Efficacy of rituximab in patients with polymyalgia rheumatica: a double-blind, randomised, placebo-controlled, proof-of-concept trial

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Summary

Background Glucocorticoids remain the cornerstone of polymyalgia rheumatica treatment, but their use has several drawbacks, such as long treatment duration and glucocorticoid-related adverse events. Effective glucocorticoid-sparing agents with a strong evidence base in polymyalgia rheumatica are absent. As B cells have been implicated in the pathogenesis of polymyalgia rheumatica, we aimed to evaluate the efficacy of rituximab for the treatment of polymyalgia rheumatica.

Methods We did a double-blind, randomised, placebo-controlled, proof-of-concept trial at Sint Maartenskliniek, Nijmegen, Netherlands. We enrolled patients with polymyalgia rheumatica according to the 2012 European League Against Rheumatism and American College of Rheumatology criteria, who were recently diagnosed or who had relapsed on prednisolone and were unable to taper their dose to less than 7·5 mg per day. Participants were randomly assigned (1:1) to a single intravenous infusion of rituximab 1000 mg or placebo, with a 17-week glucocorticoid tapering scheme. Participants and care and research personnel were masked to treatment assignment and randomisation sequence. The primary outcome was glucocorticoid-free remission at 21 weeks after infusion in patients who completed the study. This trial is registered with EudraCT (2018-002641-11) and the Dutch trial database (NL7414).

Findings Between Jan 14, 2019, and March 10, 2020, 116 patients were screened and 49 (42%) were enrolled. 47 patients (38 who were recently diagnosed, nine who had relapsed on prednisolone) completed the study: 23 (49%) in the rituximab group and 24 (51%) in the placebo group. Mean age (SD) in years was 64 (8) in the rituximab group and 66 (10) in the placebo group, the proportion of women was 11 (48%) of 23 versus 13 (54%) of 24, and all participants were White. 11 (48%) of 23 patients in the rituximab group and five (21%) of 24 in the placebo group achieved glucocorticoid-free remission at 21 weeks (difference 27% [one-sided 95% CI 4]; relative risk 2·3 [1·1]; p=0·049). Ten infusion-related complaints occurred in the rituximab group versus three in the placebo group (relative rate 3·5 [one-sided 95% CI 1·3]). One serious adverse event occurred (pulmonary embolism; in the rituximab group), and there were no deaths.

Interpretation Rituximab was shown to be efficacious in combination with 17-week glucocorticoid treatment compared with glucocorticoid treatment alone in terms of glucocorticoid-free remission in patients with polymyalgia rheumatica. If these findings are confirmed by larger trials, rituximab could be a valuable glucocorticoid-sparing treatment for patients with polymyalgia rheumatica.

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Introduction

Polymyalgia rheumatica is an inflammatory rheumatic disease that mostly affects people older than 50 years. The incidence varies from 41 to 113 cases per 100 000 population and is highest in countries in northern Europe. Typical symptoms are bilateral pain and stiffness in the neck, shoulder, and hip girdle, and patients usually have elevated inflammatory parameters (eg, C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]). The cause and pathogenesis of the disease remain largely unknown, and polymyalgia rheumatica can lead to substantial morbidity and reduction in quality of life.[1–3]

Glucocorticoids are the cornerstone of polymyalgia rheumatica treatment but their use has several unfavourable aspects.[1] First, a considerable number of patients have contraindications to glucocorticoids or experience glucocorticoid-related adverse events, which can be severe, especially after prolonged treatment.[3–6] Second, around 50% of patients experience one or more flares during glucocorticoid tapering.[4] Flares lead to a substantially prolonged treatment duration, with around 40% of patients requiring glucocorticoid treatment for 4 years or longer.[7]

The 2015 European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) guidelines on management of polymyalgia rheumatica recommend concomitant glucocorticoid-sparing agents in patients with poor prognosis

Research in context

Evidence before this study

Effective glucocorticoid-sparing agents for the treatment of polymyalgia rheumatica are not yet available. This topic remains a priority on international research agendas due to the adverse effects associated with glucocorticoid use. We searched PubMed, ClinicalTrials.gov, and the Dutch registry of clinical trials (Nederlandse Trial Register), using the snowball method, for studies from database inception to July 16, 2018, with no language restrictions, using the search terms "polymyalgia rheumatica" [MESH] and related treatment terms. We found no studies on the effect of B-cell-targeted treatments, such as rituximab (a chimeric monoclonal antibody against CD20 that causes B-cell depletion), in patients with polymyalgia rheumatica.

Added value of this study

This proof-of-concept study showed that, at 21 weeks after infusion, a single intravenous infusion of rituximab 1000 mg, in combination with a 17-week glucocorticoid tapering scheme, was marginally more efficacious than treatment with a 17-week glucocorticoid tapering scheme alone, in terms of glucocorticoid-free remission in patients with polymyalgia rheumatica who fulfilled the 2012 European League Against Rheumatism and American College of Rheumatology criteria. However, limitations of this study include the small sample size and a short follow-up duration, and data on long-term efficacy of rituximab are warranted.

