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Original article

Low-dose rituximab protocol in rheumatoid arthritis—outcome and economic impact

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Abstract

Objectives. A significant proportion of RA patients, particularly those associated with poor prognostic factors, fail on conventional DMARDs (cDMARDs). Although rituximab (RTX) has been effective in these patients, the cost of therapy makes it unaffordable, particularly in poor and developing countries. Numerous, albeit small, studies using lower doses have shown contradictory results. We aimed to analyse the effectiveness of a low-dose RTX protocol based on clinical outcomes in RA patients.

Methods. Seropositive RA patients with moderate to high disease activity (DAS28-ESR >3.2) despite combination cDMARDs, treated with RTX, were included in retrospective analysis. All patients were treated according to a predefined protocol, using 500 mg RTX with ongoing cDMARDs at baseline and repeat dosing at 6 weeks or beyond, on lack of moderate to good EULAR response. The B cell count was assessed at baseline, 2 and 24 weeks.

Results. At 12 weeks, 93% of 166 patients [mean (S.D.) age, 51.5 (11.96) years, 25 men and 141 women, with a disease duration of 10.4 (6.29) years] achieved moderate to good EULAR response. At 24 weeks, 90.8% of patients achieved moderate to good EULAR response, 19.8% achieved low disease activity and 29.5% achieved remission, with a mean change in DAS28-ESR from baseline of 2.9 (1.3). RTX failure and relapse were seen in 5.4% and 3.6%, respectively. The response was maintained for 12.3 (7.2) months with a mean RTX dose 521.1 (100.8) mg. Adverse events were seen in 9.6%. When compared with the standard dosing regimen with the originator molecule, a cost reduction of 90% was achieved.

Conclusion. A low-dose RTX regimen achieved reasonably good clinical outcomes at the end of 6 months, with a significantly lower cost.

Key words: rheumatoid arthritis, rituximab, low dose, disease activity, pharmacoeconomics

CLINICAL SCIENCE

Key message

- A low-dose rituximab regimen in seropositive rheumatoid patients achieved reasonably good clinical outcomes at the end of 6 months, with significantly lower cost.

Introduction

RA is an autoimmune disease affecting >1% of the world population [1]. Erosions and joint deformities add to morbidity, and extra-articular manifestations, including accelerated cardiovascular disease, can result in mortality [2, 3]. Thus, it is important to target

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inflammation and halt disease progression, following a treat-to-target approach.

There are multiple treatment modalities available, including conventional DMARDs (cDMARDs), biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), including several kinase inhibitors. The choice of therapy is dictated by available guidelines depending on disease activity, but patient-related factors often decide the final management. The latter is particularly relevant in resource-constrained countries, such as ours, where economic well-being, a poor rheumatologist-to-patient ratio and distance to hospital often compound the situation and play a role in shared decision-making. Guidelines recommend that patients with features of poor prognosis, such as high disease activity, presence of autoantibodies (RF and/or ACPA) should be considered for early biologic therapy (bDMARDs or tsDMARDs) [4, 5]. Introduction of biologic therapies into treatment regimen can help to reach a target of clinical remission, inhibition of progressive joint destruction and improvement in extra-articular manifestations and morbidities [6].

