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ORIGINAL RESEARCH

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

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ABSTRACT

Background The REDO trial (REtreatment with Rituximab in RhEmatoid arthritis: Disease Outcome after Dose Optimisation) showed similar disease activity for retreatment with ultralow doses (200 mg and 500 mg per 6 months) compared with standard low-dose rituximab (RTX, 1000 mg 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 (disease activity score in 28 joints C-reactive protein (DAS28-CRP)), analysed using a longitudinal mixed model by original randomisation 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 15 December 2016, up to 30 April 2021. Drop-outs continued treatment elsewhere (n=3) or did not consent (n=13).

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

Interpretation Long-term use of ultralow doses of RTX is effective in patients with rheumatoid arthritis responding to standard dose RTX.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rituximab (RTX) is effective in the treatment of rheumatoid arthritis (RA). A standard low dose of 1000 mg/6 months has equivalent efficacy to the authorised 2×1000 mg/6 months. The REDO trial showed similar results for continuing treatment with ultralow-dose (500 mg or 200 mg) RTX compared with 1000 mg, in patients responding well to previous 1000 mg RTX. However, formal non-inferiority of the ultralow doses could not be shown, and the study only included a single RTX infusion.

WHAT THIS STUDY ADDS

⇒ This extension of the REDO study to more than 3 years of follow-up shows that long-term treat-to-target use of ultralow doses of RTX is effective in a majority of patients with RA responding well to standard dose RTX. Disease activity remained low and non-inferior to standard low-dose RTX (1000 mg/6 months), either according to original randomisation or by received dose. Switching to other biological or targeted synthetic disease-modifying antirheumatic drug or use of glucocorticoids was rarely required and no clear differences in adverse events or radiographic progression could be shown.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study and the (potential) benefits of lower doses in terms of reduced costs and adverse effects suggest that ultralow doses of RTX should be considered as part of clinical practice in patients with RA responding well 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 2×1000 mg or 2×500 mg per 6 months and the authorised dose is 2×1000 mg per 6 months.[2] A previous

systematic review has shown 2×500 mg (or 1×1000 mg) to be equally effective as the authorised 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. First, a higher dose is likely associated with more frequent or more severe adverse effects of RTX treatment. Second, 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 50 mg to 200 mg, the REDO trial assessed the efficacy of ultralow doses (200 mg and 500 mg) compared with standard low-dose RTX (1000 mg) for continued treatment of patients with RA in a double-blind randomised 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 200 mg and 500 mg groups compared with the 1000 mg 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 ultralow doses and also make it possible to identify patients in whom ultralow-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 ultralow-dose RTX on a longer term in a treat-to-target context. Further objectives were to explore the use of comedication, safety and radiographic progression in relation to the dose of RTX received.

METHODS

Design and patients

The REDO trial investigated the efficacy of ultralow-dose RTX in patients with RA with stable low disease activity (at least 6 months of disease activity score in 28 joints C reactive protein (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 authorised or standard low dose (2×1000 mg, 1×1000 mg, or 2×500 mg). 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 (15 December 2016 through 20 September 2018) up to 30 April 2021. Patients were followed up in all five participating centres, comprising two university hospitals and three 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 ultralow doses if the patient responded well to one during the trial, or to revert to 1×1000 mg otherwise. Patients who had been randomised to 1000 mg 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 (erythrocyte sedimentation rate) 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.

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 and 3 years follow-up in three of the five study centres.

Randomisation and masking

In the initial randomised intervention phase of the REDO trial (months 0–6), patients were randomised 2:2:1 to a single RTX dose of 200 mg, 500 mg or 1000 mg, stratified by rheumatoid factor (RF) or anticitrullinated 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,[12] the use of RA comedication (csDMARDs and oral or intramuscular/intra-articular glucocorticoids (GC)), and the incidence density of adverse events (number, type and grade according to Common Terminology Criteria for Adverse Events v5).[13]

Radiographs were scored according to simple erosion narrowing score (SENS) by two independent readers without blinding and in known chronological order to maximise sensitivity to detect progression.[14]

Statistical analyses

Mean DAS28-CRP was analysed 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 randomisation 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, GC 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.[15] 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 treat-to-target (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 GCs, initiation or dose increase of csDMARDs and adverse events, three groups were defined based on the mean yearly RTX dose during follow-up: >1500 mg, 750–1500 mg, and <750 mg. The group >1500 mg per year corresponds to a standard low dose of 1000 mg per 6–8 months, 750–1500 mg includes an ultralow dose of 500 mg per 6–8 months or 1000 mg with a longer interval and <750 mg is any ultralow doses lower than 500 mg 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 analysis of variance 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 two raters) were compared using Fisher's exact test.[16] 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

Out of 142, 126 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 randomised to 1000 mg in the original trial, 6 to 500 mg, and the remaining 7 to 200 mg, which is in line with the 1:2:2 allocation ratio. Data were collected for each patient from the moment of inclusion in the REDO trial (ranging 15 December 2016 through 20 September 2018) up to the last visit prior to 30 April 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. One thousand twenty-six 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 randomisation group showed a mean DAS28-CRP (95% CI) during follow-up of 2.2 (2.0 to 2.5) in the 1000 mg group, 2.3 (2.1 to 2.4) in the 500 mg group and 2.4 (2.2 to 2.5) in the 200 mg group. Compared with the 1000 mg group, both the 500 mg group (0.04 points higher (95% CI −0.24 to −0.32)) and the 200 mg group (0.12 points higher (95% CI −0.16 to −0.41)) were non-inferior in terms of disease activity.