Implications of all the available evidence

If these results are confirmed in larger trials, rituximab could be a valuable treatment for patients with polymyalgia rheumatica, particularly if they have (relative) contraindications for treatment with glucocorticoids or a poor prognosis. Expected benefits of rituximab might include reduced disease duration, severity, and burden, with subsequent reduced need for glucocorticoids.

or contraindications for glucocorticoids.[3] Several conventional synthetic and biological disease-modifying antirheumatic drugs (DMARDs) have therefore been studied in patients with polymyalgia rheumatica,[1,3] but benefits were absent or insubstantial.[3,8–9] Research on glucocorticoid-sparing agents therefore remains a priority on the international research agenda for polymyalgia rheumatica.[3]

To our knowledge, B-cell-targeted treatment in polymyalgia rheumatica has not yet been studied. As polymyalgia rheumatica is not clearly associated with autoantibodies, it does not appear to be a typical B-cell-driven disease.[10–13] However, B cells are part of the inflammatory cascade and produce interleukin (IL)-6, which is involved in the pathogenesis of polymyalgia rheumatica.[1,14] In addition, disturbed B-cell homeostasis was reported in patients with newly diagnosed, untreated polymyalgia rheumatica and giant cell arteritis (a large-vessel vasculitis associated with polymyalgia rheumatica),[14] and there has been one case report of a patient with giant cell arteritis with polymyalgia rheumatica who was successfully treated with rituximab.[15] Therefore, although not yet supported by strong evidence, B cells might have a pathophysiological role in polymyalgia rheumatica.

Rituximab is a chimeric monoclonal antibody against CD20. There is sufficient clinical experience in other inflammatory rheumatic diseases to show that rituximab is well tolerated.[16] Advantages of this drug include that it is safe, although rituximab can cause infusion-related side-effects and there is a dose-dependent risk of infection.[17] We aimed to evaluate the efficacy of rituximab, and explore whether it has a glucocorticoid-sparing effect, in recently diagnosed and relapsing patients with polymyalgia rheumatica.

Methods

Study design

We did a double-blind, randomised, placebo-controlled, proof-of-concept trial at the Rheumatology Department of Sint Maartenskliniek, Nijmegen, Netherlands. Medical ethics approval was obtained from the Medical ethics committee of the region Arnhem-Nijmegen (NL66847.091.18; 2018-4609). After registration, the trial protocol was amended with regard to the following points: the cutoff point of remission by the polymyalgia rheumatica activity score, the classification criteria used for study inclusion, the inclusion of not only glucocorticoid-naive patients but also patients on short-term glucocorticoid treatment, and the inclusion of relapsing patients (appendix pp 4–5). The amendment was approved on April 18, 2019, after the eighth patient was enrolled and before the first patient reached the end of follow-up. However, due to oversight, the trial register was not immediately updated to reflect these amendments, and this was only noticed after the last patient had completed follow-up. All participants received study information including possible benefits and risks involved in study participation and provided written informed consent before enrolling. The trial was monitored according to good clinical practice. A data safety monitoring board held meetings every 3 months to safeguard study feasibility and participant safety. The trial protocol is provided in the appendix (pp 21–126).

Participants

Patients were referred to the trial by their treating rheumatologists or general practitioner. We included both newly diagnosed and relapsing patients who fulfilled the 2012 EULAR and ACR classification criteria (excluding the ultrasound criteria) for polymyalgia rheumatica.

See Online for appendix

Ultrasound criteria of the 2012 EULAR and ACR classification criteria for polymyalgia rheumatica were ultimately not used due to the logistical difficulties of organising ultrasound scans of shoulders and hips and because most patients had already started glucocorticoid treatment before inclusion in the study. Eligible newly diagnosed patients had been diagnosed within 3 months before enrolment and were glucocorticoid-naive or had been taking glucocorticoid for less than 6 consecutive weeks before enrolment, with a maximum dose of 30 mg if treatment duration was less than 1 week, and a maximum dose of 20 mg otherwise. Eligible relapsing patients were those who had clinical relapse (including elevated ESR [>30 mm/h] or CRP [>5 mg/L]) at a glucocorticoid dose of 7·5 mg per day or greater, and were not able to taper their dose to less than 7·5 mg per day.

Exclusion criteria were a daily dose of oral glucocorticoid of more than 30 mg; exposure to other immunosuppressants in the 4 months before enrolment; other concomitant inflammatory rheumatic diseases or diseases hampering assessment of polymyalgia rheumatica; previous hypersensitivity to prednisolone, rituximab, or murine peptides; and contraindications to rituximab (appendix pp 6–7).

Randomisation and masking

Eligible participants were randomly assigned (1:1) to rituximab or placebo. An independent pharmacist generated the randomisation scheme by computerised procedure with varying block size (two blocks of 20 participants, one block of ten). Participants and care and research personnel were masked to treatment assignment and randomisation sequence. Treatment allocation was not revealed to patients until at least 1 year after infusion. Researchers were unmasked only after analyses of the primary efficacy outcome were completed. Rituximab and placebo were prepared on the basis of randomisation number by the local hospital pharmacy. It was not possible to discern rituximab from placebo, and all patients received similar care and premedication before the infusion.