Rituximab (RTX), a monoclonal antibody against CD20 that selectively targets B cells, is a therapeutic alternative for patients who are refractory to non-biologic DMARDs and/or anti-TNF therapy [7–9]. The labelled dose of RTX is 2×1000 mg (1000 mg on day 1, followed by 1000 mg on day 15, with a repeat of 1–2 g every 6 months, if required) and is associated with significant improvement in clinical and radiological outcomes [8, 10]. The dose has been derived from that used for haematological malignancies, but there are numerous studies where a lower-dose regimen (2×500 mg) has also shown efficacy comparable to the standard dose of RTX [11–13]. In 2006, Emery *et al.* [12] studied the safety and efficacy of two different doses of RTX (2×500 mg or 2×1000 mg) in patients who were on a stable dose of MTX. The team observed that low-dose RTX (2×500 mg) was as effective (ACR 20 response by week 24) and well tolerated as the conventional dose (2×1000 mg) when added to MTX therapy in patients with active RA, although the difference in efficacy showed no statistical superiority for the low-dose regimen. The SERENE trial in 2010 re-established this fact and proved that additive biological therapy with RTX in bio-naive active RA patients refractory to MTX monotherapy improved the therapeutic outcome [13]. Both these studies established the non-inferiority of a low-dose regimen to the conventional dosing of RTX. Bredemeier *et al.* [14] were the first to compare low-dose (1000 mg) with high-dose RTX (2000 mg) in a meta-analysis. They found the former to have similar effectiveness and advocated the use of the low-dose regimen, considering cost benefits. There are unpublished data showing effectiveness of very low-dose RTX, resulting in depletion of the peripheral B cells and reasonably good clinical outcomes [15, 16]. However, contradictory evidence regarding the efficacy of the low dose [17, 18] has not allowed for a broader acceptance of this regimen [17, 19, 20]. There are, however, no data to support or refute these findings from India. Ethnic variations with genetic differences could play a role in the treatment response. A lower dose, if effective, in Indian patients could also bring about a cost reduction for the patients. At our centre, we have been practising a low-dose RTX-based regimen for patients with moderate to severe disease activity; hence, we carried out a retrospective analysis to assess the effectiveness of the low-dose RTX treatment protocol and evaluate the hospital cost reduction achieved.

Methods

Study design

The study was a single-centre retrospective analysis conducted in a rheumatology specialist centre.

