starting dose of RTX, 2x1000mg seems to be excessive given the previous systematic reviews showing non-inferior results of 2x500mg/1x1000mg. Based on our results of even lower doses, combined with some smaller studies or case reports, starting with an ultra-low dose may seem attractive.[6-10] Indeed, in the study of Chandramohan et al., favourable response rates were obtained from initial dosing with 500mg.[18] However, disease activity in that

study remained higher than ideal with only about half of patients reaching low disease activity (DA28-ESR<3.2). Also, the benefits of reducing the dose of the single initial infusion are smaller than those of reducing the dose of numerous retreatment infusions. In addition, the potential drawback of starting with a dose below 1000 mg is that it is unclear whether a lack of response is the result of the dose or a true non-response. A strategy of starting treatment with a 1000mg infusion and then reducing this step by step as long as disease control is maintained therefore seems most appropriate given the current evidence. A future study aiming to show non-inferiority of a starting dose smaller than 1000mg would be able to settle this question more definitively. With regards to subcutaneous administration, ultra-low doses make this a more viable option as the required injection volume is reduced. This would both negate the need for infusion facilities, and might further reduce infection risk, as these seem driven by higher peak RTX levels.[23] A bio-equivalence study comparing 336mg RTX SC to 200mg IV is currently ongoing.[24]

In summary, we show that that long term treat to target use of ultra-low doses of rituximab is effective in a majority of RA patients responding well to standard dose RTX. Disease activity remained low and non-inferior to standard low-dose RTX (1000mg/6months), either according to original randomization or by received dose. These data and the (potential) benefits of lower doses suggest that ultra-low doses of RTX should be considered as part of clinical practice in RA patients responding well to standard dose RTX.

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Chapter 7

Effect of using SENS or SHS on power of RA clinical trials to detect differences in radiographic progression

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Abstract

Objectives
The Simple Erosion Narrowing Score (SENS) is a simplification of the Sharp/van der Heijde score (SHS). Previous studies found SENS and SHS to have very similar measurement properties, but suggest that SENS has a lower discriminative ability that may result in reduced power. Therefore, we aimed to quantify the effect of using SENS rather than SHS on the power to show between-group differences in radiographic progression.

Methods
Using data from two clinical trials in rheumatoid arthritis (DRESS and BeSt), the SENS was derived from the SHS. Criterion validity of the SENS in relation to the SHS was assessed by calculating the Spearman correlation. The power of both scores to show a difference between groups was compared using bootstrapping to generate 1000 replications of each study. Then, the number of replications with a significant difference in progression (using Wilcoxon rank-sum and Kruskal-Wallis test for DRESS and BeSt, respectively) were compared.

Results
Correlations between SENS and SHS were all >0.9, indicating high criterion validity of SENS compared to SHS as a reference standard. There was one exception, the DRESS study showed a somewhat lower correlation for the change score at 18 months (0.787). The loss in power of SENS over SHS was limited to at most 12% (BeSt year 3). In addition, the difference in power between SENS and SHS is smaller at higher levels of power.

Conclusion
SENS appears to be a reasonable alternative to SHS, with only a limited loss of power to show between-group differences in radiographic progression.

Introduction

Joint damage and progression thereof is one of the main outcomes used in the assessment of rheumatoid arthritis (RA) treatment and is most often quantified using the Sharp/van der Heijde score (SHS).[1] The Simple Erosion Narrowing Score (SENS) is a simplification of the SHS and has been recommended for use in clinical practice to assess radiographic progression of RA because it combines a simpler, less time-consuming scoring method with measurement properties comparable to the SHS.[2] The SHS grades the erosions from 0 to 5 per joint in the hands and 0-10 per joint in the feet, and joint space narrowing (JSN) from 0 to 4 in each joint. In comparison the SENS assesses the presence of both erosions and JSN in the same joints as the SHS, but without grading them.

Previous studies comparing the SENS to the SHS have found very similar measurement properties,[2-6] but have suggested that the SENS may lack some discriminative ability compared to the SHS, which may result in a lower power to detect between-group differences in progression. This claim is based on the idea that the SENS score cannot measure any progression in a joint that already had erosions or JSN, resulting in a ceiling effect on the joint level, as demonstrated in data from the COBRA trial.[4] In a reanalysis of radiographic data from this study, authors showed that progression of erosions from previously eroded joints contributed relevantly to total progression of joint damage. In addition, when only focusing on joints not previously eroded, radiographic progression could not be shown past the initial phase of the study. An analysis of data from the BeSt study strengthens this finding by showing that between 11 and 27% of patients with SHS progression of ≥1 point did not have SENS progression.[6] As a result, the SENS has thus far not been recommended for use as an outcome in RA research.

While perhaps directionally convincing, the claim that SENS lacks between-group discriminative ability has not been quantified. Furthermore, there are several arguments that this effect may be quite limited. Firstly, a recent abstract compared the performance of both scores in the DRESS trial.[7,8] This trial consisted of patients with established RA, and showed a minimal difference in progression between treatment arms using SHS. This situation with existing joint damage at baseline and a minimal contrast between study arms should be where a lack of discriminative ability of the SENS is most clear. Yet, the SENS proved equally capable of detecting this minimal difference in progression, even slightly outperforming the SHS with regards to power in bootstrapped replications of the trial. Secondly, a study using data from the TEMPO trial failed to show indications of a ceiling effect affecting the total SENS score, as detection of progression using SENS was equally sensitive in all

quartiles of baseline SHS.[5] Thirdly, the studies that do suggest a lack of discriminative ability have some limitations: the analyses of the COBRA trial focused only on the erosion subscore and ignored the effects of JSN, which may somewhat compensate for a lack of discriminative ability based on erosion scores alone.[4] The analyses of the BeSt study focused on classifying individual patients as progressors or not, which is not as relevant at a group level and scores for research purposes need only to show between-group differences in progression.[6]

In summary, the SENS is a simplification of the SHS score with very similar measurement properties, but the SHS requires a factor 3.5 more time to perform.[2] There are arguments that the SENS may lack discriminative ability, but the effect of this on the power of a study to show differences in radiographic progression has not been quantified and may not be of relevant magnitude. A quantification of the effect is relevant, because it allows researchers to judge whether the advantages of SENS (reduction in time and associated costs) weigh up to the disadvantage of potentially lower power. The objective of this study is therefore to quantify the effect of using SENS rather than SHS on the power of RA trials to show differences in radiographic progression.

Methods

Data sources

This study uses data from two well-known clinical trials in RA: the DRESS and BeSt studies. These studies were selected because they detected relatively minor differences in SHS progression between treatment arms, meaning any lack of discriminative ability of SENS should become clear more easily than in studies with a large difference in progression. Both studies are on a treat-to-target background, aiming for (maintaining) low disease activity.

The DRESS study (Dutch trial register, NTR 3216, CMO region Arnhem-Nijmegen, NL37704.091.11) is an open label non-inferiority randomised controlled trial in which RA patients with low disease activity on a stable TNFi dose (adalimumab or etanercept) were randomised 2:1 to disease activity guided tapering or full dose continuation.[7] Radiographs of hands and feet were made at baseline and 18 months and independently scored by 2 trained readers using the SHS blinded for allocation and in chronological order.

The BeSt study is a 4-arm randomized controlled trial in early RA patients of sequential monotherapy vs. step-up combination therapy vs. initial combination therapy with

tapered high-dose prednisone vs. initial combination therapy with infliximab (Dutch trial register, NTR262 and NTR265).[9] Radiographs of hands and feet were made every 12 months and independently scored by 2 trained readers using SHS blinded for order and treatment allocation.

For each study, the SENS was calculated based on the individual joint scores of the SHS and not scored separately. For both scores, the mean of the two readers was used to minimise measurement error.

Analyses

First, we considered the criterion validity of SENS in relation to the SHS as a reference standard. This was assessed through correlations both cross-sectionally by determining the Spearman correlation between the absolute SENS and SHS scores, and longitudinally by determining the Spearman correlation between the change in SENS and SHS scores over the course of each study. We used the criteria set forth by the COSMIN initiative, regarding good measurement properties, to determine whether these correlations were sufficient (≥ 0.70).[10]

Secondly, we compared the power of both methods to show a difference in progression between treatment arms. For this purpose, we used bootstrapping to generate 1000 replications of each study and assessed for both SENS and SHS in how many replications a significant difference in progression could be shown using a Wilcoxon rank-sum test (for DRESS) or the Kruskal-Wallis test (for BeSt). In addition, because the effect on power might be dependent on the sample size, this process was repeated using random subsamples of each study from 90% of the sample size down to 10% in increments of 10 percentage points. For the BeSt study, this analysis was repeated for progression at years 1 through 5 as the between-group differences first increase over time and then gradually reduce again. Years 6 through 10 of the BeSt study were not considered as almost no between-arm contrast remained at this point. This allowed us to assess different between-group contrasts and the resulting relative power of the SENS and SHS.

Results

Baseline characteristics for the DRESS and BeSt are shown in Supplementary tables S1 and S2. DRESS included patients with long-standing RA and higher baseline radiographic damage (median SHS (IQR) 23 (6-50) in the tapering arm and 18 (9-47) for the usual care arm). BeSt included early RA patients with almost no radiographic damage at baseline. The median SHS (IQR) was 1.5 (0-4.5) in the sequential

monotherapy arm, 2 (0-6) in the initial combination with infliximab arm, 1.5 (0-3) in the initial combination with prednisone arm and 1.5 (0-6.5) in the step-up combination therapy arm.

