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FORTUNE JOURNAL OF RHEUMATOLOGY

ISSN: 2688-6766

# Different Dosing Regimens of Rituximab Biosimilar in Rheumatoid Arthritis: A Comparative Analysis of Disease Activity Control, B-cell Depletion and Adverse Effect Profile

**Syamasis Bandyopadhyay, Aheli Ghosh Dastidar*, Sandip Kumar Chandra**

## Abstract

**Introduction**: Rituximab is an established biologic DMARD for refractory rheumatoid arthritis (RA), but its high cost restricts access in low- and middle-income countries. Biosimilar rituximab (bRTX) provides a more affordable option with proven efficacy and safety. While reduced-dose regimens have shown non-inferiority to the standard regimen in originator RTX, real-world evidence on bRTX in India is limited. This study compares clinical outcomes and B-cell depletion with two bRTX dosing strategies in RA.

**Methods**: We retrospectively analysed bDMARD-naïve RA patients with inadequate response to conventional DMARDs who chose to receive either 1000 mg × 2 or 500 mg × 2 doses of bRTX. Disease activity (DAS28-ESR/CRP), ACR50 responses, and CD19+ B-cell counts were assessed at baseline and 12 months. Between-group comparisons were performed using Student's *t*- test.

**Results**: The mean DAS28-CRP decreased from 5.23 ± 0.10 to 3.62 ± 0.44 in the 1000 mg group and from 5.24 ± 0.09 to 3.65 ± 0.59 in the 500 mg group. ACR50 response rates were 84.6% and 78.6% in the standard- and reduced-dose groups, respectively, with no significant difference in disease activity reduction ($p > 0.05$). CD19+ counts (/uL) fell from 1222 to 127 in the 1000 mg group and from 1223to 134 in the 500 mg group.

**Conclusion:** Both standard and reduced bRTX regimens achieved comparable clinical efficacy and B-cell depletion over 12 months. The 500 mg regimen may represent an economically-viable alternative for RA management in resource-constrained settings.

**Keywords:** Rituximab; Biosimilar; Rheumatoid Arthritis; CD19; DAS28; ACR response

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition that remains challenging to manage universally, more so in resource limited countries. Both prevalence and incidence of RA are on the rise globally [1]. Effective management of RA demands early diagnosis and initiation of disease-modifying antirheumatic drugs (DMARDs) with a treat-to-target approach to achieve remission or low disease activity, thereby optimizing long-term clinical outcomes [2-5].

Treatment for RA has evolved from salicylates through non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional disease-

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**Citation:** Syamasis Bandyopadhyay, Aheli Ghosh Dastidar, Sandip Kumar Chandra. Different Aosing Regimens of Rituximab Biosimilar in Rheumatoid Arthritis: A Comparative Analysis of Disease Activity Control, B-cell Depletion and Adverse Effect Profile. Fortune Journal of Rheumatology. 7 (2025): 41-50.

