Trials

STUDY PROTOCOL

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Treat-to-target fixed dose rituximab retreatment versus fixed interval retreatment with disease activity-guided rituximab dose optimisation for patients with rheumatoid arthritis: study protocol for a multicentre randomised controlled superiority trial focusing on long-term disease impact (RITUXERA)

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Abstract

Background The optimal retreatment strategy with rituximab for rheumatoid arthritis (RA) remains a point of discussion. Depending on local guidelines, rituximab can either be administered at fixed intervals or when losing disease control, balancing therapeutic effectiveness with drug overexposure. However, treatment based on loss of disease control may significantly affect patients' lives, provoking uncertainty and potentially leading to progressive joint damage. Moreover, as low-dose rituximab proved to be effective in treating RA while decreasing toxicity, drug exposure may be limited by tapering down rituximab doses guided by disease activity.

Methods RITUXERA is a 104-week open-label multicentre randomised controlled superiority trial. In total, 134 patients with RA treated with rituximab will be 1:1 randomised when in need of retreatment (DAS28-CRP ≥ 3.2 with previous rituximab administration at least 24 weeks earlier) to either a treat-to-target-driven fixed dose retreatment strategy (usual care group) or fixed interval disease-activity guided dose optimisation strategy (experimental group). The usual care group will be retreated with fixed rituximab doses (1 × 1000 mg IV) in case of loss of disease control (DAS28-CRP ≥ 3.2). The experimental group will receive a 24-weekly rituximab treatment while tapering down the dose in a decreasing sequence if DAS28-CRP ≤ 3.2: 1 × 1000 mg IV (maximal dose), 1 × 500 mg IV, and 1 × 200 mg IV (minimal dose). If DAS28-CRP exceeds 3.2 at the six-monthly retreatment, patients will receive and remain on the previous effective dose. Study visits are planned every 12 weeks. Primary outcome is the comparison of longitudinal patient-reported disease impact over 104 weeks, measured with the Rheumatoid Arthritis Impact

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of Disease (RAID) instrument, analysed using a linear mixed model. Main secondary outcome is the comparison of longitudinal disease activity (DAS28-CRP) over 104 weeks.

Discussion The RITUXERA trial aims to explore the optimal retreatment strategy with rituximab for RA in terms of long-term patient-reported disease impact, by proposing a fixed interval disease activity-guided dose optimisation strategy as compared to a treat-to-target fixed dose strategy.

Trial registration CTIS 2023–506638-59–01 (registration date: 07 September 2023), ClinicalTrials.gov NCT06003283 (registration date: 17 August 2023).

Keywords Treatment strategies, bDMARD, Rituximab, Disease activity-guided dose reduction, Tapering, Rheumatoid arthritis

Background

Targeted B cell depletion is one of the treatment strategies for patients with rheumatoid arthritis (RA). This can be achieved with the biologic disease-modifying antirheumatic drug (bDMARD) rituximab, which is an anti-CD20 chimeric monoclonal antibody. Rituximab was originally developed for the treatment of non-Hodgkin's lymphoma, after which it became available for treating active severe RA [1]. Although treatment with rituximab has proven to be (cost-)effective compared to other bDMARDs for RA [2], it is associated with side effects, including an increased risk of potentially severe infections [3]. Furthermore, treatment with rituximab requires substantial healthcare resources, in part because it necessitates hospital admission for intravenous (IV) administration [4]. Therefore, exposure to rituximab should be limited to the furthest extent possible [5]. Different treatment strategies for rituximab are available for patients with RA. One strategy consists of retreating patients with rituximab only whenever there is a loss of disease control, defined by exceeding a cut-off of a composite disease activity measure. This option is considered a retreatment strategy in line with the treat-to-target paradigm, providing treatment to regain disease control [6]. A second strategy comprises retreatment with rituximab in case of a flare, based on clinical judgement without the use of disease activity measures, thus called an on-flare retreatment strategy. For both retreatment strategies, an interval of at least 6 months should be respected between two treatment courses. A third option is to systematically treat patients at fixed intervals, usually 6 months, regardless of disease activity. The aforementioned retreatment strategies were compared in several studies, in which no differences were found in terms of disease control between treat-to-target and fixed interval retreatment strategies [7], while on-flare retreatment strategies were found to lead to poorer disease control [8, 9].

The original proposed dosing schedule of rituximab consists of 2 infusions of 1000 mg two weeks apart, a regimen acquired from haemato-oncologic studies, with only limited dose finding studies in RA [10, 11]. Although determining the optimal rituximab dose was a research point on the agenda of the consensus statement on rituximab [12], only later studies have focussed on rituximab dose optimisation [13, 14]. In this regard, half doses of rituximab appeared to be equally effective combined with an enhanced safety profile compared with full doses [13]. As a consequence, low rituximab doses (1×1000 mg IV or 2×500 mg IV) are increasingly recommended [5, 15]. Moreover, research has demonstrated that even "ultra-low" rituximab doses, consisting of one administration of 500 mg or even 200 mg rituximab, are promising for RA treatment [14, 16, 17].