Procedures

Within 3 weeks of study enrolment, patients received a single intravenous infusion of either rituximab 1000 mg or placebo. We chose a single infusion of 1000 mg as the study dose because a systematic review and meta-analysis of rituximab regimens in rheumatoid arthritis showed similar efficacy of rituximab when given as a single infusion of 1000 mg, two infusions of 1000 mg, or two infusions of 500 mg, and a single infusion of 1000 mg was associated with fewer adverse events.[16] A higher dose than that given in patients with rheumatoid arthritis was deemed unnecessary in polymyalgia rheumatica. Two 50 mL vials containing concentrated 500 mg of rituximab (Rixathon; Sandoz, Holzkirchen, Germany; ATC code L01X C02) were diluted in 500 mL sodium chloride 0·9%. Before infusion, standard premedication according to local treatment protocol in rheumatoid arthritis (single dose intravenous methylprednisolone 50 mg, oral paracetamol 1000 mg, and oral cetirizine 10 mg) was given to patients in both groups to ensure masking for intervention.

All patients received the same prednisolone treatment from the day of infusion (appendix pp 2–3). As data from patients with rheumatoid arthritis has shown that there is a delay in efficacy after rituximab infusion,[18] we did not expect rituximab to show relevant efficacy before 11 weeks after infusion in most patients with polymyalgia rheumatica. Therefore, we started with a regular glucocorticoid tapering scheme, which was accelerated after 11 weeks. When a patient experienced a relapse after initial response (secondary non-responder), prednisolone was increased up to the last effective dose for 2 weeks and the accelerated tapering scheme was resumed when remission was reported again. If a second relapse occurred, the prednisolone dose was again increased to the last effective dose and after 2 weeks was subsequently tapered according to the slower, local usual care tapering scheme. In case of recurrence of disease after glucocorticoid cessation, prednisolone was reinitiated and subsequently tapered (accelerated approach or usual care depending on if it was the first or second relapse during the study). All patients received osteoporosis prophylaxis (alendronic acid 70 mg per week and calcium carbonate 500 mg plus colecalciferol 800 units). Use of non-steroidal anti-inflammatory drugs (NSAIDs) was permitted when necessary.

Visits and assessment of study outcomes took place at baseline, and at 2, 4, 11, 17, and 21 weeks after rituximab infusion. Extra visits were planned if necessary (eg, suspected flare or adverse event). Data on patient and disease characteristics, vital sign measurements, laboratory values, disease activity, and functional and health-related questionnaires were collected. Alternative diagnoses were ruled out by extensive history-taking, physical examination (always including palpation of temporal artery and lymph nodes), routine laboratory tests including hepatitis serology, chest x-ray, and—if needed—additional laboratory tests or imaging. During follow-up, patients were monitored by careful review and physical examination to rule out concomitant giant cell arteritis or conversion into other rheumatic disease (eg, rheumatoid arthritis).

Outcomes

The primary outcome was glucocorticoid-free remission at 21 weeks after infusion of rituximab or placebo. Remission was defined as a polymyalgia rheumatica activity score of less than 10, indicating low disease activity, as proposed by previous studies.[19] The polymyalgia rheumatica activity score is a composite score comprising CRP concentration (mg/dL), duration of morning stiffness, elevation of upper limbs (EUL)

score from 0 to 3 (0=elevation above shoulder girdle, 1=elevation up to shoulder girdle, 2=elevation below shoulder girdle, 3=no elevation possible), physician's global assessment by visual analogue score (VASph; from 0 to 10), and the patients' assessment of pain by visual analogue score (VASp; from 0 to 10).[19] The composite score is calculated as CRP + VASp + VASph + (MST × 0·1) + EUL. Relapse was defined as judged by the treating physician, if symptoms and raised ESR or CRP or both recurred and were deemed attributable to polymyalgia rheumatica.

Preplanned secondary outcomes at week 21 were proportion of patients reaching glucocorticoid dose of 5 mg per day or less, cumulative glucocorticoid dose, change from baseline in ESR and CRP, change in patients' physical function, pain, stiffness (measured by VAS), and B-cell count, change in polymyalgia rheumatica activity score, and the proportion of patients who relapsed. Additionally, differences in functional status and quality of life were assessed using the health assessment questionnaire disability index (HAQ-DI) and EQ-5D-5L, and patients' global, pain, fatigue, and stiffness visual analogue score. Post-hoc analyses included proportion of glucocorticoid-free remission judged by the treating rheumatologist (clinical assessment of patients' symptoms with or without elevated acute phase reactants, with the following possible categories: glucocorticoid-free remission, remission with glucocorticoids, doubtful glucocorticoid-free remission, doubtful remission with glucocorticoids, and flare), and proportions with glucocorticoid-free remission (polymyalgia rheumatica activity score <10) and proportions reaching glucocorticoid dose of 5 mg or less stratified by disease phase. To ensure optimal assessment reliability, visits were done by one research physician, with one other research physician as backup. In addition, the number and proportion of patients who were prescribed NSAIDs at week 21 were also assessed as a post-hoc analysis.