**Received:** October 07, 2025
**Accepted:** October 15, 2025
**Published:** October 27, 2025

Bandyopadhyay S, et al., Fortune J Rheumatol 2025
DOI:10.26502/fjr.26880050

modifying antirheumatic drugs (cDMARDs), to latest biologicals and targeted synthetic DMARDs. The American College of Rheumatology (ACR) guideline recommends biological or targeted synthetic DMARDs (tsDMARD) when patients show suboptimal response to cDMARDs like methotrexate [4]. A range of biological DMARDs have been approved for treating RA, and they include tumor necrosis factor (TNF) inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T-cell costimulatory inhibitor (abatacept), interleukin (IL)-6 receptor inhibitors (tocilizumab, sarilumab), and anti-CD20 antibody (rituximab) [4]. With the introduction of biologics, the cumulative cost of RA therapy worldwide has gone up substantially [6]. In emerging economies like India, high cost of such therapies restricts their early and effective usage thereby hindering optimum disease control. The requirement of long-term treatment with biologicals in RA imposes a significant financial burden. In this context biosimilars offer a cost-effective option for managing RA, not only in India but also in countries with similar demography [7]. The expiration of RTX patents and the advent of biosimilars have improved access to this therapy, offering cost-effective alternatives with comparable efficacy and safety [8,9]. Biosimilars to biologicals are approved for use provided their safety, purity, and potency are similar to original or reference drug [10,11]. Rituximab (RTX) is a genetically engineered chimeric anti-CD20 monoclonal antibody, approved for treatment of RA [12]. The European Medicines Agency (EMA) and the United States of America Food and Drug Administration (US-FDA) have approved a few rituximab biosimilars for treating RA [8]. A systematic review and meta-analysis of biosimilar Rituximab (bRTX) in RA and non-Hodgkin's lymphoma patients established the clinical response and safety [13]. In India, the central drug control organisation headed by drugs controller general of India has approved one such biosimilar developed by Hetero and subsequently marketed by Zydus Life sciences ltd as Vortuxi™ for treatment of RA [14]. Rituximab acts by targeting CD20, a surface transmembrane protein marker expressed on B cells throughout their differentiation from pre-B cell till plasma cell stage [16] RTX depletes pre-B cells and mature B cells sparing the stem cells, pro B cells, plasma cells and plasmablasts.[10] RTX therapy has been shown to reduce B cells in peripheral blood and brings a variable decline in bone marrow and synovial B cell population [11,12]. Nakou et al demonstrated a substantial reduction of $CD19^+$ B cells, along with a significant reduction in the activated $CD19^+HLA\text{-}DR^+$ subset in both peripheral blood and bone marrow with RTX therapy [17] This decrease in CD 19 B cells was followed by a clinical response in RA patients [17] Failure of peripheral blood CD19 B-cell depletion has been observed in non-responders to RTX therapy [15] B cell depletion following Rituximab therapy has been shown to be predictive of clinical response in RA [17] Some reports have also explored role of B cell repletion in predicting relapse in RA [16] B cell repopulation was found to precede clinical relapse by around 4 months in the study reported by Trouvin et al [15] In our centre, CD19 cell counts are routinely assessed at baseline and at specific intervals following initiation of bRTX therapy, as an aid to assess B-cell depletion which helps to estimate the optimal timing of subsequent dosing. RTX is conventionally administered as a 1000 mg intravenous infusion on days 1 and 15. (Rituxan_prescribing.Pdf, n.d.) [18] But several trials have shown comparable disease control with two doses of 500mg RTX given 14 days apart [19-22] The CERRERA collaboration combining data from 12 European registries demonstrated a comparable efficacy of 500mg x 2 dosing regimens with 1000mg x2 regimen of Rituximab [23]. However, evidence supporting lower dosing regimen of bRTX in RA is currently lacking. Utilizing a lower, yet efficacious dose may potentially confer a more favourable adverse effect profile while also improving economic sustainability at both the individual and national levels. This retrospective real-world comparative study examines the impact of conventional and low doses of bRTX on RA disease severity in Indian clinical practice and compares B cell depletion levels (measured by absolute CD19 cell count) between both regimes as a molecular marker of effectivity.

## Methods

This retrospective work was done on a cohort of RA patients attending rheumatology outpatient of a tertiary care hospital in eastern India. Prior ethical approval was obtained from the institutional ethics committee **(IEC/BR/2025/01/06)**. Adult biological-naive RA patients meeting EULAR 2010 criteria, with inadequate response to conventional DMARDs who had voluntarily opted for either 1000 mg x 2 or 500mg x 2 of bRTX, after considering all potential therapeutic options were eligible for this analysis. In situations where disease control remains suboptimal despite ongoing therapy, it is standard practice in our institute to engage in a comprehensive discussion with the patient and their family regarding all available alternative or additional therapeutic options. This includes a detailed review of each agent—whether conventional, biological, or targeted synthetic DMARDs—addressing factors such as cost, established efficacy, dosing regimens, and potential adverse effects, therapy duration. Such discussions are integral to a shared decision-making process prior to the initiation of any new therapeutic intervention. The same was followed in these patients before initiation of Rituximb therapy. After consideration of stated factors those patients who chose to receive either 500mg or 1000mg were included for the analysis. Consistent with usual care, before Rituximab therapy initiation, patients were screened for Hepatitis B, hepatitis C, HIV positivity, low IgG, IgM serum levels and cytopenias (TLC <4000 / cumm, HB <8 g/dL, platelet < 1lakh/cumm). Patients with