Which treatment strategy and which dosing regimen are preferable remains an ongoing point of discussion. In Belgium, criteria demand a loss of disease control, defined as a 28-joint Disease Activity Score (DAS28) ≥ 3.2, before a patient with RA can be retreated with rituximab, which can be considered a treat-to-target retreatment strategy. In this regard, a minimum interval of 6 months between treatment courses is required, and it seems that patients are often retreated using a standard high-dose regimen [18]. Although in certain patients it may be possible to delay retreatment courses well beyond 6 months [19], this retreatment strategy may entail some limitations. First, patients are forced to anticipate and often experience potentially debilitating flares of disease activity in order to be retreated with rituximab, which not only may invoke uncertainty but may also cause progressive joint damage. Second, as neither patients nor physicians are able to predict when a subsequent treatment cycle will take place, difficulties may arise in scheduling short-term rituximab administrations in case of sudden loss of disease control [20]. Third, high doses of rituximab seem to be frequently used in this retreatment strategy [18], entailing an increased risk of side effects. As a consequence, treat-to-target high-dose treatment strategies may not be in line with preferences of both patients and rheumatologists. Indeed, our previous qualitative research has demonstrated that both patients and rheumatologists were open towards rituximab dose reduction. Moreover, both perceived benefits of having a fixed

interval treatment strategy with rituximab, favouring a personalised approach for instance by adjusting administered doses based on individual disease activity levels [18, 20]. Considering all available evidence, an alternative therapeutic strategy in which rituximab is administered at fixed intervals with tapering of treatment doses dependent on individual disease activity levels may be a promising alternative. Such a personalised approach may reduce the overall disease impact perceived by patients with RA. Moreover, fixed interval treatment may potentially prevent flares of disease activity resulting in better retention of disease control, while using tapered doses of rituximab may simultaneously result in reduced health care costs and a beneficial safety profile. Therefore, we aimed to investigate whether a retreatment strategy of fixed interval disease activity-guided rituximab dose optimisation for patients with RA is superior in terms of reduction of patient-perceived disease impact and in terms of disease activity control, compared with a treat-to-target fixed dose rituximab retreatment strategy.

Methods

Study design and setting

The RITUXERA trial (RITUXimab tapEring in Rheumatoid Arthritis) is a 2-year multicentre investigator-initiated open-label parallel group superiority randomised controlled trial (RCT). The trial will be conducted in seven health care centres across Belgium, including two university centres (University Hospitals Leuven (UZ Leuven) in Leuven and Cliniques Universitaires Saint-Luc in Brussels), three general hospitals (Heilig Hart Leuven in Leuven, Onze-Lieve-Vrouwziekenhuis in Aalst, and Ziekenhuis Netwerk Antwerpen Jan-Palfijn in Antwerp), and two private practices (ReumaClinic in Genk and Reumacentrum in Genk). UZ Leuven takes up the role of sponsor and acts as the coordinating study centre. The trial funders had no role in the choice of study design nor will they be involved in data interpretation and analysis, writing of future reports, or publication of trial results.

Objectives

The RITUXERA trial aims to compare two retreatment strategies with rituximab in patients with RA who have already been successfully treated with rituximab. The usual care strategy consists of a treat-to-target fixed dose rituximab retreatment, and the experimental strategy comprises fixed interval disease activity-guided rituximab dose optimisation. The primary objective is to compare long-term patient-reported disease impact of both strategies. The main secondary objective is the comparison of long-term clinical effectiveness in terms of disease activity.

Study population and recruitment

Patients with RA may be considered for inclusion if they have been successfully treated with rituximab for RA before trial participation, and if they are eligible for a subsequent rituximab course in accordance with Belgian reimbursement criteria. In Belgium, rituximab is reimbursed for patients with RA with active disease (DAS28 $\geq$ 3.7) and an inadequate response to at least two conventional synthetic (cs)DMARDs as well as one tumour necrosis factor inhibitor. Subsequent rituximab treatment requires a DAS28-score $\geq$ 3.2, respecting an interval of at least 24 weeks since the previous treatment course. All patients complying with these criteria will be invited for participation by their treating rheumatologist during follow-up outpatient consultations at the participating sites. The following inclusion criteria were defined:

- Diagnosis of RA in accordance with the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) Classification Criteria for RA [21];
- Age of at least 18 years;
- Current treatment with rituximab for RA;
- A minimum of one successful treatment response to rituximab, defined as a moderate or good EULAR response 16 weeks after the first treatment with rituximab [22];
- Requirement of a subsequent treatment cycle of rituximab for RA in line with local criteria, as outlined above;
- Stable dose of concomitant therapy with csDMARDs at least 4 weeks prior to baseline;
- (Written) understanding of Dutch or French;
- Ability and willingness to give written informed consent before any study procedures.