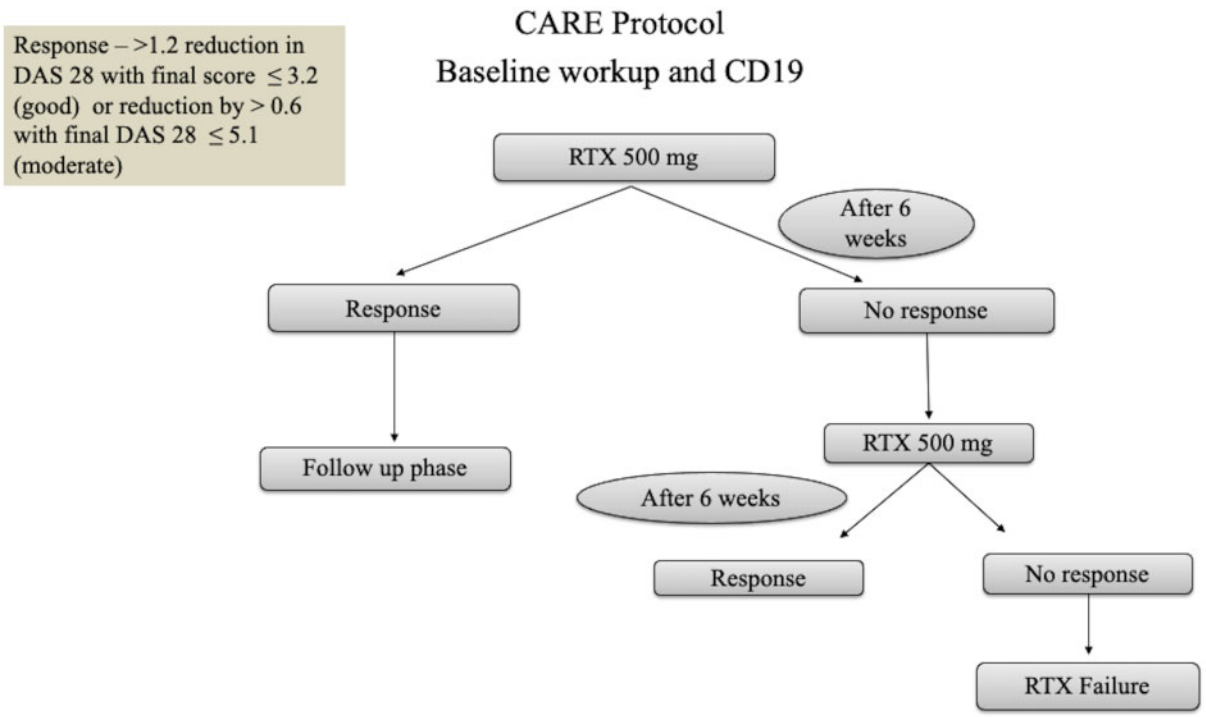
Patients and treatment regimen

At our centre, we have been treating RA patients with RTX in a protocol-based manner (Fig. 1). Seropositive (RF and/or ACPA) RA patients, classified according to 2010 ACR-EULAR classification criteria [21], who had moderate to high disease activity (DAS28-ESR >3.2) [22] despite the maximum tolerable dose of cDMARDs or TNF inhibitors, were treated with low-dose RTX (500 mg) (Fig. 1) and were included in the analysis. Data were collected from electronic medical records retrospectively for patients who visited the outpatient rheumatology section from 2015 to 2018 and had a minimum follow-up duration of 6 months. All patients continued on their background cDMARDs. RTX 500 mg infusion was given over 8 h after premedication as recommended. DAS28-ESR was used for calculation of disease activity, and EULAR response was used to measure the improvement in disease activity. The dose of cDMARDs and/or CS was kept constant for 6 weeks post-infusion. Patients who showed good or moderate EULAR response [23] at 6 weeks post-infusion [defined as >1.2 reduction with DAS28 ≤ 3.2 (good) and >0.6 reduction with DAS28 < 5.1 (moderate)] were followed up every 6 weeks by a single rheumatologist (P.S.).

Those patients who did not show any EULAR response at 6 weeks after the first infusion were treated with a second dose of 500 mg RTX (first cycle). The EULAR response was assessed 6 weeks after the second 500 mg dose in these patients, and those who did not achieve any EULAR response were categorized as RTX failures. They were taken out of the protocol, and further treatment decisions were left to the discretion of the treating physician.

During the subsequent visits if there was flare, defined as a change in DAS28 of >1.2 on two consecutive visits 1 month apart, the requirement for another dose of RTX was suggested to patient, but the final decision to take the dose was a shared one between the rheumatologist and the patient.

Fig. 1 Low-dose rituximab dosing protocol



CARE: Centre for Arthritis and Rheumatism Excellence, Kerala, India; RTX: rituximab.

High-sensitivity flow cytometry

Laboratory analysis of B cell depletion was done using flow cytometry at baseline (before the infusion) and at 2 and 24 weeks post-infusion. A peripheral blood sample was collected, and phycoerythrin (PE)-conjugated anti-CD19 (BD Biosciences-US) was added and incubated for 20 min, followed by red blood cell lysis and washing in phosphate-buffered saline. The cells were then counted in a BD FACS Canto flow cytometer. A minimum of 20 000 events were acquired and analysed with BD FACS Canto clinical software, and the CD19 percentage was determined. A percentage of B cells in the peripheral blood of $<0.01\%$ was considered as complete depletion.

Statistical analysis

Results were summarized as the mean (S.D.) or percentage as appropriate. The baseline characteristics of the study group were analysed by means of descriptive statistics. For normally distributed variables, the mean $\pm$ S.D. and Student's paired *t* test were used. Comparison of the degree of B cell depletion post-infusion with baseline CD19 levels and the change in the DAS28-ESR score after treatment were analysed by Student's paired *t* test. Statistical tests were assessed at the 0.05 significance level. The statistical analysis was performed with IBM SPSS Statistics v.20.

Ethical approval

Ethical approval was obtained from the Sree Sudheendra ethics committee, Sree Sudheendra medical mission hospital, Kochi (IEC/2017/003). Informed patient consent was not required because this study was a retrospective analysis.