Safety endpoints were any glucocorticoid-related and rituximab-related adverse events that occurred during the study. Adverse events were graded according to Common Terminology Criteria for Adverse Events version 5.0. An elaborate assessment of glucocorticoid-related toxicity was assessed at baseline, visit 4 (11 weeks), and visit 6 (21 weeks), using the glucocorticoid toxicity index.[20] At baseline and follow-up, signs for alternative diagnoses such as malignancy or aortic abnormalities were assessed.

Statistical analysis

The proportion of patients who have glucocorticoid-free remission at 21 weeks after prednisolone monotherapy is unknown and scarce literature reports different percentages.[3] Taking into account an estimated 5% dropout, we selected a sample size of 50 patients (25 per treatment group) using Fisher's exact test and with one-sided α of 0·05, this sample size has at least 86% power to detect a clinically relevant difference of 40% in favour of rituximab (appendix p 10). As described in the original protocol, a one-sided p value was used as we expected only one possible and relevant direction of efficacy of rituximab because both groups were treated with concomitant glucocorticoids.

Descriptive values are presented as mean (SD), median (IQR), or frequencies or percentages, depending on data type and distribution. The primary endpoint was compared using Fishers' exact test. Secondary outcomes were compared using either Welch *t* test, Wilcoxon rank sum, or Fishers' exact test, depending on data type and distribution. One-sided p values of less than 0·05 were considered significant. Imputation of missing CRP values is described in the appendix (pp 8–9). Safety outcomes were compared by χ^2 test (cumulative incidences). No correction for type I error was done. Statistical analyses were done using STATA IC, version 13.

This trial is registered with EudraCT (2018-002641-11) and the Dutch trial database (NL7414).

Role of the funding source

There was no external funding source for this study.

Results

Between Jan 14, 2019, and March 10, 2020, 116 patients were screened and 49 (42%) were enrolled and randomly assigned (figure 1). Study inclusion ended somewhat prematurely due to the COVID-19 pandemic, and 47 patients (38 who were recently diagnosed with polymyalgia rheumatica, nine who had relapsed on prednisolone) completed the study with 21 weeks follow-up: 23 (49%) in the rituximab group and 24 (51%) in the placebo group (table 1). Mean age was 64 years (SD 8) in the rituximab group and 66 years (10) in the placebo group. 11 (48%) of 23 in the rituximab group were women versus 13 (54%) of 24 in the placebo group, and all participants were White.

The research physician was accidently unmasked to the most likely treatment allocation of seven patients due to B-cell counts being mistakenly uploaded into the laboratory output of patients' electronic health records. Subsequent visits of these patients were thereafter done by another physician who remained masked to treatment allocation. Also, both the patients' study number and allocation labels were coded during the analysis phase to safeguard masking of the research team during analysis of the primary outcome. Further information on protocol violations is provided in the appendix (p 11).

Compared with the placebo group, significantly more patients in the rituximab group achieved glucocorticoid-free remission at 21 weeks: 11 (48%) of 23 patients versus five (21%) of 24 (absolute risk difference 27% [one-sided 95% CI 4], relative risk 2·3 [1·1]; p=0·049). Mean change in polymyalgia rheumatica activity score was –13·8 (SD 2·9) in the rituximab group and –3·8 (3·6) in the

placebo group (absolute difference –10·0 [one-sided 95% CI –2·2]; p=0·018; table 2, figure 2). The kinetics of each separate polymyalgia rheumatica activity score item is shown in the appendix (pp 12–16).

The proportion of patients who reached a glucocorticoid dose of 5 mg per day or less was 23 (100%) of 23 in the rituximab group versus 13 (54%) of 24 in the placebo group (absolute difference 46% [one-sided 95% CI 20], relative risk 1·8 [1·3]; p=0·0012; table 2). No differences were seen in other secondary outcomes, including measures of patient functioning and quality of life, with the exception of change from baseline in median morning stiffness, which favoured rituximab (table 2). Scores on the glucocorticoid toxicity index are shown in the appendix (pp 17–18).