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DOI:10.26502/fjr.26880050

history of recent hospitalisation within 3 months, pregnant women, female patients unwilling to be on appropriate contraception, patients with history of malignancy and known ischaemic heart disease especially with heart failure (EF <40%) were excluded as per routine extant clinical practice. Patients were administered intravenous infusions of two doses of either 1000 mg or 500 mg of bRTX with standard premedication and monitoring 15 days apart. Any infusion related side effects were recorded and appropriately dealt with. All patients continued cDMARD with their biological treatment and were followed up in OPD as per schedule. Data of 27 RA patients on regular OPD follow-up from October 2023 to October 2024, receiving two doses of either 500mg or 1000mg of bRTX, was retrieved from patient records system. Patient data were compiled in Microsoft Excel, encompassing sociodemographic variables, clinical disease activity parameters (tender joint counts, swollen joint counts, physician and patient global assessment scores, visual analogue score for pain), and laboratory investigations (ESR, CRP, Complete Blood Count and CD19 cell count at baseline and after 12 months of treatment). Any adverse events reported by the patients while on bRTX therapy or the clinician were also recorded.

## Statistical Methods

Baseline comparability of both groups of patients (receiving either 1000mg or 500mg) was confirmed. To account for residual imbalances, linear regression/ANOVA was performed adjusted for age, baseline DAS28, etc. No statistically significant differences in baseline characteristics between two groups were found. For accommodation of non-normal data non-parametric tests like Mann-Whitney U tests and median difference were applied. Bonferroni or false discovery rate (FDR) corrections were applied for multiple comparisons. Data of changes in CD19 count, DAS28-ESR (Disease Activity Score, Erythrocyte sedimentation rate) and DAS28-CRP scores CRP scores (C-reactive protein), ACR 50 responses at baseline and after 12 months of therapy across both groups of patients were compared using Student's t test. Microsoft Excel statistical package and Python software was used for data analysis. Correlation between DAS28 ESR and Absolute CD 19 cell count was calculated using Pearson's correlation method.

## Results

Twenty-seven RA patients with inadequate response to conventional DMARDs who opted for bRTX were included. 13 of them opted for 2 doses of 1000mg and 14 chose to receive 2 doses of 500mg of the drug, two weeks apart. These patients remained on varying combinations of methotrexate (MTX), hydroxychloroquine (HCQS) and sulfasalazine (SSZ)), as tolerated throughout bRTX therapy period. Their mean age was 40.9 ±4.83 years, 17 (62.96%) of them were females. The mean disease duration was 6.44 ± 1.44 years. Demographic characteristics were similar across both groups. (table 1) Baseline laboratory parameters and disease severity indices were comparable in both groups of patients receiving either 1000mg or 500mg bRTX. (table 2, table 3) (figure 1). Treatment with both doses of bRTX resulted in satisfactory clinical response as seen by substantial reduction in DAS28-ESR and DAS28-CRP scores at 12 months of therapy compared to baseline (table 2) (figure 2, figure 1). 84.61% patients in the 1000mg bRTX group achieved an ACR 50 response as compared to 78.57% patients in the 500mg bRTX group. (table 2) Therapy with both doses of bRTX resulted in a sustained B cell depletion as evidenced by significantly lower CD19 cell count in both 1000mg and 500mg doses of bRTX therapy group at 12 months. (table3) (figure 3). However mean CD 19 cell count at 12 months of therapy was significantly lower in the 1000mg bRTX group as compared to the 500mg group. (table 3). Both biochemical and haematological parameters were also comparable. The degree of correlation between DAS28-ESR and CD 19 count was detected as 0.4.

## Adverse Events

Two patients receiving 1000mg bRTX and one patient receiving 500mg bRTX developed infusion reaction in form of chills during the first dose infusion, all of which was

**Table 1:** Demographic parameters of patients receiving 500mg or 1000mg of bRTX.

| Parameter | bRTX1000mg (n=13) (Mean±SD) | bRTX 500mg (n=14) (Mean±SD) |
|---|---|---|
| **Gender** | | |
| Female | 8(61%) | 9(64%) |
| Male | 5 (39%) | 5(36%) |
| Age (Average) | 40.96±4.83 | 38.69±2.86 |
| **Comorbidities** | | |
| Hypertension | 5 (38.5%) | 4 (28.6%) |
| Hyperlipidaemia | 2 (15.4%) | 2 (14.28%) |
| Diabetes Mellitus | 3(23.08%) | 0 |
| **Educational Qualification** | | |
| Graduation | 6 (46.15%) | 5 (35.71%) |
| Post Graduation | 3 (23.07%) | 4 (28.57%) |
| Higher secondary | 4 (30.77%) | 5 (35.71%) |
| Time from diagnosis | 6.23±1.59 years | 6.77±1.42 years |
| **DMARD history** | | |
| Methotrexate | 12 (92.30%) | 13 (92.85%) |
| HCQ | 12 (92.30%) | 11 (78.57%) |
| SSZ | 9 (69.23%) | 9 (64.28%) |