Results

A total number of 166 seropositive RA patients, with a mean age of 51.5 (11.96) years and disease duration of 10.4 (6.29) years, were analysed. The baseline characteristics of the patients are shown in Table 1. Of the total of 166 patients, 29 had been treated with anti-TNF agents in the past. All patients were on one or more cDMARDs (Table 1).

At the end of 6 weeks, 134 (80.72%) patients achieved a moderate to good EULAR response. Thirty-two patients who continued to remain in high disease activity, with a mean DAS28-ESR of 5.39 (1.27), were advised to take a second dose of RTX 500 mg. However, 25 of these 32 patients opted to wait, partly owing to a feeling of well-being and partly for financial reasons. Of these 25 patients, 18 achieved a good to moderate EULAR response by the end of 12 weeks post-infusion (without taking a second dose of RTX). The remaining seven patients who refused the second dose of RTX, but who remained with high disease activity at 12 weeks after the first infusion, were managed at the discretion of the rheumatologist (Fig. 2). The remaining seven out of 32 patients received a second dose of RTX. Among these, five achieved a moderate EULAR response. Two patients failed to attain any EULAR response even with

a second dose of RTX and were categorized as RTX failures and treated according to the decision of the treating rheumatologist. A mean dose of 521.1 (100.8) mg RTX was required to achieve this response.

Table 1 Baseline characteristics of the study population and concomitant drugs given with low-dose rituximab therapy

Characteristic	Value
Total number of patients	166
Age, years[a]	51.5 (11.96)
Biological sex, male:female	25:141
TJC[a]	11.4 (7.71)
SJC[a]	5.63 (5.48)
ESR[a]	62.2 (34.59)
DAS28-ESR[a]	6.20 (1.20)
Bio-naive[b]	137
Duration of disease, years[a]	10.4 (6.29)
Follow-up period, months[a]	21.1 (11.12)
Autoantibodies	*n* (%)
ACPA positive	164 (98.8)
RF positive	160 (96.4)
Both ACPA and RF positive	159 (95.8)
Dose of medication, mg[a]	*n* (%)
CSs, 6.1 (3.45)	80 (48.2)
HCQ, 369. 7 (68.9)	122 (73.5)
MTX, 17(5.94)	81 (48.8)
SSZ, 2105.8 (790)	85 (51.2)
LEF, 14.1 (6.17)	45 (27.1)

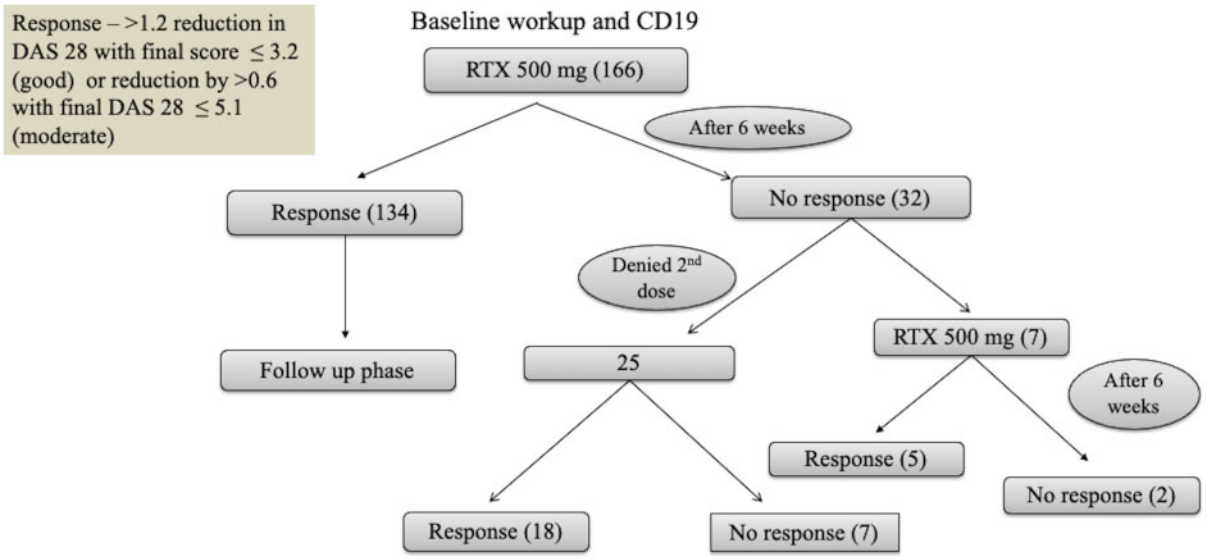
[a]Expressed as the mean (S.D.). [b]Did not receive any biologicals previously. DAS28: DAS using 28 joint count; SJC: swollen joint count ; TJC: tender Joint count.