In the post-hoc analysis of the primary outcome stratified by disease phase, the effect of rituximab versus placebo was greater in recently diagnosed patients (11 [58%] of 19 patients had glucocorticoid-free remission in the rituximab group *vs* four [21%] of 19 in the placebo group, absolute risk difference 37% [one-sided 95% CI 10], relative risk 2·8 [1·3]; p=0·022), than in patients who had relapsed on prednisolone (none of four *vs* one [20%] of five, absolute risk difference –20% [–57], relative risk not applicable; p=0·56), but this could not be formally shown in this small sample. The effect of rituximab versus placebo on proportion of patients who reached a glucocorticoid dose of 5 mg per day or less was also greater in recently diagnosed patients (19 [100%] of 19 *vs* nine [47%] of 19, absolute risk difference 53% [one-sided 95% CI 29], relative risk 2·1 [1·0]; p=0·0015) than in patients who relapsed on prednisolone (three [75%] of four *vs* four [80%] of five, absolute risk difference –5% [–54], relative risk 0·9 [0·5]; p=0·72). The proportion of patients with glucocorticoid-free remission by clinical judgement of the treating physician was seven (30%) of 23 in the rituximab group versus six (25%) of 24 in the placebo group; four (17%) versus four (17%) had remission in combination with glucocorticoid use; five (22%) versus none had doubtful remission without glucocorticoid use; two (9%) versus five (21%) had doubtful remission with glucocorticoid use; and five (22%) versus nine (38%) had overt clinical flare. Four patients who were classified as in glucocorticoid-free remission based on the polymyalgia rheumatica activity score (<10) were classified as in doubtful remission by clinical judgement of the treating physician. The results of the analysis of primary outcome stratified by sex are shown in the appendix (p 19).

NSAIDs were used by week 21 in nine (39%) of 23 patients in the rituximab group and ten (42%) of 24 in the placebo group (absolute risk difference –3% [one-sided 95% CI –31%], relative risk 0·9 [0·5]; p=0·55). In the rituximab group, NSAIDs were prescribed in three (27%) of 11 patients who achieved glucocorticoid-free remission, and in six (50%) of 12 who did not achieve glucocorticoid-free remission. In the placebo group, NSAIDs were prescribed in three (60%) of five patients who achieved glucocorticoid-free remission, and in seven (37%) of 19 who did not achieve glucocorticoid-free remission. Outcomes at 21 weeks in patients who had glucocorticoid-free remission versus

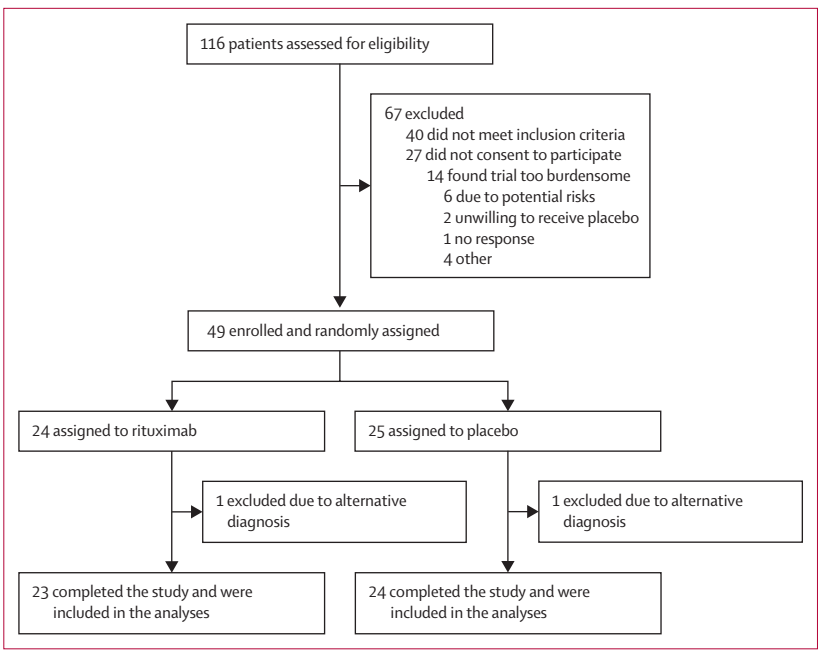

Figure 1: **Trial profile**

	Rituximab group (n=23)	Placebo group (n=24)
Age, years	64 (8)	66 (10)
Sex		
Female	11 (48%)	13 (54%)
Male	12 (52%)	11 (46%)
Body-mass index, kg/m²	28 (4)	27 (4)
Newly diagnosed polymyalgia rheumatica	19 (83%)	19 (79%)
Relapsing polymyalgia rheumatica	4 (17%)	5 (21%)
Disease duration		
Newly diagnosed polymyalgia rheumatica, weeks*	12 (8–26)	12 (8–22)
Relapsing polymyalgia rheumatica, months†	9 (2–15)	9 (7–33)
Duration of morning stiffness, min	90 (30–180)	30 (25–120)
Systemic symptoms‡	4 (17%)	7 (29%)
CRP at diagnosis, mg/L	20 (15–41)	32 (22–55)
CRP at baseline visit, mg/L	4 (2–10)§	9 (5–20)
ESR at diagnosis, mm/h	28 (29)	44 (38)
ESR at baseline visit, mm/h	25 (21)	28 (25)¶
Polymyalgia rheumatica activity score‖	22 (14)§	18 (11)

Data are n (%), mean (SD), or median (IQR). CRP=C-reactive protein. ESR=erythrocyte sedimentation rate. VAS=visual analogue score. *Disease duration from onset of symptoms until diagnosis, in weeks. †Disease duration from diagnosis until study inclusion, in months. ‡Fever, cold chills, weight loss, night sweats, or fatigue. §n=22. ¶n=23. ‖Polymyalgia rheumatica activity score=CRP + VAS patient + VAS physician + (morning stiffness duration × 0·1) + elevation of upper limbs score.