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DOI:10.26502/fjr.26880050

**Table 2:** Disease activity at baseline and after 12 months of therapy with bRTX

| Parameter | B RTX 1000mg | | B RTX 500mg | |
|---|---|---|---|---|
| | At Baseline | After 12 months | At Baseline | After 12 months |
| DAS 28 ESR | 6.36 ± 0.10 | 4.48 ± 0.52 | 6.35 ± 0.09 | 4.53 ± 0.70 |
| DAS 28 CRP | 5.23 ± 0.10 | 3.62 ± 0.44 | 5.24 ± 0.09 | 3.65 ± 0.59 |
| VAS for pain | 8.30 ± 0.85 | 4.0 ± 1.15 | 8.35 ± 0.77 | 3.92 ± 1.47 |
| % of ACR 50 response | | 84.61% | | 78.57% |

**Table 3:** Cumulative table of Disease parameters, Laboratory parameters and CD 19 cell counts at baseline and at 12 months of bRTX therapy

| Parameter | bRTX 500mg (Mean ± SD) | bRTX 1000mg (Mean ± SD) | Mean Difference (95% CI) | p-value |
|---|---|---|---|---|
| **Disease Activity** | | | | |
| DAS28 CRP Baseline | 5.23 ± 0.09 | 5.23 ± 0.10 | 0.00 (-0.08, 0.08) | 0.999 |
| DAS28 CRP 12 months | 3.65 ± 0.55 | 3.62 ± 0.45 | 0.02 (-0.39, 0.44) | 0.903 |
| DAS28 ESR Baseline | 6.35 ± 0.09 | 6.36 ± 0.10 | -0.01 (-0.09, 0.07) | 0.821 |
| DAS28 ESR 12 months | 4.53 ± 0.65 | 4.48 ± 0.52 | 0.04 (-0.44, 0.53) | 0.846 |
| VAS Baseline | 8.36 ± 0.74 | 8.31 ± 0.85 | 0.05 (-0.63, 0.72) | 0.874 |
| VAS 12 months | 3.93 ± 1.38 | 4.00 ± 1.15 | -0.07 (-1.14, 0.99) | 0.885 |
| **Laboratory Markers** | | | | |
| Platelet Baseline (Lakh/cu mm) | 1.74 ± 0.09 | 1.85 ± 0.32 | -0.12 (-0.32, 0.08) | 0.225 |
| Platelet 12 months (Lak/cu mm) | 1.75 ± 0.09 | 1.85 ± 0.48 | -0.11 (-0.40, 0.19) | 0.443 |
| WBC Baseline (cells/uL) | 6137.86 ± 977.45 | 5992.31 ± 1426.80 | 145.55 (-887.59, 1178.69) | 0.762 |
| WBC 12 months (cells/uL) | 6157.14 ± 1904.13 | 6653.85 ± 1349.45 | -496.70 (-1873.08, 879.68) | 0.44 |
| WBC Baseline (cells/uL) | 6137.86 ± 977.45 | 5992.31 ± 1426.80 | 145.55 (-887.59, 1178.69) | 0.762 |
| WBC 12 months (cells/uL) | 6157.14 ± 1904.13 | 6653.85 ± 1349.45 | -496.70 (-1873.08, 879.68) | 0.44 |
| ESR Baseline (mm/hr) | 56.93 ± 3.38 | 55.77 ± 4.59 | 1.16 (-2.24, 4.56) | 0.465 |
| ESR 12 months (mm/hr) | 28.57 ± 9.23 | 26.69 ± 7.66 | 1.88 (-5.22, 8.97) | 0.569 |
| CRP Baseline(mg/L) | 7.04 ± 0.78 | 6.55 ± 0.94 | 0.50 (-0.23, 1.23) | 0.151 |
| CRP 12 months (mg/L) | 2.91 ± 1.11 | 2.71 ± 1.14 | 0.20 (-0.74, 1.14) | 0.649 |
| **B-Cell Depletion** | | | | |
| CD19% Baseline | 13.36 ± 1.08 | 12.92 ± 1.50 | 0.43 (-0.67, 1.54) | 0.4 |
| CD19% 12 months | 2.34 ± 0.59 | 1.98 ± 0.43 | 0.36 (-0.07, 0.79) | 0.078 |
| CD19 Absolute Baseline (cells/uL) | 1217.29 ± 231.42 | 1221.54 ± 270.14 | -4.25 (-215.93, 207.43) | 0.965 |
| CD19 Absolute 12 months (cells/uL) | 134.21 ± 4.95 | 126.77 ± 3.42 | 7.45 (3.90, 10.99) | <0.001 |