At 12 weeks, 155 patients (93.3%) achieved a moderate to good EULAR response. Forty-one (26.4%) were in remission, and 34 patients (20.4 %) achieved low disease activity (Fig. 3). The duration of response was 12.3 (7.2) months after the first infusion (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). Two patients who initially responded at 6 weeks showed increased disease activity at 12 weeks. They were managed by increasing the dose of CSs to prednisolone 5 mg/day for 1 month. At 6 months, 151 (90.9%) patients still maintained a moderate to good EULAR response, whereas 5.4% showed no response and 3.6% relapsed (Fig. 3). Among these, 49 (29.5%) were in remission and 33 (19.8%) in low disease activity.

The duration of response obtained with each cycle of RTX and the mean dose given are described in Supplementary Table S1, available at *Rheumatology Advances in Practice* online. Out of 166 patients, 73 patients relapsed after a mean duration of 12.3 (7.2) months with a mean DAS score of 5.52 (1.32), and they were retreated with a second cycle of RTX 500 mg with same protocol. A mean DAS28-ESR of 3.45 (1.12) was achieved by the end of 12 weeks post-infusion.

Sixteen patients (9.6%) had minor infusion reactions which were managed by temporary stoppage of the infusion, and all tolerated the infusion at a lower rate. Seven patients had lower respiratory tract infections that required hospitalization and were treated with antibiotics according to standard guidelines. Of the 166 patients, 132 (79.5%) achieved complete peripheral B cell depletion at 2 weeks. There was no correlation between B cell

Fig. 2 Number of patients in each phase of dosing



Response was defined using EULAR response criteria and assessed at the end of 6 weeks. RTX: rituximab.

FIG. 3 The EULAR response at 3 and 6 months expressed as a percentage (number)

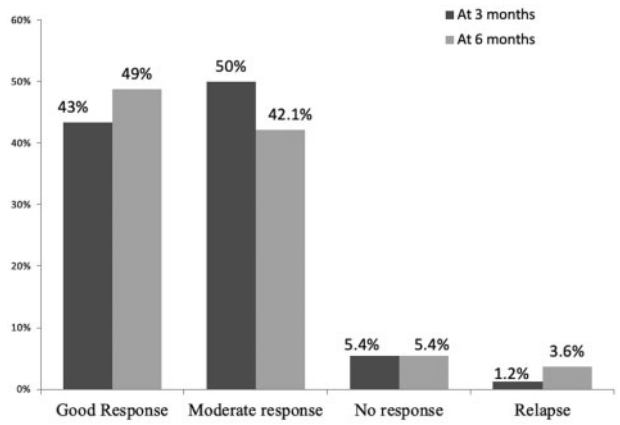


TABLE 2 Association between peripheral B cell count and EULAR response at 3 and 6 months

B cell depletion, B cell count (%)	Moderate to good EULAR response at 3 months [*n* (%)]	Poor response/failure at 3 months [*n* (%)]	Moderate to good EULAR response at 6 months [*n* (%)]	Poor response/failure at 6 months [*n* (%)]
Complete (<0.01)	129 (77.7)	9 (5.4)	127 (76.5)	11 (6.6)
Incomplete (≥0.01)	26 (15.6)	2 (1.2)	24 (14.4)	4 (2.4)
Total	155 (93.3)	11(6.6)	151 (90.9)	15 (9.03)

TABLE 3 Comparison of costs of therapy of low-dose rituximab (500 mg × 1) regimen with conventional 2 g protocol

Regimen	Cost (INR)	Retreatment	Monthly cost (INR)
2 g regimen	1 53 121/patient/year	6 monthly	25 520
Low-dose protocol at our centre	18 000/patient/year	Treat to target	1500

INR: Indian rupee.

depletion at 2 weeks and the clinical and EULAR response at 3 or 6 months (Table 2).