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 to 0.25) points higher per 1000 mg less RTX in the past year. The upper limit of this CI 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 to 0.40) higher for the lowest (200 mg per 6 months) compared with the highest (1000 mg per 6 months) RTX dose. Sensitivity analyses restricting the calculations of RTX dose to infusions within a 6-month or 9-month window gave similar outcomes of 0.27 (95% CI 0.14 to 0.40) and 0.25 (95% CI 0.11 to 0.40) points higher for the 200 mg per 6 months dosing compared with 1000 mg per 6 months, respectively.

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

Table 1 Baseline characteristics

Original randomised dose	1000 mg RTX (n=26)	500 mg RTX (n=52)	200 mg 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.[24 25]
†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 to 86 and higher scores indicate more damage.
ACPA, anticitrullinated protein antibody; ACR, American College of Rheumatology; b/tsDMARD, biological or targeted synthetic disease modifying antirheumatic drug; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28, disease activity score in 28 joints; RA, rheumatoid arthritis; RF, rheumatoid factor; SENS, simple erosion narrowing score.

RTX USE

RTX persistence was 93%: nine patients switched to another b/tsDMARD during follow-up. Their last RTX dose was 1000 mg in six patients and 500 mg in three 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 978 mg (IQR: 684–1414): 1374 mg (IQR: 973–1777) in the original 1000 mg/cycle group, 915 mg (IQR: 704–1241) in the 500 mg/cycle group and 889 mg (IQR: 565–1212) in the 200 mg/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. Individual patient doses and intervals are shown in online supplemental figure 1.

FLARES, COMEDICATION AND ADVERSE EVENTS

The incidence of flares, start or dose increases of csDMARDs, oral or injected GCs and adverse events is shown in table 4. The incidence rate of flare and GC injections was significantly higher in the group receiving the highest RTX doses.

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).

DISCUSSION

This study shows that long-term treat-to-target use of ultralow doses of RTX is effective in a majority of patients with RA responding well to standard dose RTX. Disease activity remained low and non-inferior to standard

Table 2 Latest DAS28-CRP at study end

Original randomised dose	1000 mg RTX (n=26)	500 mg RTX (n=52)	200 mg RTX (n=48)
DAS28-CRP, mean (SD)	2.5 (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.
DAS28-CRP, disease activity score in 28 joints C reactive protein; RTX, rituximab.

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

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

*Percentages do not sum to 100% because of rounding.

low-dose RTX (1000 mg/6 months), either according to original randomisation 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 ultralow-dose RTX: that RTX can be tapered to a much lower proportion of the authorised dose than other bDMARDs such as TNF inhibitors (TNFi).[6–10 17] In TNFi, tapering strategies are able to reach, at a group level, about 50% of the authorised dose, while the mean yearly RTX dose of about 1000 mg per year in this study is only a quarter of the authorised yearly dose.[2 18] This may be explained by the lack of dose-finding studies for RTX in RA, which may have resulted in an authorised dose too high on the dose–response curve.

The use of ultralow-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 ultralow-dose groups of the original REDO trial.[10] This is of additional relevance given the increased risk of severe COVID-19 for patients using RTX.[19] Contrary to our earlier results, we were unable to confirm a lower rate of infections with ultralow 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 3 monthly if they experienced any adverse effects, while all data for the extension study were 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 ultralow doses: a better response to COVID-19 vaccinations.[20 21] A possible concern of ultralow-dose RTX is that patients with a higher RTX dose over time appear to have slightly lower disease activity and lower radiographic progression in this study. However, these differences are limited and could also be a consequence of transient flares during the tapering process, which are then addressed by reinstating the previous dose.

Strengths of this study include the long follow-up, the setting as part of regular T2T care in multiple centres which ensures good generalisability, 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. First, the COVID-19 pandemic and lack of standardised measurement frequency for disease activity could have influenced our results. It 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

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

Group	>1500 mg RTX per year (n=28)	750–1500 mg RTX per year (n=61)		<750 mg RTX per year (n=37)	
Outcome	Incidence rate (per 100 py)	Incidence rate (per 100 py)	IRR	Incidence rate (per 100 py)	IRR
Flare DAS28-CRP	38	33	0.86 (0.57 to 1.3)	17	0.46 (0.27 to 0.79)
Intramuscular/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 categorised and graded according to the Common Toxicity Criteria Adverse Events v5.[13]
AE, adverse event; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP, disease activity score in 28 joints using CRP; IA, intra-articular; IRR, incidence rate ratio; py, patient years; RTX, rituximab.