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DOI:10.26502/fjr.26880050

**Table 4:** Lab parameters at baseline and after 12 months of therapy

| Parameter | bRTX 1000mg | | bRTX 500mg | |
|---|---|---|---|---|
| | At Baseline | After 12 months | At Baseline | After 12 months |
| Haemoglobin (g/dL | 10.88 ± 0.94 | 11.16 ± 0.55 | 10.00 ± 0.66 | 10.05 ± 0.64 |
| WBC Count (/cu.mm | 5992.31 ± 1426.80 | 6653.84 ± 1349.45 | 6179.23 ± 1044.34 | 6284.61 ± 1949.10 |
| Platelet Count(lakh/cumm) | 1.85 ± 0.32 | 1.85 ± 0.47 | 1.73 ± 0.09 | 1.74 ± 0.10 |
| ESR (mm/hr) | 55.77 ± 4.58 | 26.69 ± 7.66 | 56.92 ± 3.67 | 28.92 ± 9.69 |
| CRP (mg/dL) | 6.54 ± 0.94 | 2.71 ± 1.13 | 7.04 ± 0.85 | 2.95 ± 1.16 |
| CD19 Absolute Count(/uL) | 1221.53 ± 270.14 | 126.77 ± 3.42 | 1222.07 ± 249.65 | 133.84 ± 5.15 |