Exclusion criteria were defined as follows:

- Current treatment with a bDMARD other than rituximab, or a targeted synthetic (ts)DMARD;
- Pregnancy (wish) in female patients;
- Presence of an absolute contraindication to treatment with rituximab according to the summary of product characteristics (SmPC) of rituximab (i.e. hypersensitivity to rituximab or to its excipients, active severe infection, severe immune deficiency, severe heart failure, or other severe uncontrolled cardiac condition) and according to medical judgement.

The inclusion and exclusion criteria were chosen to not be too restrictive, aiming for a study sample which is an adequate reflection of the diverse patient population with established RA treated with rituximab in clinical

practice. Enrolment of participants is performed by study investigators. Patients will be allowed all time necessary to review the informed consent form (ICF) and discuss it with third parties. If patients do not wish to participate, no reasons for refusal will be collected. A model ICF in Dutch can be found in the additional materials (Supplement 1).

Randomisation and blinding

RITUXERA is an open-label trial; thus, no blinding procedures are involved. At baseline, participants will be 1:1 randomised to either the experimental or the usual care retreatment strategy, stratified by study centre and by number of previous rituximab cycles (≤ 2 or > 2). We chose not to stratify randomisation according to serologic status (rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA)), as we expect that most patients with established RA treated with rituximab are RF and/or ACPA seropositive. A randomisation tool is incorporated within the web-based platform Research Electronic Data Capture (REDCap), which is also used as electronic case report form (eCRF). A random allocation sequence in blocks of 2 or 4 was generated by an independent person, using a free-access online tool (https://www.sealedenvelope.com), and is concealed from investigators within the REDCap environment.

Intervention

At baseline, all participants will receive a standard dose of 1×1000 mg IV rituximab. Throughout the trial, patients randomised to the usual care arm (treat-to-target fixed-dose rituximab) will receive the same standard dose of rituximab only in case of a relapse of RA, defined by a DAS28-C-reactive protein (CRP) score ≥ 3.2, while respecting a minimum interval of at least 24 weeks between treatment cycles. In contrast, participants randomised to the experimental arm (fixed interval disease activity-guided rituximab dose optimisation) will be treated with rituximab at fixed intervals of 24 weeks, while tapering down the administered dose of rituximab in subsequent treatment cycles in case of low disease activity, defined as a DAS28-CRP score ≤ 3.2. In this regard, dose tapering of rituximab follows a fixed sequence, starting with 1×1000 mg rituximab IV, then 1×500 mg IV, and finally 1×200 mg IV, which is defined as the minimum administered dose per treatment cycle. In case of uncontrolled disease (DAS28-CRP score > 3.2) at the time of retreatment, patients will be treated with the last effective dose in the tapering sequence, and further tapering below this dose will not be performed further on. In both arms, every treatment cycle consists of one administration of rituximab IV (original biologic or biosimilar), preceded by IV administration of 1×125 mg methylprednisolone, and oral intake of 1 g paracetamol and an antihistamine. Detailed information on treatment procedures can be found in the additional materials (Supplement 2). In case of contraindications to rituximab as mentioned in the SmPC or according to medical judgement, rituximab will not be administered. When the disease activity is insufficiently controlled despite rituximab treatment, glucocorticoid (GC) bridging may be considered until the next treatment cycle. To ensure that the effect of the latest rituximab infusion can be adequately assessed, and to determine the right dose for the subsequent treatment cycle, GC doses should be kept stable and should not exceed baseline doses (in case of chronic GC use) between week 8 and 12 and between week 20 and 24 following rituximab administration. At every study visit, participants will be questioned regarding their concomitant medication, specifically GCs and DMARDs.

Trial procedures

During the trial duration of 104 weeks, study visits are scheduled every 12 weeks (Table 1), as in our daily clinical practice. If necessary, additional "unplanned" study visits can be scheduled.