Correlation between SENS and SHS

The correlations between both absolute SENS and SHS scores and changes in both scores over time are shown in table 1. For all time points, absolute correlations were high or very high, indicating high criterion validity of the SENS compared to the SHS as a reference standard. For change scores, only the DRESS study showed a somewhat lower correlation, at 0.787 for progression at 18 months. This could be explained by the higher baseline radiographic damage in this group, which means there is no possibility for progression with SENS in those joints with baseline damage.

Table 1. Spearman correlation between SENS and SHS in terms of absolute scores and as change from baseline.

	Absolute scores *Median (IQR)*		Spearman correlation	Change from baseline *Median (IQR)*		Spearman correlation
	SHS	SENS		SHS	SENS	
DRESS baseline	18.5 (6.5-49)	9.5 (4-21.5)	0.988	-	-	-
DRESS 18 months	19.5 (7-49)	10 (4-21.5)	0.987	0 (0-1)	0 (0-0.5)	0.787
BeSt baseline	1.5 (0-5)	1 (0-2.5)	0.976	-	-	-
BeSt 1 year	3 (0-7.5)	1.5 (0-4)	0.977	0 (0-1.5)	0 (0-1)	0.931
BeSt 2 year	2.5 (0.5-9)	1.5 (0.5-5)	0.986	0 (0-2.5)	0 (0-1.5)	0.961
BeSt 3 year	3 (0.5-10)	1.5 (0.5-5)	0.986	0.5 (0-3)	0 (0-1.5)	0.965
BeSt 4 year	3.5 (1-11)	2 (0.5-6)	0.982	1 (0-4)	0.5 (0-2)	0.957
BeSt 5 year	4 (1-11.5)	2 (0.5-6)	0.975	1 (0-5.5)	0.5 (0-3)	0.971

Power of SENS and SHS

Figure 1 shows the bootstrapped estimated power for the DRESS and the BeSt study at different times of follow up. It can be seen that the loss in power by using SENS over SHS is limited to at most 12% (BeSt study year 3). In addition, the difference in power between SENS and SHS is smaller at higher levels of power, and in some cases SENS even outperformed SHS (BeSt study year 4). Interestingly, despite the lower correlation between SENS and SHS progression in the DRESS study, the resulting loss in power was limited to less than 5%.

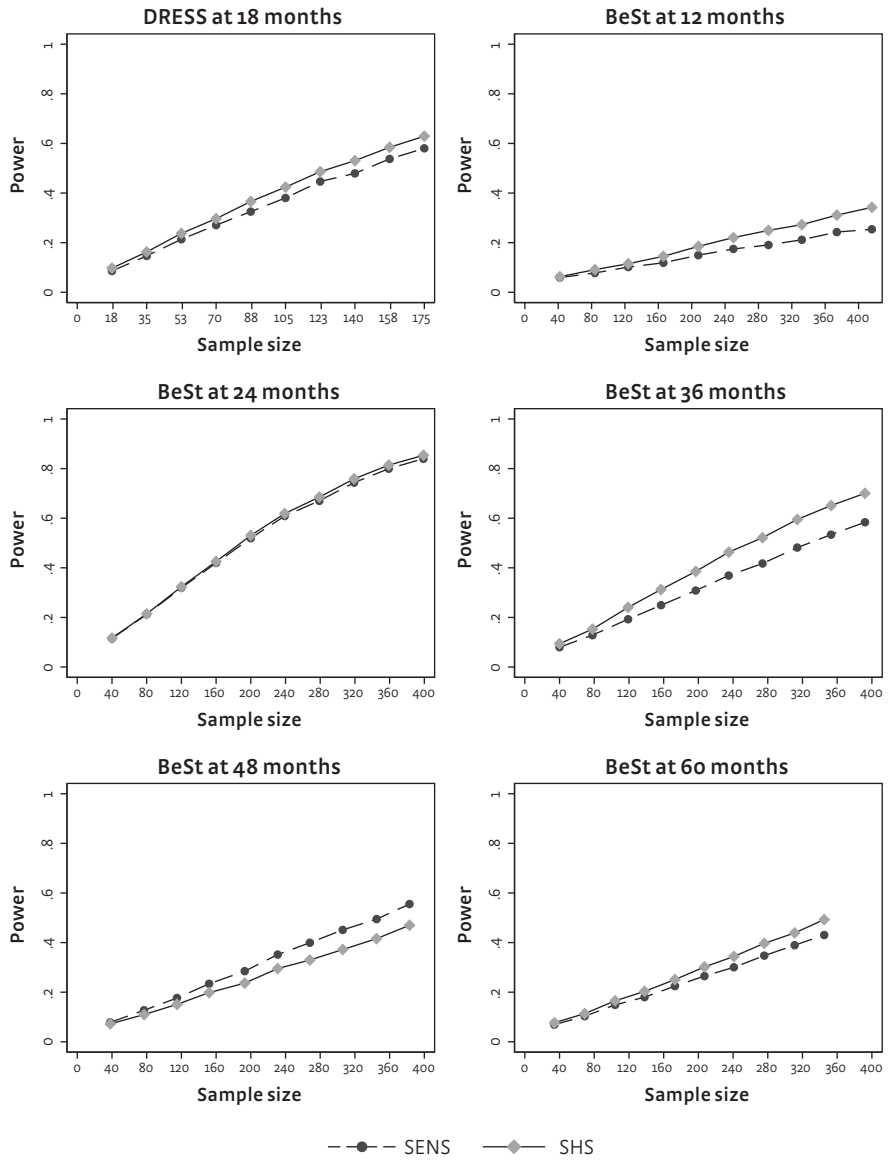

Figure 1: Power of SENS and SHS scores in bootstrapped replications of the DRESS and BeSt studies at various sample sizes and time points. Power is calculated as the proportion of bootstrapped replications with $p<0.05$ for either the Wilcoxon rank-sum test (for DRESS) or the Kruskal-Wallis test (for BeSt) for both scoring systems.

Discussion

This study shows that, at the trial level, the loss in power from using SENS over SHS is fairly limited. Interestingly, the results seem to suggest that the difference between the SHS and SENS in terms of power is smaller when SHS had higher power (DRESS 18 months, BeSt 24 months), which is where a difference in power is most relevant if a trial is powered to detect radiographic progression.

These results are consistent with earlier studies that have argued that the SENS may have lower discriminative ability due to its inability to score progressive erosions in joints with a previous erosion.[3-6] This is also reflected by the fact that criterion validity of SENS progression is lowest in the DRESS study which had a higher level of baseline radiographic damage. The added value of this study compared to the existing literature is a quantification of the limited degree with which this limitation impacts study power. This may be explained by several factors. For example, it is possible that patients with progression of previous erosions also develop new erosions in other joints, though there are indications that inflammation tends to recur in the same joints resulting in progression.[11,12] Another possibility is that the grading of damage does add some information, but also increases the amount of measurement error, as the subtle differences between 2 grades of erosions of JSN in SHS may be harder to score than simply the presence of erosions or JSN in SENS.

Results from this study can aid researchers in selecting a scoring system for radiographic damage in RA studies. The ideal scoring system for a specific study depends on the relative importance of the radiographic progression as an outcome, and on other considerations that may influence the sample size. For example, in a study that has radiographic progression as a secondary outcome, which already requires a high sample size for its primary outcome, SENS may be considered. On the other hand, a study with a limited sample size in established RA patients with high baseline radiographic damage, with radiographic progression as a primary outcome, may require the use of the more laborious SHS. The latter scenario may become increasingly uncommon as the diagnosis and treatment of RA improves and results in lower levels of radiographic damage. Of note, the substantial savings in scoring time and cost when using SENS could also be reinvested in optimizing power for radiological outcome by other means, such as scoring with an additional reader.

Strengths of this study include the inclusion of data from two landmark trials, which reflect a broad spectrum of RA patients. Furthermore, long-term follow-up was available for the BeSt study. A limitation of this study is the use of SENS derived from SHS instead of directly scoring radiographs using SENS, but previous research has shown the correlation between calculated and derived SENS to be very high.[2] Moreover, as this study was focused on power of the SHS and SENS at the group level, it does not provide information on the use of SENS to assess progression in individual patients.

In conclusion, SENS appears to be a reasonable alternative to SHS, with only a limited loss of power to show between-group differences in progression in clinical trials.

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Appendix

Supplementary table S1: baseline characteristics of the DRESS study

	Dose reduction (n=116)	Usual care (n=59)
Age, mean (sd)	59 (10)	58 (9)
Female, n (%)	71 (61%)	41 (69%)
Disease duration in years, median (IQR)	10 (5-16)	10 (6-16)
Erosive disease, n (%)	65 (61%)	34 (62%)
Rheumatoid factor, n (%)	91 (78%)	49 (83%)
Anti-CCP, n (%)	82 (71%)	45 (76%)
Baseline SHS, median (IQR)	23 (6-50)	18 (9-47)
Baseline SENS, median (IQR)	10 (4-22)	10 (5-20)

Numbers differ from full trial population as only participants with available radiographs were included.