A low-dose regimen using a bio-similar achieved very similar results with 1/17th of the 2 g protocol (Table 3). The monthly cost of the low-dose regimen was $21 (1500 INR), when compared with $364.50 (25 520 INR) with the standard regimen using the original molecule. The annual cost was 18 000 INR/patient/year using the low-dose protocol.

Discussion

The results of this retrospective analysis, which aimed to assess the efficacy of a lower dose of RTX (500 mg × 1) with a repeat dose only if needed as indicated by disease activity, with a treat-to-target approach, showed >90% of the patients achieving and maintaining a good to moderate EULAR response, and half of the patients either in low disease activity or remission at 6 months. The response achieved was comparable to the standard 2 g dose used in RA, as evident from three randomized controlled trials (RCTs) and a meta-analysis [12, 13, 17, 24]. The results from our cohort open up the possibility of a new regimen for use of RTX with significant cost reduction.

Although EULAR and ACR response criteria have comparable validity in RA trials [25], we have been using EULAR response criteria in our clinic. EULAR response criteria do not characterize a patient to have good response even if there is marked improvement but the patient has not reached a certain level of disease inactivity. This is the standard protocol adopted in our clinic using RTX with a treat-to-target strategy and with the first assessment at 6 weeks, to gauge clinical response and the need for a second dose of RTX. This is a shared decision between the patient and the treating rheumatologist. Interestingly, 70% of the patients who refused to take second dose of RTX despite an

inadequate response at 6 weeks showed a moderate to good EULAR response after another 6 weeks. This not only reiterates the fact that RTX takes time to act but also indicates that further fine-tuning of the protocol can be done, which might reduce the dose and cost further.

RTX-based regimens in rheumatic diseases, including RA, have been derived from those used for haematological malignancies and have used a dose of 2 g. There are multiple dosing regimens that have been tried lately, including 100 and 200 mg (100 mg × 2), 1000 mg (500 mg × 2) and licensed dosing (1000 mg × 2) [15–17, 26, 27], but this is probably the first and largest study to use a single dose of 500 mg RTX in a protocol-based manner. Previously, a meta-analysis of RCTs and comparative cohort studies conducted by Bredemeier *et al.* [24] proved non-inferiority of a low-dose RTX regimen (1000 mg) to the conventional dose (2000 mg) in attaining the primary clinical outcomes and suggested making the low-dose regimen into the standard labelled dose for the treatment of RA, considering factors such as the lower cost of therapy and fewer infusion-related reactions. Likewise, the SMART trial, which was done in France, showed non-inferiority of a half dose to the conventional dose for maintenance treatment after a first course at a licensed dose, and a similar long-term (5 years) clinical efficacy with 39% cumulative decrease in RTX dose over time and with a lower rate of infections [28, 29]. The recently reported REDO study included patients who responded well to RTX and randomized them to lower doses for maintenance therapy. They found that 500 mg was comparable to 1000 mg at 3 months but that at 6 months it could not achieve statistical significance for non-inferiority [30]. Owing to the hierarchical testing procedure, analysis of the 200 mg group was not done. Nevertheless, the DAS was comparable between all three groups, and the authors concluded that lower doses can be effective in selective patients and that further studies are warranted comparing both doses. Although statistically insignificant, a higher number of patients achieved remission when compared with low disease activity in our cohort. The reasons for a higher response rate could be multifactorial, including the inclusion of only seropositive patients and the continuation of background therapy, which was not limited to MTX alone. All our patients were on two or more cDMARDs. Moreover, only 17.4% of patients had received biologics (TNF inhibitors) previously in our cohort. Most of the RCTs that have been conducted had different inclusion criteria and differed in baseline characteristics, such as RF positivity and prior use of bDMARDs. Moreover, none of the RCTs had representation of the Indian population. These differences need to be studied in more detail before we can draw more meaningful conclusion(s).