Data collection at baseline includes age, sex, medical history (including comorbidities, RA disease duration, RF and ACPA status, start date of rituximab treatment and number of previous rituximab treatment cycles, and prior and concomitant use of DMARDs and GCs), smoking status (never, past, or current, including pack years), alcohol consumption (units per week), employment status, and education level. At every study visit, participants are evaluated by an investigator, who will perform a general and routine rheumatologic clinical examination, including 66/68 swollen and tender joint counts. In addition, disease activity measures (DAS28-CRP, DAS28-Erythrocyte Sedimentation Rate (ESR), and Simple Disease Activity Index (SDAI)) will be calculated, and a blood sample will be collected (including CRP levels, ESR, and toxicity measures), as is the case in routine clinical practice. The body mass index (BMI) of participants will be calculated at baseline and at the study visits at week 48 and week 104. At all study visits, the investigator will complete the Physician's Global Assessment of disease activity (PhGA) on a visual analogue scale (VAS), and participants will be invited via e-mail or via QR code to complete patient-reported outcome measures (PROMs) in the eCRF platform (Table 1). If preferred by participants, a paper version of all PROMs is available for use. Throughout the trial, all concomitant use of GCs and csDMARDs will be registered. At the moment of retreatment with rituximab, as well as at baseline and week 104, additional laboratory parameters will be collected, which include immunoglobulin counts (IgG, IgA, and

Table 1 Study procedures and outcome measures

		Study visit										
Timepoint	***SCR***	***BL***	***W12***	***W24***	***W36***	***W48***	***W60***	***W72***	***W84***	***W96***	***W104***	***U***
Enrolment:												
Eligibility	X											
ICF	X											
Demographics[a]		X										
Randomisation		X										
Assessments:												
Medical history[b]		X										
RF/ACPA status		X										
DMARDs/GCs use		X	X	X	X	X	X	X	X	X	X	X
General clinical exam		X	X	X	X	X	X	X	X	X	X	X
BMI		X				X					X	
66/68 joint counts		X	X	X	X	X	X	X	X	X	X	X
CRP/ESR		X	X	X	X	X	X	X	X	X	X	X
IgG/M/A[c]		X		(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	(X)
B cell counts[c]		X		(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	(X)
DAS28-CRP/ESR		X	X	X	X	X	X	X	X	X	X	X
SDAI		X	X	X	X	X	X	X	X	X	X	X
EULAR response[d]			X		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
RAID		X	X	X	X	X	X	X	X	X	X	X
VAS pain/fatigue		X	X	X	X	X	X	X	X	X	X	X
PGA		X	X	X	X	X	X	X	X	X	X	X
PhGA		X	X	X	X	X	X	X	X	X	X	X
HAQ-DI		X	X	X	X	X	X	X	X	X	X	
ASES		X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L		X	X	X	X	X	X	X	X	X	X	
WPAI/employment		X	X	X	X	X	X	X	X	X	X	
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X
Interventions:												
Rituximab (usual care)[e]		X		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Rituximab (experimental)		X		X		X		X		X		

SCR Screening, *BL* Baseline, *W* Week, *U* Unplanned visit, *ICF* Informed consent form, *RF* Rheumatoid factor, *ACPA* Anti-citrullinated protein antibody, *DMARD* Disease-modifying antirheumatic drug, *GC* Glucocorticoid, *BMI* Body mass index, *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate, *Ig* Immunoglobulin, *DAS28* 28-joint Disease Activity Score, *SDAI* Simple Disease Activity Index, *EULAR* European Alliance for Associations of Rheumatology, *RAID* Rheumatoid Arthritis Impact of Disease questionnaire, *VAS* Visual analogue scale, *PGA* Patient's Global Assessment of disease activity, *PhGA* Physician's Global Assessment of disease activity, *HAQ-DI* Health Assessment Questionnaire – Disability Index, *ASES* Arthritis Self-Efficacy Scale, *EQ-5D-5L* 5-level 5-dimentional EuroQol measure, *WPAI* Work Productivity and Activity Impairment questionnaire, *AE* Adverse event

[a] Including patient age, sex, working status, education level, smoking status, and alcohol consumption

[b] Including comorbidities, RA disease duration, start date of rituximab treatment and number of previous rituximab treatment cycles, and prior and concomitant use of DMARDs and GCs

[c] Measured at baseline, at the week 104 study visit, and every visit where rituximab is administered, thus dependent on the participant's allocated treatment strategy

[d] Assessed 12 weeks after administration of rituximab, thus dependent on the participant's allocated treatment strategy

[e] Patients allocated to the usual care arm will only be retreated with rituximab when DAS28-CRP $\geq$ 3.2, respecting a minimum interval of 24 weeks between treatment cycles

IgM) and CD19 + B cell counts. No blood samples will be stored for future analysis. Concerning safety reporting, the following events will be captured in the eCRF: adverse reactions, adverse events related to RA or related to RA treatment, and adverse events of special interest, which are defined as major cardiac and cerebrovascular events, non-traumatic bone fractures, malignancies, serious infections, COVID-19 infections, negative pregnancy outcomes, and death. Cases of toxicity will be monitored as closely as possible, and necessary actions will be taken according to good clinical practice. All events will be monitored until resolution or any other definite outcome.