Supplementary table S2: baseline characteristics of the BeSt study

	sequential monotherapy, n=112	initial combination with infliximab, n=120	initial combination with prednisone, n=113	step-up combination therapy, n=113
Age, mean (sd)	54 (13)	54 (14)	54 (14)	54 (13)
Female, n (%)	75 (67%)	78 (65%)	74 (65%)	81 (72%)
Symptom duration (weeks), median (IQR)	23 (14-54)	22 (13-39)	23 (14-52), n=112	26 (15-56)
Erosive disease, n (%)	82 (75%), n=109	87 (73%), n=119	80 (72%), n=111	76 (68%), n=111
Rheumatoid factor, n (%)	37 (33%)	40 (33%)	40 (36%)	41 (36%)
Anti-CCP, n (%)	35 (34%), n=103	38 (32%), n=117	49 (47%), n=105	41 (39%), n=105
Baseline SHS, median (IQR)	1.5 (0-4.5)	2 (0-6)	1.5 (0-3)	1.5 (0-6.5)
Baseline SENS, median (IQR)	1 (0-2.75)	1 (0-3)	1 (0-1.5)	1 (0-3)

Numbers differ from full trial population as only participants with available radiographs were included.

Chapter 8

General discussion

General discussion

Main findings

This thesis focusses on two aspects of efficient use of biologicals for rheumatoid arthritis (RA): reducing the dose, and switching to another drug. I will first highlight the main findings, and thereafter discuss some of the overarching issues that characterize these findings.

In **Chapter 2**, we looked at the cost-effectiveness of tapering TNF-inhibitors in RA patients with low disease activity. To do this, data from the DRESS trial was used. In this study, RA patients were randomized between protocolized tapering and usual care during the initial 18-month study. During the extension up to month 36, the usual care group also tapered as part of clinical practice. This allowed us to assess how well cost-effectiveness of protocolized tapering was maintained in the original tapering group, if tapering in clinical practice was cost-effective compared to usual care, and to compare cost-effectiveness of strictly protocolized tapering with tapering in clinical practice.

We found that cost-effectiveness of protocolized tapering was maintained up to 36 months. Tapering in clinical practice was less cost-saving and resulted in higher QALY loss than protocolized tapering, but was still cost-effective compared to usual care without tapering.

In **Chapter 3**, we assessed the effects of switching from tocilizumab to sarilumab, both IL-6 inhibitors, in RA patients responding well to tocilizumab. Given the similarity of both drugs, we expected that disease control would be maintained when switching to sarilumab, while providing advantages in terms of injection frequency, costs, and flexibility in times of drug shortages.

We found, however, that disease activity increased significantly after switching to sarilumab, and that many patients required to switch back to tocilizumab. We therefore conclude that both drugs are not interchangeable at the individual patient level.

Chapters 4, 5 and 6 concern the effectiveness of continued treatment with ultra-low doses of rituximab. Several case reports and a small study showed promising effects of rituximab doses of 50-200mg, much lower than the registration dose (2x1000mg per 6 months) or even the standard low dose often used in clinical practice (1x1000mg or 2x500mg per 6 months). We therefore designed the REDO trial. In this study, we

randomized RA patients 2:2:1 to doses of 200mg, 500mg and 1000mg, after they had responded well to higher doses of rituximab.

Results of the REDO trial showed that disease activity at 6 months was similar in all groups, but we could not show formal non-inferiority of the 200mg and 500mg doses. To expand on these results, we further followed these patients up to 3 years in an observational extension study.

The extension of the REDO trial showed that disease activity remained low and very few patients required a switch from rituximab to another biologic or targeted synthetic disease modifying anti-rheumatic drug (b/tsDMARD). These results were achieved with an average dose of rituximab of around 1000mg per year, about half of the standard low dose. A longitudinal mixed model showed that disease activity was significantly higher with lower doses of rituximab, but to a negligible degree, and confirmed non-inferiority of the lowest 200mg per 6 months dose compared to standard low dose.

Chapter 7 was focused on the Simple Erosion and Narrowing Score (SENS), which can be used to assess radiographic damage in RA. Compared to the gold standard Sharp-van der Heijde Score (SHS), the SENS is faster and easier to perform, but was suggested by previous studies to lack discriminative ability. We used data from 2 landmark RA trials to explore the effect of using the SENS over the SHS on the power to show between-group differences in radiographic progression.

The results showed that the loss in power from using the SENS over the SHS was limited. The results allow for trialists to weigh the small advantage in power of the SHS to the practical advantages of the SENS when deciding which radiographic scoring system to use.

Discussion

I would like to use this discussion as an opportunity to go more in depth on several aspects of research in rheumatoid arthritis (RA), and medical research more generally, that I found deserving of further elaboration. The first relates to one of the main topics of this thesis: tapering of medication. Previously, studies on this subject are often performed on a per-drug basis, or sometimes a per-class basis (e.g. tapering of TNF-inhibitors). I will argue that in fact the drug you are using may be one of the least important aspects of a tapering strategy, and that the treatment strategy itself is of greater importance than the drug to which it is applied. The second relates to the

authorized dose of rituximab, the factors that may have led to it being authorized in a dose that in retrospect was far higher than needed, and whether this may apply to other drugs too. The third and final aspect is more theoretical. At multiple points during this PhD, clinical findings of our studies ran contrary to the expected results based on what we thought we knew about the working mechanisms of drugs, disease or even measurement instrument. This raises the question of how much we should rely on this mechanistic knowledge to conduct clinical research. In my opinion, the mechanistic approach and the more epidemiological way of treating the body as a 'black box' without guessing as to the inner workings can reinforce each other far more than is currently the case.

Reinventing the tapering wheel

Landré-Beauvais finished his thesis describing several cases of rheumatoid arthritis rather boldly, by stating: "There is no need to report further cases of primary asthenic gout [as he named what we now call RA]; the ones I have just described provide sufficient evidence of the characteristics (...)".[1] While I dare not be quite as bold, I will argue that performing a randomized controlled trial of disease activity guided tapering for each different drug (be it a biologic, targeted synthetic, or conventional synthetic disease modifying anti-rheumatic drug (b/ts/csDMARD)) is no longer necessary in rheumatoid arthritis.

The necessity to show the effects of tapering separately for each DMARD rests on the assumption that the results of tapering strategies might be different for different drugs. While at first glance a logical assumption given the variety in drug targets, dosing schemes and routes of administration, this assumption is not strongly supported by the data we have on tapering strategies in RA and beyond. In fact, there are plentiful examples of the opposite.

Over the years, many tapering studies have been performed for the various types of DMARDs used to treat RA. The comparable results of these studies contradict the assumption that the drug used is the determining factor for the results of a tapering strategy in two ways.

Firstly, comparing studies using a similar tapering strategy but applying it to different DMARDs often reveals very similar study outcomes in terms of disease activity. For example, the TARA trial compared the tapering of a tumor necrosis factor inhibitor (TNFi) or csDMARD in patients using both. Results were very similar regardless of which drug was tapered first.[2,3] The SEAM-RA trial similarly compared stopping of methotrexate to tapering of etanercept in patients using both.[4] However, in this case the treatment strategy was different, as re-escalation of treatment required either

multiple visits with an increased disease activity, or a strongly increased disease activity, compared to the re-instatement of full dose after the first flare in the TARA trial. This did result in a difference in outcome between both strategies, because the outcome required sustained remission without worsening. However, regain of response after re-starting either methotrexate or etanercept on flare was almost identical. And indeed, some counting of dots in the supplemental figure shows us that the proportion of patients with low disease activity at 1 year was almost identical for all groups. This illustrates well, that although the potential for tapering is higher in csDMARDs (fewer showed disease worsening when stopping methotrexate in SEAM-RA, and csDMARDs could be tapered more than TNFi in TARA), the clinical outcomes of tapering either drug are the same after treat-to-target (T2T, perhaps better called taper to target in this context) is allowed to kick in.

Secondly, if one compares studies that taper the same DMARD, but use different tapering strategies, the results can be quite dissimilar. An example is the comparison between stepwise T2T tapering of TNFi in the DRESS study, compared to the immediate stopping of TNFi in the POET study.[5,6] While in the DRESS, disease activity only temporarily differed between the tapering and continuations groups, in POET there was a significant difference in disease activity between the stopping and continuation group at all time points past baseline.

Based on these studies, we can conclude that the clinical outcomes of a tapering strategy are not primarily determined by the drug that is being tapered. There are two caveats to this conclusion. Firstly, the degree to which a drug can be tapered is certainly different between drugs. An obvious example is rituximab, which can be tapered to around a quarter of the registered dose, while TNFi can be tapered to around half of the registered dose.[5,7] The reasons for these differences I will explore later in this discussion. Secondly, stepwise tapering strategies require that it is possible to re-instate the previous dose to regain control over disease activity should a flare occur. If there is strong reason to doubt that this is possible for some drug (or disease) due to the possibility of irreversible consequences of flare, then a more thorough investigation into its tapering potential is warranted. For the currently available DMARDs, though, this seems not to be the case. It has been consistently shown in many different DMARDs that after a flare caused by tapering or discontinuation, the majority of patients regain response by re-instating the previous dose.[2,4,5,8-10] One possible exception could be tapering or stopping concomitant csDMARDs (often methotrexate) used together with a bDMARD. Although there is no direct evidence supporting this, the rationale would be that withdrawing the protective effect of concomitant csDMARDS on antidrug antibody formation might result in formation of antidrug antibodies that is not reversed by reinstating the csDMARD.[11,12] Therefore, in the absence of evidence to the contrary, regaining effect when re-instating a higher dose seems to be a safe assumption.