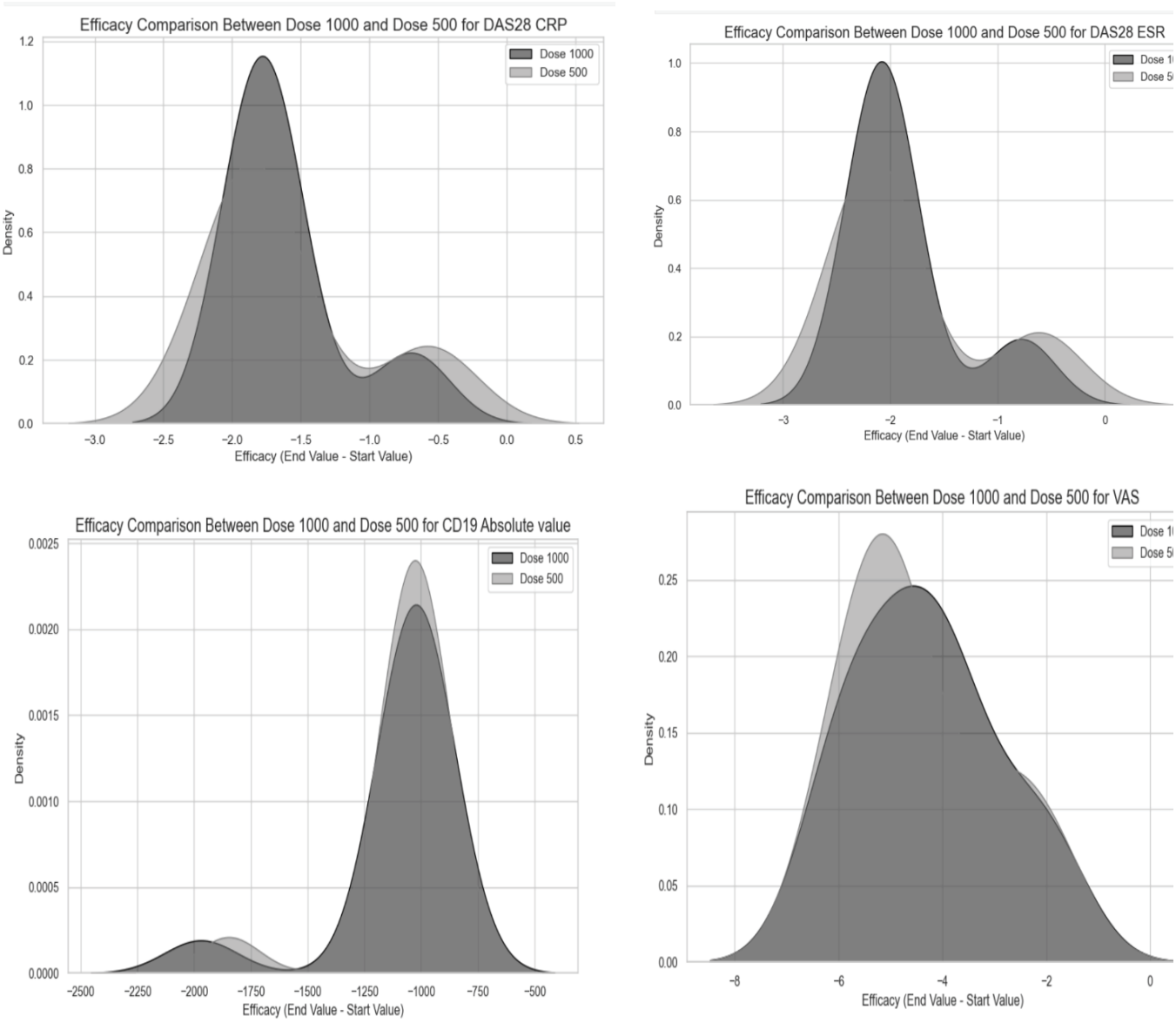


**Figure 1:** Population distribution of various parameters across both groups of patients at baseline and