Table 5 Radiographic outcomes as measured by the simple erosion and narrowing score

Yearly RTX dose	<750 mg (n=22)	750–1500 mg (n=37)	>1500 mg (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 (0–2)	0 (–0.5 to 1)	0.20
Median follow-up, years (IQR)	2.3 (2.0–2.7)	2.2 (2.0–2.6)	2.1 (2.0–2.3)	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 to 86 and higher scores indicate more damage.
RTX, rituximab; SDC, smallest detectable change; SENS, simple erosion narrowing score.

per year. In addition, the pandemic caused some infusions to be delayed. This was most likely for 1000 mg infusions given their higher (perceived) risk regarding COVID-19, and may have resulted in lower yearly doses and potentially higher disease activity especially for those patients. Second, several outcomes (flares and GC injections) appeared more favourable in the lower dose groups, which may be indicative of confounding by indication, that is, that the patients doing best are more likely to reduce their dose. This would mean we both *overestimate* the efficacy of ultralow 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 GC injections. Third, as no systematic attempts to discontinue treatment were made, it is possible that in some patients even ultralow-dose treatment was unnecessary. While using ultralow-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 200 mg group ends up at an average yearly dose of 889 mg shows that returning to higher doses was considered necessary in a sizeable proportion of patients, further supporting assay sensitivity. Also, there is vast experience that stopping of RTX 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

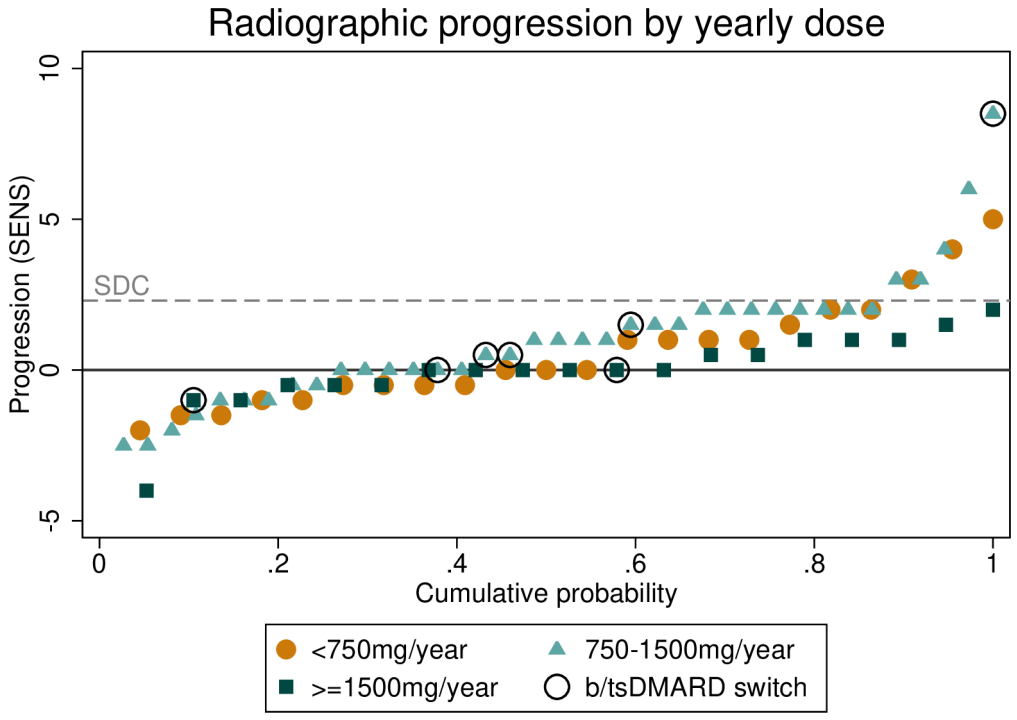

Figure 1 Cumulative probability plot of radiographic progression. Progression was scored using the simple erosion and narrowing score (SENS), split by average yearly rituximab (RTX) dose from study start until biological or targeted synthetic disease modifying antirheumatic drug (b/tsDMARD) switch or censoring. Scores on the SENS (indicating the level of erosions and joint space narrowing seen on radiographs of hand and feet) range from 0 to 86 and higher scores indicate more damage. SDC denotes smallest detectable change.

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 ultralow-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 ultralow dose, or to replace ultralow-dose infusions with a subcutaneous injection. With regards to the optimal starting dose of RTX, 2×1000 mg seems to be excessive given the previous systematic reviews showing non-inferior results of 2×500 mg/1×1000 mg. Based on our results of even lower doses, combined with some smaller studies or case reports, starting with an ultralow dose may seem attractive.[6–10] Indeed, in the study of Chandramohan *et al*, favourable response rates were obtained from initial dosing with 500 mg.[17] However, disease activity in that study remained higher than ideal with only about half of patients reaching low disease activity (DAS28-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. The somewhat lower rate of LDA and remission at the end of follow-up for the group randomised to 200 mg in REDO reinforces this argument. A strategy of starting treatment with a 1000 mg 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 1000 mg would be able to settle this question more definitively. With regards to subcutaneous administration, ultralow 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.[22] A bioequivalence study comparing 336 mg RTX SC to 200 mg intravenous is currently ongoing.[23]

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

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