Should we then just start tapering any new DMARD without first doing a study? In my opinion, the most appropriate approach at this point would be to perform an uncontrolled prospective cohort study. This study could serve to answer a number of questions that are of importance prior to implementation into clinical practice. One important outcome is how much there is to gain by tapering. As mentioned before, the degree to which the dose can be reduced differs between drugs. Given the effort put into tapering strategies (on the part of physicians but also the risk of flare for patients), the return on this investment affects the desirability of a tapering strategy. This also applies to some other factors such as the cost of a drug, its safety profile and its route of administration. A safe, cheap, oral drug that can be tapered on average by 10% is not an attractive candidate for tapering compared to an expensive, intravenously administered drug that causes frequent or highly impactful adverse effects which can be tapered by 75%. In addition to this, more practical aspects can be addressed such as the way tapering is performed: is a lower dose available? should the intervals be extended instead? Or perhaps tablets can be broken in half? How motivated are patients to taper?

Rituximab

The results of our studies on ultra-low doses of rituximab may be considered somewhat surprising. After all, we show that an average of approximately 1000mg per year is sufficient to maintain disease control in the REDO extension study (Chapter 6). That is only a quarter of the authorized dose! While tapering has also been shown possible in other DMARDs, the degree to which rituximab can be tapered is exceptional. For example, TNFi can be tapered to around 50% of the authorized dose.[5] Surely this means something has gone quite wrong at some point as this means many RA patients have been receiving much higher doses of rituximab than needed for a long time, with all the extra costs and side effects that come with this.

Interestingly, it was already after just 5 RA patients had been treated with RTX that researchers sought to reduce the amount of medication used, to quote Leandro et al. “After encouraging progress in the first five cases, further patients were treated with protocols involving a reduction in one or more components of the original protocol.”[13] Despite these good intentions, we still ended up with an authorized those that was in retrospect far too high, so what went wrong? And how can we prevent this happening in the future, or identify other drugs that may have a similarly high tapering potential?

The overly high authorized dose of rituximab for rheumatoid arthritis was caused by a combination of factors. The first factor is the lack of acute dose-limiting toxicity, which is common for biologics due to their specifically targeted nature.[14,15] A dose-escalation trial of rituximab showed no severe toxicity even at weekly doses of 2250mg/m^2 (approximately 4000mg) for 3 weeks.[16] This means there is a wide therapeutic window which encourages the selection of higher doses even if these are only marginally more effective, because, in the words of Primož Roglič, 'why not eh?'.[17] However, this strategy of basing the dose on what is tolerable all but ensures that most patients are being overtreated when a drug has a wide therapeutic window. Treatment with a higher dose than needed is still a problem if it does not lead to toxicity because the toxicity that is assessed is usually acute and severe. That means that using a lower dose may still give a relevant improvement regarding side effects occurring after chronic treatment, or less severe side effects that still impact patients' lives. This can be seen for rituximab in the occurrence of infections, which become less common with lower doses.[7,18]

A second factor leading to rituximab's high dosing was that rheumatoid arthritis was not its initial indication. It is far from unlikely that patients with non-Hodgkin lymphoma, the original indication for rituximab which comes with a higher B-cell load, require much higher doses than those with rheumatoid arthritis. Combined with the lack of acute dose-dependent toxicity, this meant that a relatively high dose was already known to be effective and safe for another indication. It then becomes very convenient to base the dose for rheumatoid arthritis on this knowledge and that is exactly what happened.

The third and final factor is one of incentives. Already we see there is not a lot of clear incentive to completely re-do the dose-finding phase just from a medical perspective. This incentive becomes even more limited when one considers the price of rituximab was also already set for the dosing in lymphoma. This means that not only would dose-finding specifically for rheumatoid arthritis require quite some effort, it then also has the potential to reduce the profitability of the drug if a lower dose turns out to be sufficient.

Finally, it is interesting to note that even after the clinical trial program of rituximab for rheumatoid arthritis found very similar results for the 2x500mg and 2x1000mg per 6 month doses,[19] the higher of the two was selected as the authorized dose. So even the limited dose-finding that was done, was not very well used. This is especially obvious in retrospect, as systematic reviews showed equivalence for both doses on most outcomes.[19,20] Anecdotally, it appears that concerns over possible immunogenicity (development of anti-drug antibodies) and small differences in radiographic outcomes outweighed the fact that both doses had equivalent clinical outcomes. Certainly with the data we now have of the effectiveness of even lower doses, we can safely say that both 2x500mg and 2x1000mg per 6 month are both on the flat plateau of the dose-response curve.

In summary, rituximab's overly high authorized dose, and resulting potential for tapering, are caused by 3 factors: a wide therapeutic window, the addition of a new indication, and the resulting lack of incentives for dose-finding for this new indication. As more specifically targeted drugs (whether they are a monoclonal antibody or small molecule) are developed, drug repurposing is likely to become more and more common as these targets play a role in multiple disease processes. Therefore, the circumstances that allowed rituximab to be overdosed in rheumatoid arthritis for many years will likely be applicable to many more drugs in the present and near future, both in rheumatology and in other specialties. Special attention should be paid in these cases to ensure that the right dose is selected when a drug is authorized for an additional indication. To achieve this, regulators could mandate manufacturers to show what the lowest effective dose is for a drug, rather than only showing it is more effective than placebo and acceptably safe. A way to do this may be to temporarily approve an initial dose (that was used in phase 3 trials, likely inspired by the earlier indications for that drug), but then require a trial to compare this dose with one or more lower doses until an inferior dose is found (or a dose that has practically no dose-dependent side-effects, though this is harder to demonstrate). Then, the lowest dose that is non-inferior to the temporarily approved dose should become the definitive approved dose.[3]

Clinicians should be aware of the possibility that the approved dose is overly high for many targeted immunomodulators, if not at the group-level, then certainly at the individual level for a considerable proportion of patients. Armed with this knowledge, physicians and patients should freely attempt tapering if the necessary T2T conditions are in place, and otherwise work to enable proper T2T as soon as possible to allow routine tapering (and the other benefits of T2T).[21]

The black box

At the start of this PhD, I submitted the protocol for the SAARTOOS study (Chapter 3) to the local ethics committee. We wanted to see if we could switch from one IL-6 inhibitor (tocilizumab) to another (sarilumab). We thought this could be possible

3 The process is eerily similar to T2T tapering, except it would be performed at a group level rather than at the individual patient level. Between-patient variability in required dose means it is likely still possible to taper individual patients further with T2T tapering, but at least this approach avoids starting with a dose that is needlessly high for everyone.

given their similarity and promising prior work.[22] If this was the case it would result in lower injection burden for the patients, lower costs for society and more flexibility in case of shortages (which became increasingly relevant during the COVID pandemic). The committee claimed that the study was not relevant because it was already clear that this switch would be possible without issues, and therefore did not approve it. We were suggested to just perform the switch as part of clinical practice and record the results in an observational study. A few years and a pandemic later, we stopped switching less than halfway through because it was becoming quite clear a lot of the patients were flaring.[23]

I give this example not just to get back at the ethics committee for not approving our initial protocol, but because it is a great illustration of how little we know about how these drugs work. Logically, the sarilumab should have worked fine. It inhibits the same receptor. Yet, in practice, only about half of the patients successfully switched, with the rest all flaring, going back to tocilizumab, or both. And there are plenty more examples like this, including one closely related to this thesis: Patients with lower b-cell counts did not respond better to lower doses of b-cell depleting rituximab.[24]

There are two possible reactions to situations like these. The first is the mechanistic approach: try to figure out where the theory went wrong, update it so that it does explain the observed results. The second is the black box approach: accept that you do not understand what's going on, treat the patient as a black box and focus on anything except the content of that black box. Both of these approaches are important, but the black box approach is sometimes underrated. Above all, it is crucial not to mix these up, because this leads to studies that are useful for neither approach and results in research waste.

The fact that the black box approach is underrated can be observed at almost every conference presentation. When it is time for the Q&A session, the questions are usually of the mechanistic type, such as "why does the treatment work in some patients but not in others?". Only very rarely do you see people accept this uncertainty and instead ask "how can we best deal with the fact that not everyone responds the same way to treatment?". The benefits of the mechanistic approach are undeniable and have enabled countless advances such as new treatment options and much more. However, the mechanistic approach provides these great benefits to the patients 10+ years from now, whereas the black box approach can bear fruit much sooner. Even better, unless a disease is outright cured later on, the black box advances on dealing with uncertainty maintain their benefit even if newer, more effective treatments are later introduced.

The T2T paradigm used in RA essentially follows a black box approach and is a good example in how it deals with the uncertainty of not knowing which patient will respond to what drug. We try to have the right inputs by using the most effective drugs, we try to measure the outputs by regularly scoring disease activity, and then we react to this (switch DMARD when one does not work, lower the dose when it works well). Regarding which drugs to use in each patient, we essentially just try a bunch until one works. But in all of its simplicity, this does actually work and allows the vast majority of patients to reach low disease activity or remission.