after 12 months

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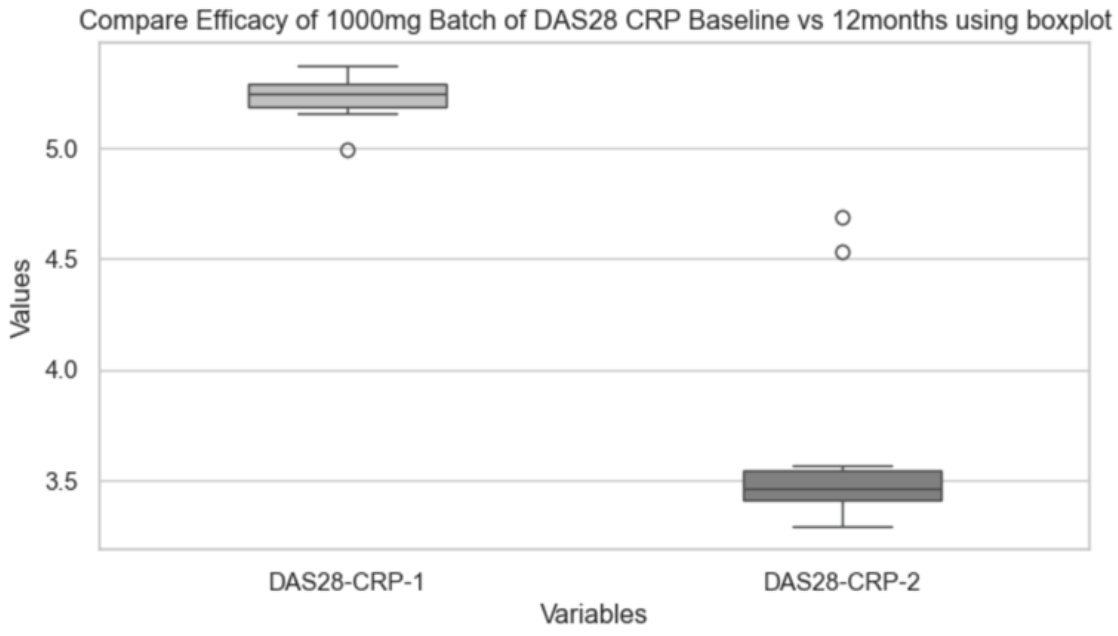
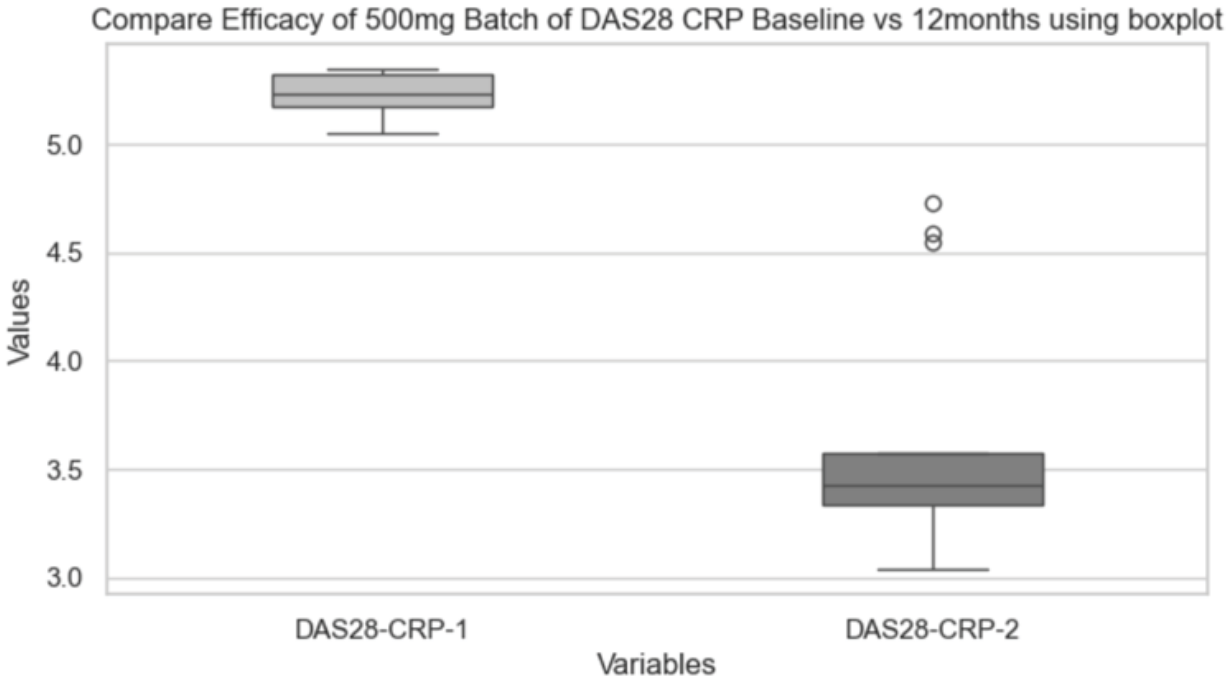