Local reimbursement criteria may not be met for certain patients in the experimental arm when being retreated, which is the case if DAS28-CRP is < 3.2. For these specific circumstances, the pharmaceutical company Celltrion is funding a supply of rituximab in the hospital pharmacies of UZ Leuven and Cliniques Universitaires Saint-Luc. As a consequence, patients from other participating centres requiring a treatment with rituximab outside the scope of the local reimbursement criteria will receive this administration in UZ Leuven under the supervision of local medical staff and in accordance with the standards of care. All other study-related procedures will take place at the original centre of inclusion. To compensate for the travel costs, a voucher will be offered each time a patient receives rituximab in UZ Leuven, when rituximab is normally administered in another centre.

Data entry in the eCRF (REDCap) will be performed by investigators and/or clinical research associates. On the eCRF platform, all participants are referred to by a randomly generated code. No personal identifiers will be captured in the eCRF. To optimise participant response rates, automatic reminders will be sent to participants via e-mail if PROMs have not been completed yet on the eCRF platform. If data fields are empty in REDCap, automatic queries will appear to alert persons responsible for data entry. In addition, data management will follow-up on the completion of the eCRF and will contact study personnel in case of potentially erroneous or missing data.

After the end of the trial, patients will be followed up in line with the standards of care. Included patients may decide to stop participating in the trial at any time, without having to disclose a reason. Premature trial discontinuation will be imposed on patients who acquire a definite contraindication against the use of rituximab and patients who switch to a bDMARD other than rituximab or start a tsDMARD.

Outcome measures

During the trial, the following outcome measures are collected (Table 1):

- Rheumatoid Arthritis Impact of Disease (RAID) questionnaire: a PROM consisting of 7 patient-important domains, including pain, functional disability, fatigue, emotional wellbeing, sleep, coping, and physical wellbeing [23, 24]. The RAID score is calculated using a weighted formula including all domains, quantifying patient-reported disease impact. The score ranges from 0 to 10, with higher scores indicating more impact
- Patient Global Assessment of disease activity (PGA), VAS pain, and VAS fatigue: these PROMs are based on a VAS ranging from 0 to 100, with higher scores reflecting worse assessments
- PhGA: a VAS (ranging from 0 to 100) which is completed by the rheumatologist. Higher scores reflect a worse assessment
- Health Assessment Questionnaire-Disability Index (HAQ-DI): a measure of functional status [25]. The score ranges from 0 to 3, and higher scores correspond to worse functional status
- Arthritis Self-Efficacy Scale (ASES): a PROM measuring perceived self-efficacy [26]. In the RITUXERA trial, a two-subscale version is used consisting of 5 questions on pain and 6 questions on other symptoms [27]. The resulting score ranges from 11 to 110, with higher scores indicating higher perceived self-efficacy
- Five-level version of the EuroQol five-dimensional health status measure (EQ-5D-5L): a PROM consisting of 5 dimensions of health, more specifically mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which are all scored based on 5 levels, quantifying quality of life [28]. In addition, patients must report their current health on a VAS from 0 to 100, with 100 reflecting the best imaginable health state. Thereafter, the responses to the 5 dimensions are linked to a country specific value set, providing a health status index value, which can be used for future health-economic analyses [29]
- Work Productivity and Activity Impairment questionnaire (WPAI): a 6-item questionnaire measuring absenteeism, presenteeism, overall activity, and work impairment over the last 7 days [30, 31]
- DAS28-CRP: a composite disease activity measure calculated using a weighted formula containing PGA, 28 swollen and tender joint counts, and CRP levels [32, 33]
- SDAI: a composite disease activity measure calculated using 28 swollen and tender joint counts, CRP levels, PGA, and PhGA [34]
- EULAR response 12 weeks after administration of rituximab: A good response is defined as a DAS28-CRP-decrease of > 1.2 with present DAS28-CRP ≤ 3.2. A moderate response reflects a decrease in DAS28-CRP > 0.6 to ≤ 1.2 with present DAS28-CRP ≤ 5.1 or a DAS28-CRP-decrease of > 1.2 with present DAS28-CRP > 3.2 [22, 33]
- Hypogammaglobulinaemia: patients are classified as having hypogammaglobulinemia in case IgM, IgG, or IgA are below the lower limit of the normal value. The following lower limits of normal were defined

in accordance with Evangelatos et al.: 7 g/L for IgG, 0.4 g/L for IgM, and 0.7 g/L for IgA [35]
- B cell (CD19+) counts: complete peripheral B cell depletion was defined as < 18 cells/μL, in accordance with Ghossan et al. [36]

PROMs may be completed either in Dutch or French, depending on the patient's language preference. All mentioned outcomes are considered to be part of the standard of care and will be assessed by a study investigator.