In the literature, I often see studies that are a mix between both approaches. This results in designs that answer no useful research question and conclusions that cannot be well supported. In my experience, this is especially common for prediction studies, so I will focus on that type of study in this section to illustrate the issue. For example, it is common to see a study that measures some biomarker, and correlates this with some measure of disease activity at the same time point. The problem is that the question "Is this biomarker associated with disease activity?" falls squarely in between the mechanistic and black box approaches and is useful for neither of them. Mechanistically, one is fundamentally interested in causal questions, which this question is not and so neither is its answer. The black box approach, however, is fine with an unexplained association. But, this then needs to be predictive in some way that improves patient outcomes (or maintains them, but at lower cost). All too often though, studies report correlations of concurrent biomarker and clinical measures, even in longitudinal studies. But there is no need for a biomarker of current disease activity. We already have perfectly adequate disease activity scores and have no need for another "interleukin-almost-CRP".

Then what about the studies that do actually use a biomarker to predict future rather than present outcome? They still often suffer from a very overlooked issue, and that is the fact that predicting some outcome (e.g. non-response to a DMARD), still is not very useful unless it also tells us that there is another DMARD to which the patient will respond well. Simply informing us that a patient is unlikely to respond doesn't really help unless we can do something about it. In other words, we require not simply a predictor, but a differential predictor.

A good example of this issue is the R4RA trial.[25] This study avoids many of the pitfalls mentioned above and assesses response to rituximab vs. tocilizumab in patients who are b-cell rich or poor in a synovial biopsy. Its primary finding is that "in patients with low or absent of B cell expression signature in synovial tissue an alternative treatment—such as IL-6 receptor inhibition with tocilizumab—is superior to B-cell targeting with rituximab". This seems quite logical, if there's no b-cells to target,

another therapy may a better option. Indeed, though not the primary outcome, the authors find that CDAI major treatment response is higher for tocilizumab 19/41 (46%) than for rituximab 9/38 (24%) in the b-cell poor group. However, the result is very similar for the b-cell rich group! There, it is 11/31 (36%) for tocilizumab vs. 5/33 (15%) for rituximab.[4] Using these numbers one can fairly easily conclude that there is no clear interaction between the drug and b-cell biopsy status. So why even bother with the biopsy then? One might as well give patients tocilizumab whether they are b-cell rich or not, and spare them a synovial biopsy.

In summary, it is of great importance to decide whether you are running a black box or mechanistic study and to make sure the design and desired conclusions of your study match with the type of study. Otherwise, it is likely all the effort of doing your study is wasted as it does not answer any relevant research question.

Conclusions and future research

To conclude, I would like to re-iterate what for me have been the most important take-aways from the work described in this thesis. Furthermore, I will propose some additional avenues of research that could be of value.

My main take-aways from the research that resulted in this thesis are the following:

- In RA, the success of tapering depends primarily on the taper to target strategy, not on the specific drug that is used. For the next drug, we should not re-invent the wheel with another tapering trial, but can suffice by tapering a cohort of patients to identify the degree to which it can be tapered and address practical concerns of tapering.
- Rituximab has been overdosed in RA for a long time, the authorized dose (2x100mg) is needlessly high for almost all patients, and the standard low dose (1000mg) is still more than most patients need. In addition, the conditions that allowed this to happen are common to many other targeted drugs. This means regulators should require manufacturers to determine the lowest effective dose to approve new drugs or indications, rather than just superiority over placebo with an acceptable level of safety.

4 In the paper, Humby et al. place a lot of emphasis on the results when measuring b-cell rich/poor status using RNA sequencing instead of histology, and indeed these results more closely correspond to the hypothesis that there is a difference between tocilizumab and rituximab only in the b-cell poor population. However, neither the trial protocol nor the trial registration mentions the use of RNA to classify patients as b-cell rich/poor. I therefore consider those results exploratory and focus only on the predefined histological classification.

- To avoid research waste, we should be very mindful of whether we are running a black box or mechanistic study and to make sure the design and desired conclusions of our study match with the type of study. We should also not forget the benefits of the black box approach. When faced with uncertainty, we should remember to ask ourselves not only how the uncertainty may be explained by increasing our knowledge of disease mechanisms, but also how we can best deal with the uncertain outcomes in clinical practice. Both approaches are needed: the former is quicker and more certain to lead to improved outcomes, while the latter has to potential to have much greater impact.

It is a tradition to end a discussion saying more research is needed. I want to break with that tradition a little, because for a large part RA treatment has been 'solved'. As I write this, the average DAS28-CRP of RA patients in the Sint Maartenskliniek is 2.24, i.e. below the threshold for remission.[26] This can also be seen in the type of studies that are performed. After a period with many studies aiming to achieve the same treatment results with fewer downsides, recent studies have aimed at prevention of RA rather than treatment.[27,28]

Of course, there are always questions remaining. One is particularly related to the efficient use of DMARDs, namely what target should be used when following the T2T paradigm. Recommendations differ on whether to target low disease activity or the more stringent remission.[29,30] There are potential benefits to both, with a more lenient target preventing overtreatment while a more stringent target may improve disease control but may also result in increased side effects and costs due to more intensive treatment.

Another subject that deserves further study is rituximab, for which I have both a black box and a mechanistic question that I'd love to see answered in the future. The former is to determine whether ultra-low doses can also be used when starting rituximab treatment, or if 1000mg is the group-level optimum for initial dosing and lower doses should be reserved for when initial response has been attained. The latter is fairly speculative and comes down to whether it actually works through B-cell depletion or in another way. The reason for this question is that there are indications that rituximab also binds to another protein, Sphingomyelin Phosphodiesterase Acid-Like 3b (SMPDL3b), that is also involved in inflammatory processes.[31,32] Studies have suggested that effects of rituximab to treat kidney disease and myositis may be (partly) caused by its effects on SMPDL3b.[33-35] I am very interested to see if this is confirmed and may also play a part in rituximab's effects (or side-effects) in RA and polymyalgia rheumatica.[36,37]

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Nederlandstalige samenvatting

Nederlandstalige samenvatting

Achtergrond

De ziekte die wij nu kennen als reumatoïde artritis (RA) werd voor het eerst beschreven in 1800 door een Franse arts genaamd Augustin Jacob Landré-Beauvais. Zijn beschrijvingen van de patiënten en de ziekte is anno 2023 nog steeds herkenbaar: een chronische ziekte die leidt tot ontstoken, gezwollen en pijnlijke gewrichten, die meer bij vrouwen voorkomt, en die veel verschillende gewrichten kan aantasten en zelfs kan beschadigen. Deze gewrichtsschade is hedendaags een stuk beter te zien door middel van röntgenfoto's. Tegenwoordig weten we dat een auto-immuunziekte die ontsteking van de gewrichten veroorzaakt. In Nederland worden ongeveer 90.000 mensen voor RA behandeld bij de reumatoloog.

Er zijn verschillende soorten medicijnen waarmee RA behandeld kan worden. NSAID's (niet-steroïde anti-inflammatoire geneesmiddelen) kunnen ook worden gebruikt om de symptomen te verlichten, maar kunnen de schade aan de gewrichten niet voorkomen. Corticosteroïden (bijvoorbeeld prednison) remmen ook de ontstekingen. Deze middelen kunnen de symptomen snel verlichten en de progressie van gewrichtsschade vertragen, maar zijn niet ideaal voor langdurig gebruik vanwege hun bijwerkingen (vooral in hogere doses). Daarom zijn anti-reumatische geneesmiddelen de voornaamste behandeling van RA. Deze middelen, vaak DMARDs (disease-modifying anti-rheumatic drugs) genoemd, remmen de ontstekingen en verminderen ook het optreden van gewrichtsschade. Er zijn verschillende klassen van deze DMARDs: de eerste keus bestaat uit de klassieke DMARDs. Dit zijn kleine moleculen die breed op het immuunsysteem inwerken. Het belangrijkste middel uit deze klasse is methotrexaat: de eerste keuze bij de behandeling van RA wegens zijn effectiviteit. Andere veelgebruikte klassieke reumaremmers zijn leflunomide, sulfasalazine en hydroxychloroquine. Als een patiënt niet reageert op een of meerdere van deze middelen, of hiervan te veel bijwerkingen krijgt is een volgende optie nodig. Dat zijn middelen die recenter ontwikkeld zijn: zogenaamde biologic DMARDs of targeted DMARDs. Biologic DMARDs bestaan uit eiwitten (vaak antilichamen) die specifieke ontstekingsstoffen in het lichaam remmen. De targeted middelen zijn kleine moleculen net zoals de klassieke DMARDs. Beide klasses hebben een meer gericht effect op een specifieke ontstekingsroute. Het zijn deze biologische reumaremmers waarop de focus ligt in dit proefschrift.