In the SERENE trial, where only 75% patients were seropositive, 62.9–66.4% of patients achieved a moderate to good EULAR response, unlike our cohort, in which all patients were seropositive [13]. In the MIRROR trial, where 70% were RF positive and 30% had received anti-TNF, moderate to good EULAR response rates were achieved in 72–89% of patients in different groups at week 48 [18]. Keystone *et al.* [31], using a 2 g dose of RTX, showed that 88% patients had a moderate to good EULAR response in their open-label extension analysis of RA patients previously treated with RTX. Krause *et al.* [32] showed that RTX was safe and effective in a real-life setting, with 72.1 and 80.5% of RF-positive patients showing a moderate to good EULAR response after one and two treatment cycles, respectively. Regression to the mean could also be a possible cause of an observed change, although this is more noticeable when follow-up measurements are made only on a subsample [33].

The peripheral B cell depletion achieved in our cohort at 2 weeks was 79.5%. This was low when comparted with other studies, but we used a more stringent cut-off for complete depletion ($<$0.01%). There is a wide variation in extent of B cell depletion, onset and rate of B cell recovery in peripheral blood in various autoimmune diseases, including RA, making the pharmacodynamics and pharmacokinetics more complex. The mean terminal half-life of RTX in RA ranges from 5 to 78 days [34, 35]. A prospective study design and a control arm could improve our understanding of the pharmacokinetics. However, effective peripheral depletion is not always correlated with clinical response [34].

Infections and infusion reactions remain a major challenge with the use of biologics, and there are multiple studies that prove the risk of serious infections with high-dose B cell depletion therapy [36]. Among our patients who were treated with low-dose RTX, there were only 16 minor adverse events, although this might be somewhat underestimated owing to recall bias because minor infections are often managed by a family physician and might not have been recorded in the rheumatology hospital records. However, it is highly unlikely that major infections requiring i.v. antibiotics would be missed. Meta-analysis reports suggest that the incidence of first infusion reactions might be reduced with the use of a low-dose regimen [14]. More studies are required to analyse these advantages of low-dose regimens.

Another important finding of the present study is the economic advantage of this protocol. By using biosimilar RTX in a protocol-based regimen, the cost was compared with the recommended dose of bio-originator every 6 months. Low-dose RTX might lead to a significant reduction in the costs of treatment of RA, given that biologic agents cause a significant burden to patients and health-care systems [37]. Among bDMARDs, RTX is the least costly therapy, and the costs might be reduced significantly with the use of a lower-dose regimen [20]. Analogous to the meta-analysis and above studies, our study echoed the same findings as far as the economic burden was concerned [24] Therefore, in developing nations, where the health-care cost is a major issue and the prevalence of infections is high, a low-dose regimen of RTX could be relevant either from the start of treatment or after a first course at the full dose [38].

Our study has many limitations, including the retrospective design. Also, there was no comparator arm to compare effectiveness and to assess cost-effectiveness. Another bias inherent in all open label studies is that of patients and physicians overestimating the response, resulting in increased response rates. However, this is the first study from India focusing on a lower dose of RTX and opens up the possibility of a new regimen and future controlled studies. We are planning to validate our results in future prospective studies with a comparator arm. This will allow us to discern the generalizability of our results and to compute the cost-effectiveness better.

In the view of the outcome of this study, we conclude that in seropositive RA, with 30% of the recommended dose of RTX along with concomitant cDMARD therapy, nearly 93% of the study population were able to achieve moderate to good control of disease activity and successfully maintained it for >1 year. Given the significantly lower cost and possibly better safety profile, this protocol, if validated in RCTs, might replace the current regimen.

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Data availability statement

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

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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