Table 1: **Baseline characteristics**

	Rituximab group (n=23)	Placebo group (n=24)	Absolute difference (one-sided 95% CI)	Relative risk (one-sided 95% CI)	One-sided p value
Glucocorticoid dose ≤5 mg per day	23 (100%)	13 (54%)	46% (20)	1·8 (1·3)	0·0012
Cumulative glucocorticoid dose (total), mg	1356 (151)	1406 (189)	–50 (34)	..	0·16
Median CRP, mg/L*	3 (1 to 5)	2 (1 to 12) [n=21]	..	..	..
Change from baseline in median CRP	–2 (–9 to 2) [n=22]	–5 (–13 to 0) [n=21]	4 (NA)	..	0·16
Mean ESR, mm/h	19 (11) [n=21]	16 (13) [n=22]	..	..	..
Change from baseline in mean ESR	–7 (25) [n=21]	–12 (19) [n=21]	5 (17)	..	0·79
Relapsed during follow-up†	7 (30%)	8 (33%)	–3% (20)	0·9 (0·4)	0·54
Median polymyalgia rheumatica activity score	5·5 (2·1 to 10·0)	11·7 (4·0 to 18·7)	..	..	..
Change from baseline in mean polymyalgia rheumatica activity score	–13·8 (2·9)	–3·8 (3·6)	–10·0 (–2·2)	..	0·018
Mean physicians' VAS	17 (16)	23 (19)	..	..	..
Change from baseline in mean physicians' VAS	–18 (17)	–16 (17)	–2 (11)	..	0·41
Mean patients' morning stiffness VAS	24 (28)	37 (24)	..	..	..
Change from baseline in mean patients' morning stiffness VAS	–28 (33)	–12 (37)	–16 (1)	..	0·061
Median morning stiffness duration, min	5 (0 to 30)	30 (9 to 90)	..	..	..
Change from baseline in median morning stiffness duration	–60 (–120 to –5)	–20 (–60 to 0)	–40 (NA)	..	0·023
Mean patients' pain VAS	27 (26)	37 (24)	..	..	..
Change from baseline in mean patients' pain VAS	–24 (30)	–11 (38)	–13 (4)	..	0·10
Mean patients' fatigue VAS	35 (30)	38 (26)	..	..	..
Change from baseline in mean patients' fatigue VAS	–18 (36)	–15 (34)	–3 (15)	..	0·40
Mean patients' global VAS	34 (29)	41 (20)	..	..	..
Change from baseline in mean patients' global VAS	–20 (30)	–17 (31)	–3 (12)	..	0·37
Mean HAQ-DI	0·66 (0·62)	0·76 (0·49) [n=23]	..	..	..
Change from baseline in mean HAQ-DI	–0·45 (0·61)	–0·58 (0·69) [n=23]	0·13 (0·47)	..	0·26
Mean EQ-5D-5L total score	0·67 (0·12)	0·65 (0·11)	..	..	..
Change from baseline in mean EQ-5D-5L total score	0·14 (0·24) [n=22]	0·09 (0·20) [n=22]	0·05 (–0·07)	..	0·25
Use of non-steroidal anti-inflammatory drugs‡	9 (39%)	10 (42%)	–3% (–31)	0·9 (0·5)	0·55
Mean $CD19^+$ B-cell count, cells per µL	0·01 (0·02) [n=19]	0·21 (0·09) [n=21]	..	..	..
Change from baseline in mean $CD19^+$ B-cell count	–0·20 (0·10) [n=15]	–0·07 (0·18) [n=19]	–0·13 (–0·04)	..	0·0078

Data are n (%), mean (SD), or median (IQR), unless otherwise stated. Higher VAS indicates worse outcome (range 0 to 100). Higher HAQ-DI score indicates worse function and greater disability (range total score 0 to 3). Higher EQ-5D-5L score indicates more severe or more frequent problems (range of total score for the Netherlands –0·446 to 1). No correction for type I error was done. CRP=C-reactive protein. NA=not applicable. ESR=erythrocyte sedimentation rate. VAS=visual analogue score. HAQ-DI=health assessment questionnaire disability index. *Wilcoxon rank sum (Mann-Whitney) test. †Relapse as judged by research physician. ‡This was a post-hoc analysis.

Table 2: **Treatment, disease characteristics, and quality-of-life-related secondary outcomes at 21 weeks after infusion**

patients who did not have glucocorticoid-free remission are shown in the appendix (p 20).

One serious adverse event (pulmonary embolism) was reported in one patient in the rituximab group; there were no deaths. Infusion-related adverse events and other adverse events of special interest are shown in table 3.