Outcomes

The primary outcome of the RITUXERA trial is the longitudinal comparison of the RAID score over 104 weeks (area under the curve (AUC)) between the two randomisation groups. The main secondary outcome is the longitudinal analysis (AUC) of the DAS28-CRP-score over 104 weeks, compared between both randomisation groups. Similarly, a secondary outcome is SDAI AUC over 104 weeks. Other secondary outcomes include cumulative rituximab and GC-doses over 104 weeks as well as the rituximab retention rates in both trial arms. Furthermore, in the experimental arm, we aim to determine the proportion of patients able to taper rituximab to 200 or 500 mg. In the usual care arm, we want to determine the interval between subsequent rituximab cycles. Additional secondary outcomes are the proportion of patients achieving a good or moderate EULAR response 12 weeks after administration of rituximab and longitudinal maintenance of disease control (DAS28-CRP ≤ 3.2). Moreover, the proportion of patients with serious adverse events or reactions as well as serious infections will be determined in both arms over the trial duration. Additionally, we defined the longitudinal evolution over 104 weeks in HAQ, VAS pain, VAS fatigue, PGA, and ASES in both study arms as exploratory endpoints. Furthermore, the professional and vocational participation (WPAI) and quality of life (EQ-5D-5L) over 104 weeks will be explored in both randomisation groups. Finally, rates of hypogammaglobulinaemia and complete peripheral B cell depletion will be determined among the groups over the whole trial period.

Sample size

We hypothesise that administering rituximab according to a fixed interval disease activity-guided dose optimisation strategy would result in better reduction of patient-reported disease impact, compared with treat-to-target fixed dose rituximab administration. Therefore, our primary endpoint is based on the AUC of the RAID score over the full trial duration of 104 weeks. Our null hypothesis was that both treatment strategies would result in equal RAID AUC (H0: $\delta = 0$). The alternative hypothesis was that fixed interval disease activity-guided dose optimisation of rituximab would be superior, resulting in a lower RAID AUC (H1: $\delta \neq 0$). For the sample size calculation, we considered a difference in RAID AUC of at least 20% over 104 weeks of treatment as an important difference of the overall disease impact. An effect size of 20% was chosen pragmatically and intuitively, taking into account the minimal clinically important difference of RAID in patients with active RA reported in the literature [37]. In the absence of a 2-year RAID AUC value in the literature, a pooled RAID score of patients in DAS28-CRP remission and low disease activity of the study by Salaffi et al. was used to estimate the two-year RAID AUC reference value [38]. In this study, data were reported of patients with RA from 13 European countries, resembling the Belgian RA population. Based on their data, a pooled mean RAID AUC of 293.26 (standard deviation (SD) 119.24) over a period of 104 weeks was determined as reference. We assumed a drop-out rate of 20% based on data of the IMAGE trial, a rituximab-tapering trial, and the 2-year CareRA trial conducted in Belgium [39, 40]. According to the sample size calculation for a superiority trial, in order to have an 80% chance of detecting a difference in primary outcome measure from 293.26 in the usual care group to 234.60 in the experimental group with a significance level of 5% along with an estimated drop-out rate of 20%, a total of 134 patients are required to be included in the trial. Consequently, 67 patients need to be enrolled in both treatment arms. Furthermore, a sample size calculation was performed for the main secondary outcome (DAS28-CRP AUC over 104 weeks). For this purpose, data of the SMART trial were used [41]. In this trial, one group was retreated based on loss of disease control (DAS28 > 3.2) with one rituximab infusion of 1000 mg, like the comparator arm of our study. In this group, patients had a mean DAS28-CRP AUC over 2 years of 2761 (SD 508). Based on these numbers, a sample size of 134 participants would result in a power of > 95% for the main secondary outcome.

Statistical analysis

Statistical analyses will be performed using software from the R Project for Statistical Computing. Missing data will be handled using appropriate imputation techniques, for instance multiple imputation (MI) when data are assumed to be missing at random. In case of MI, analyses will be carried out on each imputed database, whereafter results will be pooled based on Rubin's rules [42]. Baseline characteristics will be described descriptively for the total population and the two randomisation groups. Categorical variables will be based on numbers and proportions. Continuous variables will be reported as means, medians, SDs, and interquartile ranges, depending on

the data distribution. All randomised patients, irrespective of whether they received the assigned treatment, will be considered as the intention-to-treat (ITT) population and will be analysed according to their allocated treatment. The per-protocol (PP) population includes all randomised patients who received their treatment according to protocol. All analyses will be performed on the ITT population. In addition, sensitivity analyses will be conducted on the PP population. The primary endpoint will be investigated using a linear mixed model with RAID as dependent variable, adjusted for its baseline value [43]. Similarly, the main secondary endpoint will be determined using a linear mixed model with DAS28-CRP as dependent variable and adjusted for baseline DAS28-CRP. Furthermore, interactions between the independent variables will be checked. Formal hypothesis tests will only be carried out for the primary and main secondary outcome, with a significance level of 0.05. For the additional outcomes, data will be presented descriptively and 95% confidence intervals will be reported. If differences between the groups are shown by a descriptive analysis and if appropriate, a data driven analysis may be carried out. In order to determine rituximab retention rates and maintenance of disease control (DAS28-CRP < 3.2), Kaplan–Meier survival analyses and log-rank tests will be carried out. Cox proportional hazards models will be used to identify factors associated with rituximab retention and maintenance of disease control. A health economic analysis might be conducted depending on the results of the primary and main secondary outcomes.