Misschien wel net zo belangrijk als de gebruikte medicijnen is de manier waarop ze worden gebruikt. Dit gebeurt in RA volgens het treat-to-target (T2T) principe. Deze strategie bestaat uit drie onderdelen:

1. Stel een doel voor een gewenst niveau van ziekteactiviteit
2. Meet of dit doel wordt bereikt of niet
3. Verander de behandeling totdat het doel is bereikt

Uit deze onderdelen volgt dat het nodig is om de ziekteactiviteit te kunnen meten. Hiervoor zijn in RA verschillende scores beschikbaar. Het meest is de Disease Activity Score met 28 gewrichten (DAS28) (of DAS28-CRP), alternatieven zijn de Simple Disease Activity Index (SDAI) en de Clinical Disease Activity Index (CDAI). Deze scores bestaan allemaal uit verschillende onderdelen. Als eerste een oordeel over de mate van ziekteactiviteit door de patiënt en/of de arts. Daarnaast volgen een meting van het aantal pijnlijke en gezwollen gewrichten, en in de meeste gevallen ook ontstekingsmarkers in het bloed: C-reactief proteïne (CRP) of erytrocytsedimentatiesnelheid (ESR). Als behandeldoel worden lage ziekteactiviteit of remissie nagestreefd.

Het vinden van de juiste behandeling gebeurt stapsgewijs. Op enkele uitzonderingen na hebben de meeste biologic en targeted DMARD's namelijk een vergelijkbare werkzaamheid: ongeveer een derde van de patiënten reageert goed, een derde vertoont een matige respons en een derde vertoont geen respons. Omdat het niet mogelijk is te voorspellen welke patiënten zullen reageren op welk middel is het belangrijk om het T2T-principe te volgen en op tijd over te stappen op een ander medicijn bij onvoldoende respons. Dit proces herhaalt zich totdat het behandeldoel is bereikt. De volgorde waarin de verschillende DMARDs worden geprobeerd is hierbij naast de werkzaamheid, ook gebaseerd op de bijwerkingen, kosten en voorkeuren van de patiënt.

Ondanks dat dit stapsgewijze proces wat weinig verfijnd lijkt, lukt het hiermee wel om de grote meerderheid van de patiënten hun behandeldoel te laten bereiken. Daarom gaat dit proefschrift vooral over wat we moeten doen als het behandeldoel eenmaal bereikt is.

Meer dan ziekteactiviteit

We hebben gezien hoe het met het vallen en opstaan van T2T mogelijk is om bij de meeste patiënten remissie of een lage ziekteactiviteit te bereiken. Probleem opgelost! De ziekte is onder controle, de patiënt is tevreden, wat wil men nog meer?

Wat we tot nu toe niet hebben meegenomen zijn de minder fijne kanten van medicatiegebruik. Het kan leiden tot bijwerkingen, veel medicijnen voor RA zijn erg duur, en het gebruik ervan is niet altijd even gemakkelijk (denk aan patiënten die zichzelf moeten injecteren of naar het ziekenhuis moeten komen voor een infuus). Nog voordat de naam RA bestond, merkte Landré-Beauvais al op dat er ook naar de nadelen van mogelijke behandelingen moet worden gekeken, hij zei namelijk: "de nadelen van plaatselijke verzachtende middelen zwaarder wegen dan hun werkzaamheid".

De meest voor de hand liggende manier om de nadelen van medicatiegebruik te verminderen is natuurlijk om er minder van te gebruiken. Omdat de laagste effectieve dosis van een medicijn van persoon tot persoon varieert en tot nu toe niet te voorspellen is, gaat dit het beste door opnieuw het toepassen van T2T. Dit noemen we ook wel ziekteactiviteitsgestuurd afbouwen. De effectiviteit van deze strategie is duidelijk in RA, en ook voor andere aandoeningen zowel binnen als buiten de reuma wordt deze soms toegepast.

Resultaten

In **hoofdstuk 2** hebben we de kosteneffectiviteit van dit afbouwen bekeken. Hiervoor gebruikten we data uit het DRESS onderzoek. Hierin werd bij RA patiënten met een rustige ziekte het gebruik van TNF-remmers stapsgewijs afgebouwd. Het onderzoek bestond uit twee delen, in de eerste 18 maanden werd door loting bepaald of deelnemers in de groep kwamen die zou afbouwen volgens een protocol of in de controlegroep die zou doorgaan met de huidige dosering. In het tweede deel, van maand 18 tot 36, werd het ook voor de controlegroep mogelijk om af te bouwen omdat dit toen deel werd van normale zorg. Hierbij werd dus wat minder geprotocolleerd gewerkt dan in de eerste 18 maanden. Deze verschillende groepen en periodes hebben we toen vergeleken. Doel hierbij was om te zien of het afbouwen van TNF-remmers ok na 18 maanden kosteneffectief bleef, of afbouwen in reguliere zorg kosteneffectief was, en of er een verschil zat in kosteneffectiviteit tussen het afbouwen volgens een streng protocol of in de reguliere zorg.

De resultaten van dit onderzoek lieten zien dat de kosteneffectiviteit van afbouwen grotendeels behouden bleef. Ook werd duidelijk dat het afbouwen in de reguliere zorg tot grote kostenbesparingen leidde zonder relevant verlies aan effectiviteit. Het geprotocolleerde afbouwen was echter wel duidelijk meer kosteneffectief dan het afbouwen in de reguliere zorg.

In **hoofdstuk 3** onderzochten we een andere manier om de nadelen van medicatiegebruik te verminderen. Hier keken we naar het wisselen tussen verschillende middelen. De twee medicijnen waar we naar keken waren tocilizumab en sarilumab. Tocilizumab en sarilumab lijken erg op elkaar, ze werken namelijk beide op dezelfde wijze in op het lichaam. Ook zijn de effecten van beide middelen vergelijkbaar.

Waarom dan toch proberen te wisselen van tocilizumab naar sarilumab? Hier zijn verschillende redenen voor. Ten eerste hoeft sarilumab minder vaak geïnjecteerd te worden: elke twee weken in plaats van elke week. Ten tweede, als we makkelijk zouden kunnen wisselen verhoogt dit de concurrentie tussen deze middelen, waardoor een lagere prijs bedongen kan worden. Ten derde zijn er soms medicijntekorten. Het is dan handig om een alternatief achter de hand te hebben. Dit bleek ook wel toen er door de coronapandemie een tekort aan tocilizumab ontstond.

Het onderzoek volgde mensen die wisselden van tocilizumab naar sarilumab. Hierbij wilden we aantonen dat de ziekte rustig bleef, en het niet vaak nodig was om terug te gaan naar tocilizumab. Na slechts 22 deelnemers bleek echter het tegenovergestelde te gebeuren: veel patiënten kregen een opvlamming van hun reuma en moesten extra medicijnen krijgen en/of terug naar de tocilizumab. Onze conclusie is dan ook dat tocilizumab en sarilumab niet zomaar uitwisselbaar zijn voor elke patiënt.

Hoofdstukken 4, 5 en 6 gaan over het middel rituximab, een andere biologische reumaremmer. Dit middel is ooit voor een bepaald type lymfeklierkanker (Non-Hodgkin lymfoom) ontwikkeld en wordt met een infuus gegeven. Later bleek het ook voor RA goed te werken. Hierbij is alleen niet goed meer gekeken welke dosis er minimaal nodig was. Origineel was de dosis elk half jaar een kuur van 2x1000mg, waarbij de 2 infusen ongeveer 2 weken na elkaar gegeven werden. Al snel bleek dat elk half jaar 1x1000mg of 2x500mg net zo goed werkte. Dit werd dus op veel plekken de standaard.

Later kwamen er aanwijzingen dat nog lagere doses ook effectief waren. Daarom voerden we de REDO studie uit in 5 Nederlandse ziekenhuizen. Hierbij gaven we een lagere dosis van 200mg of 500mg aan 142 mensen met RA die eerder goed reageerden op 1000mg rituximab. Door loting werden patiënten over deze doses verdeeld. Daarna werden ze 6 maanden gevolgd, waarbij de ziekteactiviteit, bijwerkingen en medicatiegebruik gemeten werden.

Uit de REDO studie bleek dat 200mg en 500mg een vergelijkbare werkzaamheid hadden als 1000mg, maar een relevant verschil in ziekteactiviteit konden we net niet uitsluiten. Ook leken de groepen die een lagere dosering kregen wat meer extra medicijnen nodig te hebben. Positief was ook dat er met de lagere doseringen minder infecties voorkwamen.

Om de resultaten van de REDO studie te bevestigen hebben we daarna de deelnemers nog een aantal jaar gevolgd. Hierbij werden de deelnemers in de klinische praktijk behandeld en de gegevens achteraf verzameld uit hun dossier. De dosis rituximab kon

door de arts in samenspraak met de patiënt zelf worden bepaald en aangepast worden aan de ziekteactiviteit.

Uit deze verlenging van de REDO studie bleek dat de lagere doses rituximab voor een groot deel van de patiënten een goede optie waren. We zagen dat over de hele groep de ziekte mooi onder controle bleef. Daarnaast was het voor een groot deel van de patiënten mogelijk om de lagere doses te gebruiken. Gemiddeld over de hele studie werd ongeveer 1000mg per patiënt per jaar gebruikt, de helft van de meest gebruikte dosering en zelfs maar een kwart van de officiële dosering. Daarnaast was het slechts zelden nodig om te wisselen naar een ander medicijn of om extra medicatie toe te voegen. Op röntgenfoto's van de handen en voeten zagen we ook geen duidelijke verschillen in gewrichtsschade. Bij mensen die goed reageren op 1000mg rituximab is het dus een goede optie om af te bouwen naar lagere doseringen.