Discussion

To our knowledge, this is the first clinical study on B-cell-targeted treatment in polymyalgia rheumatica. The marginally significant efficacy of rituximab in terms of the primary outcome in our study is supported by positive effects on some secondary outcomes, such as proportion of patients who reached a glucocorticoid dose of 5 mg per day or less, and mean change in polymyalgia rheumatica activity score (figure 2). The results of our study are in line with previous preclinical studies showing that B cells might have an important part in the pathogenesis of polymyalgia rheumatica.[1,9] The safety profile of rituximab in our small study is similar to that in patients with rheumatoid arthritis, although this study was not powered to detect differences in safety profile.[16]

With regard to other biological DMARDs in polymyalgia rheumatica, so far no clear effect of tumour necrosis factor inhibitors has been shown in case reports and series, small open-label studies, or small randomised controlled trials.[1,21,22] A small placebo-controlled study did not show short-term efficacy of secukinumab (IL-17 inhibitor) and canakinumab (IL-1β inhibitor), but these drugs might have some steroid-sparing effects.[23]

The IL-6 receptor inhibitor tocilizumab has shown efficacy in patients with polymyalgia rheumatica in previous case series and small open-label studies.[8,9,24–26] In these studies, efficacy was shown in the outcomes of low disease activity scores (defined as polymyalgia rheumatica activity score ≤10), and glucocorticoid-free remission (judged by physician),[8,9] with one study also reporting

long-term remission after monotherapy.[8] However, although these findings appeared promising, a considerable number of patients withdrew from some of the tocilizumab studies due to adverse events or inefficacy, and randomised blinded studies with tocilizumab have not been done. Additionally, tocilizumab has some conceptual disadvantages, such as the difficulty of monitoring disease activity using CRP and the need for frequent administration of the drug.

Strengths of our study are the adequate (although small) sample size, the double-blind, randomised, and placebo-controlled design, and blinding during the analyses, which minimised risk of bias. Also, none of the patients were lost to follow-up. In addition, the primary outcome of glucocorticoid-free remission defined by polymyalgia rheumatica activity score is a composite outcome measure reflecting both objective and subjective symptoms of disease activity, and both patients' and physicians' perspectives. Lastly, the glucocorticoid toxicity index was used, which makes the registration of any adverse event very sensitive, resulting in the relatively high rate of adverse events recorded in both study groups.

This study has some limitations and challenges that need to be considered. First, the sample size was limited, partly by premature ending of enrolment due to the COVD-19 pandemic, and the positive results could be due to chance. However, the reasonably large effect size is somewhat reassuring in this regard, as are the effects on some of the secondary outcomes and in the exploratory post-hoc analyses. No significant differences were found in the cumulative glucocorticoid dose and other secondary outcomes, or in the subgroup of relapsed patients. With regard to the cumulative glucocorticoid dose, this could be expected to be different after longer follow-up, because the prednisolone induction and tapering schedule did not allow for large differences to occur within the timeframe of this study. Of note, the benefits and risks of rituximab and glucocorticoids should be carefully weighed in patients with polymyalgia rheumatica, which is not a life-threatening disease. Both repeated infusions of rituximab (dose-dependent and after a few cycles), and long-term use of glucocorticoids are associated with increased risk of infection.[5,16,17] Now that a first signal of rituximab efficacy in polymyalgia rheumatica has been found, a larger confirmatory study should be done with due regard to weighing benefits and risks, investigating long-term effects, effects of rituximab retreatment, and effect on secondary outcomes including glucocorticoid use.

A more general limitation in polymyalgia rheumatica clinical studies is the absence of a better standard for diagnosis, as classification criteria have low specificity, which might lead to erroneous inclusion of patients in the study. Two patients who developed clinically suspected rheumatoid arthritis were excluded from this study, but further misclassification cannot be fully ruled out. However, misclassification can only lead to an overestimation of the effect when rituximab is effective in the misclassified disease, and this could only realistically be true for rheumatoid arthritis.

The same applies to measuring disease activity; the polymyalgia rheumatica activity score, although partially validated, has not been universally adopted as a core outcome measure. Indeed, a clear consensus core outcome measure is absent in polymyalgia rheumatica. However, the polymyalgia rheumatica activity score is the most frequently used outcome in recent and ongoing randomised clinical trials in polymyalgia rheumatica.[27] In addition, as in polymyalgia rheumatica research in