Ethics and dissemination

The RITUXERA trial was approved by an independent ethics committee via the Clinical Trials Information System (CTIS) procedure of the European Medicines Agency. The trial was registered in CTIS (reference 2023–506638-59–01) and on ClinicalTrials.gov (NCT06003283) before its commencement. The trial will be conducted in compliance with the Declaration of Helsinki [44], applicable regulations, and good clinical practice. Confidentiality of participants will be safeguarded in accordance with the Belgian "law on the protection of natural persons with regard to the processing of personal data." As rituximab, the investigational medicinal product in this trial, is used within its registered label, and as this is an open-label trial involving no placebo nor blinding procedures with the majority of study procedures being part of the standards of care, RITUXERA is considered to be a low-risk trial. As a result, monitoring by a qualified individual independent of the study team was deemed unnecessary as it will provide little added value in protecting the safety of trial participants or assuring collected trial data integrity. Nonetheless, risk-based data electronic data monitoring will be performed by members of the study team via the eCRF. In addition, a trial steering committee (TSC) oversees and evaluates the safe conduct of all trial procedures during 4-monthly meetings. The TSC charter can be found in the additional materials (Supplement 3). Annual reports on safety will be reported to CTIS. This study protocol is reported in accordance with the SPIRIT 2013 Statement along with the 2022 extension on reporting of outcomes [45]. The SPIRIT checklist and full trial protocol are available in the additional materials (Supplement 4 and Supplement 5, respectively). Future trial results will be disseminated via national and international conferences, via publications in peer-reviewed journals, and via patient organisations. Moreover, results will be made available on clinicaltrials.gov and CTIS.

Patient and public involvement

In line with the EULAR recommendations for the inclusion of patient representatives in research projects [46], two patient experts (AM, MT) are engaged in the RITUXERA trial. These patient experts were well acquainted with the research topic of the RITUXERA trial, as they were already involved in previous research regarding patients' and rheumatologists' perceptions on the rituximab retreatment strategy and dose reduction [18, 20]. First, detailed information regarding the rationale and design of RITUXERA was provided to the patient experts. Next, both patient experts critically revised the proposed trial protocol and comprehensibility of the ICF. During the trial, one patient expert will attend TSC meetings, providing feedback on matters of trial conduct, participant safety, and preliminary results. Both patient experts will critically revise the manuscript on trial results before submission to peer-reviewed journals. In addition, trial results will be communicated via patient organisations. Lastly, RITUXERA's primary outcome includes the RAID, a PROM important to and developed in collaboration with patients [23, 24].

Discussion

The RITUXERA trial aims to investigate in patients with RA whether a fixed interval disease activity-guided dose optimisation treatment strategy is superior to a treat-to-target fixed dose retreatment strategy with rituximab in terms of patient-reported disease impact. In addition, both treatment strategies will be compared in terms of disease activity over time. We hypothesised that this strategy will lead to decreased patient burden, an appealing balance between efficacy and safety, and facilitation of health care planning in advance, as

both patients and rheumatologist will know 6 months beforehand when a subsequent treatment cycle is scheduled. Additionally, administration of lower doses of rituximab could reduce infusion times. Therefore, we believe that a fixed interval disease activity-guide dose optimisation strategy is more in line with preferences and expectations of both patients and rheumatologists. Subsequently, we opted for a superiority design.

By using the longitudinal analysis of disease impact measured by the RAID questionnaire as the primary outcome, this trial emphasises the need to investigate therapeutic strategies in terms of patient-important outcomes. For our primary and main secondary outcomes, we chose to compare the RAID and DAS28-CRP of both strategies over 104 weeks using linear mixed effects models respectively, as a reflection of cumulative burden considering clinically important parameters like maintenance of response and flare rates.

This trial could provide further insights on the use of rituximab in RA, an effective bDMARD which is often feared due to its associated increased risk of infections, which was highlighted during the COVID-19 pandemic [47]. As side effects may be dose-dependent [48], we aimed to compare the currently used tapering strategy in Belgium of prolonging intervals between rituximab treatment cycles ("spacing") guided by loss of disease control with a treatment strategy based on administering rituximab six-monthly in tapered doses in case of adequate disease control. Comparison of tapering strategies involving interval spacing versus dose reduction are an ongoing research topic in other bDMARDs as well [49]. If proven successful, the use of low-dose rituximab may lower the threshold to opt for rituximab in insufficiently controlled RA, further establishing the position of rituximab within the treatment sequence of bDMARDs.