Het beoordelen van gewrichtsschade is de focus van **hoofdstuk 7.** Gewrichtsschade kan bij RA optreden als het gevolg van de ontstekingen. Juist bij het verminderen van de medicatie is dit dus iets dat we goed in de gaten willen houden. Om dit op röntgenfoto's te beoordelen werd tot nu toe vaak de Sharp-van der Heijde score (SHS) gebruikt. Daarmee wordt een score gegeven aan schade in specifieke gewrichten. Het kost echter veel tijd en daarmee geld om deze score te gebruiken.

De SENS (Simple Erosion and Narrowing Score) lijkt erg op de SHS maar is sneller uit te voeren. Dit komt omdat per gewricht niet meer gekeken wordt hoe erg de schade is, maar alleen óf er schade is in dat gewricht. De vraag is alleen of deze score dan nog wel goed genoeg is om een verschil in gewrichtsschade tussen twee groepen aan te tonen.

In dit hoofdstuk hebben we data van twee grote RA studies (DRESS en BeSt) gebruikt om het verschil tussen de SENS en SHS beter in beeld te krijgen. We vergeleken hoe goed beide scores de verschillende groepen van beide studies uit elkaar konden houden qua gewrichtsschade. Hieruit bleek dat de SENS dit inderdaad iets minder goed doet dan de SHS, maar het verschil is slechts beperkt. Onze conclusie is dus dat de SENS ook voor onderzoek ingezet kan worden, de SHS nog wel de betere optie is als het erg belangrijk is om een klein verschil in schade aan te kunnen tonen.

Conclusies

Dit proefschrift beschrijft verschillende manieren om biologische reumaremmers bij RA zo efficiënt mogelijk in te zetten. Het stapsgewijs afbouwen is kosteneffectief, al helemaal als het geprotocolleerd gebeurt **(hoofdstuk 2)**. Het wisselen tussen twee vergelijkbare biologische reumaremmers (tocilizumab en sarilumab) bleek te leiden tot opvlammingen van de RA, waardoor er weer terug gewisseld moest worden. Deze strategie is dus ook niet aan te raden **(hoofdstuk 3)**. Het gebruik van lagere doses rituximab liet een stuk positievere resultaten zien. Het bleek voor de meerderheid van de patiënten mogelijk een lagere dosis te gebruiken, en dit bleef ook langere tijd goed werken **(hoofdstukken 4, 5 en 6)**. Als laatste vergeleken we de SENS en SHS, twee methodes om gewrichtsschade te scoren. Hierbij bleek de SENS een goed alternatief voor de SHS, hoewel de laatste wel iets beter in staat was om verschillen aan te tonen **(hoofdstuk 7)**.

Dankwoord

Dankwoord

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Emma, mijn lieve zusje, ik word altijd blij als ik je zie.

Opa en oma, als ik even mijn hoofd leeg moest maken ging ik vaak op de fiets langs bij jullie. Dat zal ik blijven doen want het is supergezellig. Daarnaast moet ik opa bedanken voor het verbouwen van ons halve appartement, en oma dat ze ons opa een paar maanden heeft uitgeleend daarvoor.

Stijn, ik zet jou maar gewoon bij het rijtje familie, maar ik had je ook bij vrienden, collega's, of student-assistenten kunnen zetten. Bedankt voor jouw steun op al die verschillende manieren.

Femmie, mijn officiële mentor tijdens mijn master en PhD, het was altijd fijn om je te zien, lekker bij te kletsen en jouw kijk op dingen te horen. Ook hebben we regelmatig iets samen kunnen doen voor onderwijs, wat altijd leuk was.

Wietske, mijn andere, minder officiële mentor, maar daarom niet minder belangrijk want ook jou heb ik regelmatig om advies kunnen vragen. Ik hoop dat we binnenkort weer eens samen aan een studie of onderwijs kunnen werken, dat is voor mijn gevoel alweer een tijdje terug.

Mijn (oud-)collega's van de Sint Maartenskliniek wil ik bedanken voor de hele fijne sfeer in ons ziekenhuis. Ik was begonnen iedereen los te noemen maar kwam er al snel achter dat het dan een eindeloos verhaal werd omdat ik al te lang op de SMK rondloop. Dus van Nadine nog voor de start van mijn promotie tot Thomas bij de laatste paper wil ik alle collega's van de afdelingen reumatologie en research bedanken voor de fijne samenwerking, vele gezellige momenten, en leuke congressen samen, jullie maken de SMK tot een unieke plek.

Daarnaast heb ik tijdens mijn promotie ook met veel plezier een dagje in de week gewerkt bij de IBD-groep in het Radboudumc. Frank en Marjolijn, bedankt dat jullie mij erbij haalden/erbij houden. Fenna, Maarten, Edo, Michiel, Vince, Lisa, Dorien, Monica, Pepijn, dank voor de fijne samenwerking en vele leuke momenten samen, of dit nu op de fiets in de Zuiderzeeklassieker was, in het ziekenhuis of bij een van de ~~etentjes~~ werkoverleggen.

Als laatste dan mijn paranimfen Celia en Léon. Celia, jij was er altijd. En als je er niet was, hing je aan de telefoon dus was je er toch. Ik heb enorm veel van je geleerd in onze vele gesprekken, misschien wel het meeste over mezelf, en daar ben ik je enorm dankbaar voor. Onze vriendschap maakt voor mij de hele PhD al de moeite waard. Léon, jij bent een absolute kopman maar een die het juist ook leuk vindt om de meesterknecht te zijn. Dit zowel in letterlijke zin als we samen fietsen, maar ook juist daarbuiten, of beide tegelijk (Passo Cereda, never forget). Wat ben ik blij dat wij al

sinds de middelbare school zulke goede vrienden waren en zijn gebleven. Ik hoop dat dit nog heel lang zo blijft, wellicht gaat zelfs het niveau van onze grappen een keer omhoog, maar dat zal wel niet.

Biography

Curriculum Vitae

Nathan den Broeder werd 21 december 1995 geboren in Nijmegen. In 2013 behaalde hij zijn VWO-diploma aan het Stedelijk Gymnasium Nijmegen, en begon hij aan de bachelor Biomedische Wetenschappen bij de Radboud Universiteit. Nadat hij in 2016 zijn bachelor diploma had behaald startte hij aan de master Biomedical Sciences, ook bij de Radboud Universiteit. Zijn masterstage deed hij bij afdeling operatiekamers onder begeleiding van Maroeska Rovers. In 2018 rondde Nathan zijn master *cum laude* af.

In datzelfde jaar startte hij met zijn promotietraject bij de Sint Maartenskliniek onder begeleiding van prof. dr. Frank van den Hoogen, prof. dr. Bart van den Bemt, dr. Aatke van der Maas en dr. Lise Verhoef. Dit traject had een focus op het efficiënt inzetten van biologicals bij reumatoïde artritis en heeft tot dit proefschrift geleid. Daarnaast was Nathan betrokken bij veel andere onderzoeken binnen de reumatologie bij de Sint Maartenskliniek, en ook als methodoloog werkzaam bij de afdeling Maag-, Darm-, Leverziekten van het Radboudumc.

Nathan is eind 2023 begonnen aan zijn huidige functie als onderzoeker bij de Sint Maartenskliniek, waarbij hij zich met name bezighoudt met klinische trials binnen de inflammatoire reumatische aandoeningen.

List of publications

List of publications

This thesis

den Broeder N, Bouman CAM, Kievit W, van Herwaarden N, van den Hoogen FHJ, van Vollenhoven RF, Bijlsma HWJ, van der Maas A, den Broeder AA. Three-year cost-effectiveness analysis of the DRESS study: protocolised tapering is key. Ann Rheum Dis. 2019 Jan;78(1):141-142.

den Broeder N, den Broeder AA, Verhoef LM, van den Hoogen FHJ, van der Maas A, van den Bemt BJF. Non-Medical Switching from Tocilizumab to Sarilumab in Rheumatoid Arthritis Patients with Low Disease Activity, an Observational Study. Clin Pharmacol Ther. 2023 Jul 10.

den Broeder AA, Verhoef LM, Fransen J, Thurlings R, van den Bemt BJF, Teerenstra S, Boers N, **den Broeder N**, van den Hoogen FHJ. Ultra-low dose of rituximab in rheumatoid arthritis: study protocol for a randomised controlled trial. Trials. 2017 Aug 30;18(1):403.

Verhoef LM, **den Broeder N**, Thurlings RM, van der Laan WH, van der Weele W, Kok MR, Moens HBJ, Woodworth TG, van den Bemt BJF, van den Hoogen FHJ, den Broeder AA. Ultra-low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial. Lancet Rheumatology. 2019 Nov;1(3):e145-e153,

Other publications

Jansen FM, **den Broeder N**, Lubeek SFK, Savelkoul EHJ, Marcus CM, Hoentjen F, van Dop WA. Cumulative thiopurine dosing and keratinocyte skin cancer in inflammatory bowel disease: a case-control study. Eur J Gastroenterol Hepatol. 2023 Oct 1;35(10):1123-1130.