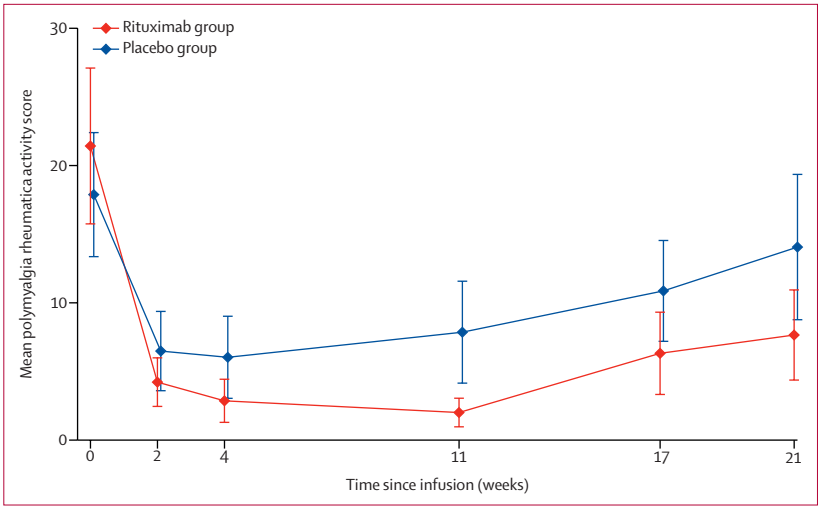

Figure 2: **Mean polymyalgia rheumatica activity score over time**
Error bars indicate 95% CI. This figure shows two-sided 95% CIs for each measurement at the specific timepoint, rather than for the differences, which is different to the one-sided 95% CIs for the differences between groups that are presented elsewhere in this Article.

	Rituximab group (n=23)	Placebo group (n=24)	Rate ratio (one-sided 95% CI)
Any adverse event (number of events)	136	148	1·0 (0·8)
Serious adverse events*	1	0	..
Deaths	0	0	..
Adverse events of special interest			
Infections†	15	8	2·0 (1·0)
Serious infections grade ≥3	0	0	..
Infusion-related events‡	10	3	3·5 (1·3)
Serious infusion-related events grade ≥3	0	0	..

Data are n unless otherwise stated. All adverse events that occurred during the study period were included in the safety analyses. Adverse event numbers are number of events, not number of patients with events. *The one serious adverse event was a pulmonary embolism in one patient. †Labelled as such by the research physician; in the rituximab group there was upper respiratory tract infection in eight patients (documented by anamnesis patients), lower respiratory tract infection in two patients (diagnosed and treated by general practitioner), urinary tract infection in two patients (diagnosed and treated by general practitioner), herpes zoster virus in one patient (diagnosed and treated by general practitioner), onychomycosis in one patient (diagnosed and treated by dermatologist), and eczema with secondary infection in one patient (diagnosed and treated by general practitioner); in the placebo group there was upper respiratory tract infection in three patients (documented by anamnesis patients), influenza-like symptoms in two patients (documented by anamnesis patients), acne in one patient (physical examination by research physician), and stomach flu in two patients (documented by anamnesis patients). ‡Labelled as such by the research physician; in the rituximab group there was restlessness (n=1), malaise (n=1), hypersomnia (n=2), palpitations (n=1), hot flashes (n=1), fatigue (n=1), hypotension (n=1), cough (n=1), and maculopapular rash (n=1); in the placebo group there was palpitations (n=1), fatigue (n=1), and hot flashes (n=1).

Table 3: **Adverse events**

general, this study was limited by the non-uniform definition of relapse.

It should be noted that most patients had received (short-term) glucocorticoid treatment before study inclusion; this might have resulted in lower baseline polymyalgia rheumatica activity score, ESR, and CRP values, and other patient-reported outcomes. Balancing this, enrolling patients who have recently commenced glucocorticoids is reflective of usual care and thus increases the generalisability of our study, and this would not lead to higher risk of a false-positive result. Interestingly, it is still unknown whether glucocorticoid treatment results in a shorter disease course, or if glucocorticoids only have a disease-modifying effect in polymyalgia rheumatica while being used. The findings of this study argues against the possibility that glucocorticoid treatment shortens the disease course, as glucocorticoid-free remission was seen infrequently in the control group after 17 weeks of prednisolone.

In conclusion, this proof-of-concept study showed marginally significant efficacy of rituximab in patients diagnosed with polymyalgia rheumatica. A larger phase 3 trial with longer follow-up, possibly with rituximab retreatment on indication, is now needed to confirm these findings.

Contributors

DEM contributed to the literature search, study design, data collection, data analysis, data interpretation, drafting of figures, and writing of the trial manuscript. NdB contributed to study design, checking and assisting with data analysis, drafting of figures, data interpretation, and writing of the trial manuscript. FHJvdH and AAdB contributed to study design, data interpretation, and writing of the trial manuscript. AvdM was principal investigator of this study and contributed to study design, data interpretation, and writing of the trial manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

FHJvdH reports personal fees from Abbott, outside of the submitted work. AAdB reports personal fees from Boehringer, Fresenius, Amgen, Merck, Abbvie, and Novartis, congress invitations from Galapagos and Sanofi, and grants from Abbvie, Pfizer, Lilly, Novartis, and Sanofi, outside of the submitted work. AvdM reports personal fees from Pfizer and Cellgene, outside of the submitted work. DEM and NdB declare no competing interests.

Data sharing

Data was collected by electronic health record of patients and entered in a Castor EDC database. Patient partners were involved in the design of the study. The results of the study will be disseminated to all study participants after completion of data entry of the BRIDGE-extension study. Data may be shared on request to the corresponding author and principal investigator.

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