Although complete B cell depletion has been associated with better short-term response rates to rituximab in patients with RA [50, 51], we did not choose to investigate an administration strategy based on CD19 + B cell counts given the insufficient evidence for a potential benefit in long-term treatment [36]. Nonetheless, CD19 + B cell counts will be determined in the study population for exploratory analysis.

A challenge of our trial design consists of limiting the participant dropout rate in order to reach sufficient power, since our primary outcome is measured over 2 years. Considering previous trial data, we accounted for a 20% drop-out rate [39]. Although an open-label design is accompanied by certain limitations, including study participants' potential wish to receive a "novel" treatment strategy, or a nocebo effect of lower doses [52], absence of blinding procedures was deemed necessary to reflect daily clinical practice and because the patients' perceptions and experiences on the received therapeutic strategy would impact their overall perceived disease impact, the trial's primary outcome.

Trial status

The trial protocol (version 2.0) and ICF (version 2.0) were approved by an independent ethics committee via CTIS on 28 November 2023. Screening of participants started on 9 January 2024 and is currently ongoing. Accounting for a trial duration of 104 weeks along an inclusion period of 1 year, the last study visit of the last included patient is expected in the first quarter of 2027.

Abbreviations

ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
ASES	Arthritis Self-Efficacy Scale
AUC	Area under the curve
bDMARD	Biologic disease-modifying antirheumatic drug
BL	Baseline
BMI	Body mass index
CD	Cluster of differentiation
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
CTIS	Clinical Trials Information System
DAS28	28 Joint-Disease Activity Score
DMARD	Disease-modifying antirheumatic drug
eCRF	Electronic case report form
EQ-5D-5L	5-Level 5-dimentional EuroQol measure
ESR	Erythrocyte sedimentation rate
EULAR	European Alliance of Associations for Rheumatology/European League Against Rheumatism
FWO	Fonds Wetenschappelijk Onderzoek – Vlaanderen
FWRO	Fonds voor Wetenschappelijk Reuma Onderzoek
GC	Glucocorticoid
HAQ(-DI)	Health Assessment Questionnaire (-Disability Index)
ICF	Informed consent form
Ig(G/M/A)	Immunoglobulin (G/M/A)
ITT	Intention-to-treat
IV	Intravenous
MI	Multiple imputation
P GA	Patient Global Assessment of Disease Activity
PhGA	Physician Global Assessment of Disease Activity
PI	Principal investigator
PP	Per protocol
PROM	Patient-reported outcome measure
RA	Rheumatoid arthritis
RAID	Rheumatoid Arthritis Impact of Disease questionnaire
RCT	Randomised controlled trial
REDCap	Research Electronic Data Capture
RF	Rheumatoid factor
SCR	Screening
SD	Standard deviation
SDAI	Simple Disease Activity Index
SmPC	Summary of product characteristics
TSC	Trial steering committee
tsDMARD	Targeted synthetic disease-modifying antirheumatic drug
U	Unplanned visit
VAS	Visual analogue scale
W	Week
WPAI	Work Productivity and Activity Impairment questionnaire

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08542-7.

Supplementary Material 1: Supplement 1. Model ICF NL V2.0.pdf. Most recent version (2.0) of model informed consent form of RITUXERA in the Dutch language.

Supplementary Material 2: Supplement 2. Infusion procedures.docx. Clarification of administration procedures for rituximab in the RITUXERA trial.

Supplementary Material 3: Supplement 3.TSC charter.docx. Trial Steering Committee charter of the RITUXERA trial.

Supplementary Material 4: Supplement 4. SPIRIT-2013 checklist with 2022 extension.pdf. Completed SPIRIT-2013 checklist along with 2022 extension on reporting of outcomes.

Supplementary Material 5: Supplement 5. Full trial protocol V2.0.pdf. Most recent version (2.0) of the full study protocol of RITUXERA.

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Authors' contributions
DB, EDM, JJ, BN, RW, and PV designed the study. EDM and DB drafted the manuscript. All authors approved the last draft of the paper. Patient experts revised the protocol and informed consent form, and contributed in writing the protocol paper.

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Data Availability
Data collection is currently ongoing. Data will be available based on reasonable request.

Declarations

Ethics approval and consent to participate
The RITUXERA trial was approved by an independent ethics committee via the Clinical Trials Information System (CTIS) procedure of the European Medicines Agency (reference 2023-506638-59-01). All study participants will give written informed consent before study participation.

Consent for publication
Not applicable.

Competing interests
Elias De Meyst and Michaël Doumen received a grant from Research Foundation – Flanders (FWO). All other authors have no conflict of interest to declare.

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