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Jansen FM, Smits LJT, Thomas PWA, de Jong DJ, Kreijne JE, van Dop WA, **den Broeder N**, Hoentjen F. Feasibility of Reduced Clinical Monitoring in Patients with Inflammatory Bowel Disease Treated with Thiopurine Therapy. Dig Dis Sci. 2023 Jul;68(7):2936-2945.

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Heuvelmans J, **den Broeder N**, van den Elsen GAH, den Broeder AA, van den Bemt BJF. Effectiveness and tolerability of oral vs subcutaneous methotrexate in patients with rheumatoid arthritis. Rheumatology (Oxford). 2021 Dec 24;61(1):331-336.

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de Jong ME, Smits LJT, van Ruijven B, **den Broeder N**, Russel MGVM, Römkens TEH, West RL, Jansen JM, Hoentjen F. Increased Discontinuation Rates of Anti-TNF Therapy in Elderly Inflammatory Bowel Disease Patients. J Crohns Colitis. 2020 Jul 30;14(7):888-895.

Michielsens CAJ, Boers N, **den Broeder N**, Wenink MH, van der Maas A, Mahler EAM, Mulder MLM, van der Heijde D, van den Hoogen FHJ, Verhoef LM, den Broeder AA. Dose reduction and withdrawal strategy for TNF-inhibitors in psoriatic arthritis and axial spondyloarthritis: design of a pragmatic open-label, randomised, non-inferiority trial. Trials. 2020 Jan 15;21(1):90.

Kersten BE, **den Broeder N**, van den Hoogen FHJ, Knaapen-Hans HAK, van den Ende CHM, Vonk MC. Treatment with cyclophosphamide i.v. pulse therapy is an option for effective treatment of skin fibrosis in patients with early systemic sclerosis. Rheumatology (Oxford). 2020 Jul 1;59(7):1550-1555.

Mahler EAM, den Broeder AA, **den Broeder N**, Bijlsma JWJ, Snijders GF, van den Hoogen FHJ, van den Ende CHM. Short-term clinical worsening is a clear predictor for worsening at 2 years in established knee and hip osteoarthritis. Clin Exp Rheumatol. 2019 May-Jun;37(3):414-421.

Tweehuysen L, **den Broeder N**, van Herwaarden N, Joosten LAB, van Lent PL, Vogl T, van den Hoogen FHJ, Thurlings RM, den Broeder AA. Predictive value of serum calprotectin (S100A8/A9) for clinical response after starting or tapering anti-TNF treatment in patients with rheumatoid arthritis. RMD Open. 2018 Apr 9;4(1):e000654.

Lesuis N, **den Broeder N**, Boers N, Piek E, Teerenstra S, Hulscher M, van Vollenhoven R, den Broeder AA. The effects of an educational meeting and subsequent computer reminders on the ordering of laboratory tests by rheumatologists: an interrupted time series analysis. Clin Exp Rheumatol. 2017 May-Jun;35(3):379-383.

Lesuis N, van Vliet J, Boers N, **den Broeder N**, Cats H, Hulscher ME, Verrips A, den Broeder AA. The value of routine creatine kinase and thyroid stimulating hormone testing in patients with suspected fibromyalgia: a cross-sectional study. Rheumatology (Oxford). 2016 Jul;55(7):1273-6.

Research data management

Research data management

General information on data collection

The research data in this thesis was collected at the department of Rheumatology in the Sint Maartenskliniek. Research Data Management was conducted according to the Findable, Accessible, Interoperable and Reusable (FAIR) principles. A detailed prescription of how these FAIR principles were applied is provided below.

Ethics and privacy

The data and serum samples that were collected for this thesis were obtained from human subjects. The studies in Chapters 2, 5 and 7 were approved by the medical and ethical review board committee (METC, Medisch Ethische Toetsings Commissie) on Research Involving Human Subjects region Arnhem Nijmegen, the Netherlands, numbers NL37704.091.11, NL57520.091.16, and NL225 (Dutch Trial Register). Chapters 3 and 6 were provided a waiver for ethical approval, numbers 2019-5828 and 2019-5083. All participants provided informed consent. All the studies involving human subjects were performed in accordance with the Declaration of Helsinki. The privacy of the participants in these studies was warranted by using encrypted and unique identification codes. The encryption keys were stored separate from study data and were only accessible to members of the study team or to those who are involved with quality control of scientific research.

FAIR principles

Findable

All the data that was obtained during the studies is stored on department servers (Sint Maartenskliniek under V:\research_reuma_studies). Non-electronical data is stored in a filing cabinet with a keyed lock to prevent unauthorized access to the documents, at the rheumatology department (room P.1.16) of the Sint Maartenskliniek. Serum samples are pseudonymized and stored at the department of clinical chemistry of the Sint Maartenskliniek, in freezers belonging to the Canisius Wilhelmina Hospital.

Accessible

All data will be available upon reasonable request to the corresponding author. The following manuscripts were published open-access:

- den Broeder AA, Verhoef LM, Fransen J, Thurlings R, van den Bemt BJF, Teerenstra S, Boers N, den Broeder N, van den Hoogen FHJ. Ultra-low dose of rituximab in rheumatoid arthritis: study protocol for a randomised controlled trial. Trials. 2017 Aug 30;18(1):403. doi: 10.1186/s13063-017-2134-x. PMID: 28854956; PMCID: PMC5577818.

• den Broeder N, den Broeder AA, Verhoef LM, van den Hoogen FHJ, van der Maas A, van den Bemt BJF. Non-Medical Switching from Tocilizumab to Sarilumab in Rheumatoid Arthritis Patients with Low Disease Activity, an Observational Study. Clin Pharmacol Ther. 2023 Jul 10. doi: 10.1002/cpt.2999. Epub ahead of print. PMID: 37429827.

Interoperability

All data was documented in predefined Excel file formats, resembling the METC filing format to ensure interoperability. For the studies in Chapters 3, 5 and 6, data was collected using electronical case report forms (CASTORedc).

Reusable

Serum samples from the REDO study (chapter 5) will be saved for 10 years after study termination. Data from this study will be saved for 25 years after study termination. Data from chapters 3 and 6 will be saved for 15 years after study termination. Data from chapters 2 and 7 was already reused from the original trials.

PhD portfolio

PhD portfolio

Training activities	Hours
Courses	
- DAS gewrichtsscoretraining (2018) afdeling reumatologie, Radboudumc	6.00
- Radboudumc - eBROK course (2019)	42.00
- RIHS - Introduction course for PhD candidates (2019)	15.00
- Radboudumc - Scientific integrity (2020)	20.00
- Missing data: consequences and solutions (2021) EpidM, Amsterdam UMC	18.00
- Multilevel analyse (K74) (2021) EpidM, Amsterdam UMC	21.00
- Introduction to Bayesian Statistics (R84) (2022) EpidM, Amsterdam UMC	16.00
- Radboudumc - Re-registration BROK (2023)	5.00
Seminars	
- Symposium Treatment of rheumatic diseases: developments and opportunities (2019) Sint Maartenskliniek	2.00
- Workshop regressietechnieken (2019) Sint Maartenskliniek	2.00
- Webinar Social Media for Scientists (2020) RIHS PhD Council	1.00
- WORKSHOP: SUPERVISING YOUR STUDENTS (2020) RIHS PhD Council	2.00
- WEON Pre conference: Teaching Epidemiology in an Online Society (2021) Netherlands Epidemiology Society	4.00
- WEON Pre-conference Accounting for missing data in statistical analyses (2021) Netherlands Epidemiology Society	2.00
Conferences	
- Oral presentation, WEON conference 2018 (2018) Netherlands Epidemiology Society	16.00
- Poster presentation, EULAR conference Madrid (2019) European League Against Rheumatism	32.00
- Oral presentation, WEON conference 2021, online (2021)	16.00
- Oral presentation, ACR 2021, online conference (2021) American College of Rheumatology	32.00
- Poster presentation, EULAR conference 2022 Copenhagen (2022) European League Against Rheumatism	40.00
Other	
- Press-conference and interviews at ACR 2021 (2021) American College of Rheumatology	5.00
- Junior refereren epidemiologie (2021) Opleiders epidemiologie, Radboudumc	252.00
- RIHS PhD Retreat (2022)	8.00
- Reviewer for Rheumatology (Oxford) (2023) Rheumatology (Oxford)	48.00
Teaching activities	
Lecturing	
- Invited talk on ultra-low dose rituximab for VuMedi.com (2021) VuMedi	2.50
- Lecture Study population and patient inclusion in practice (2020) Radboudumc	2.00

Supervision of internships / other	
- TA for computer practicals BMS61 Statistical modeling in observational research (2018) Radboudumc	20.00
- TA for computer practicals MMST MMSK MSc Molecular Mechanisms of Disease (2019) Radboudumc	90.00
- Supervision BSc student project for clinical research minor (2021) Radboudumc	25.00
- Supervision MSc internship Amy Peeters (2023) Radboudumc	30.00
- Organization of journal club (2023) Sint Maartenskliniek	50.00
- BMS74 section on clinical trials (2019-23) Radboudumc	30.00
- Supervision internship turned PhD Evy Ulijn (2024) Sint Maartenskliniek	375.00
Total	**1,229.50**

Theses SMK

Theses SMK

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.

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