(2A)




(2B)

**Figure 2:** Boxplot for DAS 28 CRP at baseline and at 12 months with (A) 1000mg and (B) 500mg of b RTX (DAS28-CRP1: At baseline, DAS28-CRP2: At 12 months)

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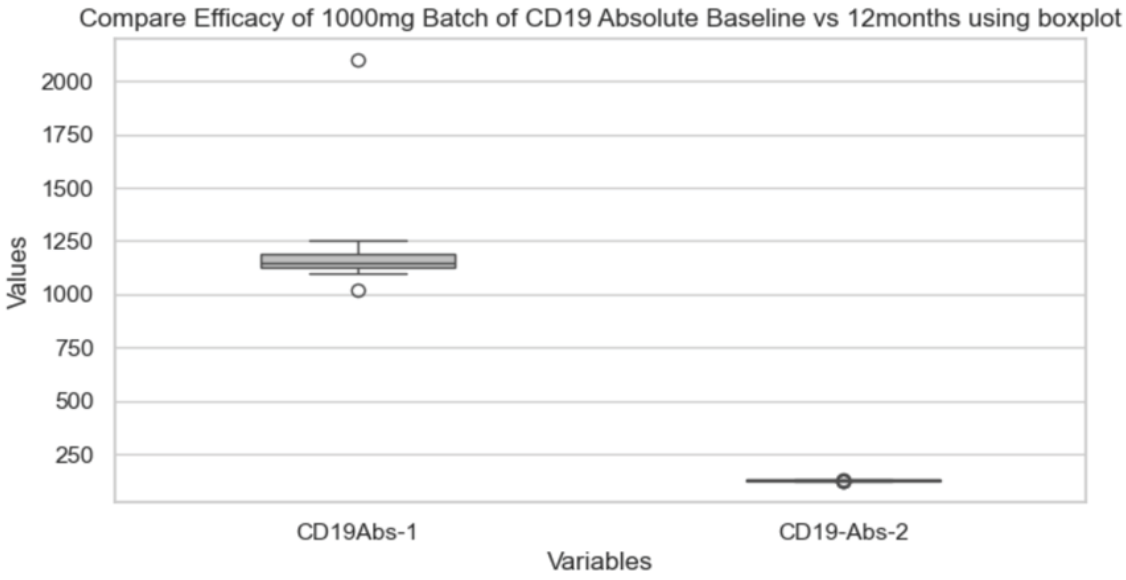
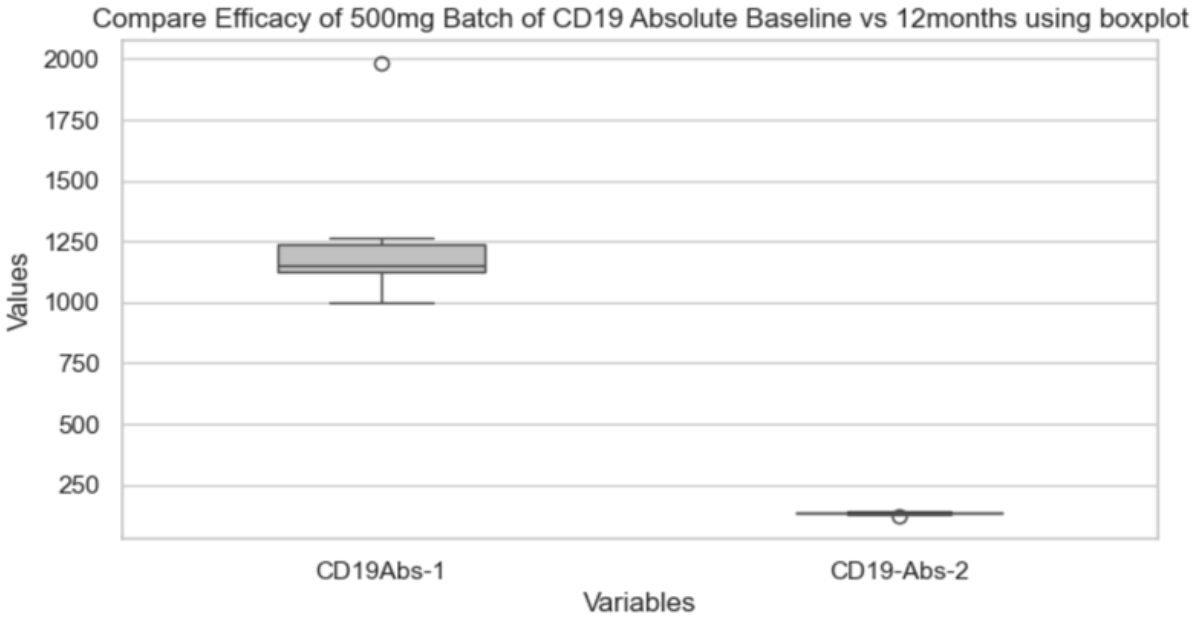



(3A)




3(B)

**Figure 3**: Boxplot for CD 19 absolute count at baseline and after 12 months with (A)1000mg and (B) 500mg b RTX (CD19-Abs1: C19 Cell count at baseline, CD19-Abs2: CD19 cell count at 12 months)

managed conservatively and subsequently they received full planned dose as per schedule. No major side effects requiring drug discontinuation or hospitalisation were observed. The patients did not report any infection requiring hospitalisation or adverse health event possibly linked to bRTX therapy in the year following initial bRTX infusion.

## Discussion

This real-world comparative analysis demonstrates that administration of two doses of both 1000mg and 500mg bRTX showed a significant reduction in disease activity among biologic-naïve RA patients. DAS28-ESR and DAS28-CRP showed significant improvement at 12 months in both groups, reinforcing bRTX's role in reducing inflammation and joint involvement. Impressive ACR50 responses in both groups were indicative of the same. These findings align with prior studies of RTX in RA, which highlight its ability to modulate B-cell-driven pathogenesis, bringing about sustained disease

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control [3,24]. The comparable clinical response brought about by the two dosing regimens of bRTX is consistent with some studies on originator RTX [13]. Clinical effectiveness of RTX is well established across multiple rheumatological disorders and also beyond domains of rheumatology. There exists variation of recommended dosing of Rituximab among individual conditions. In ANCA vasculitis 500mg 6 monthly Rituximab proved a better agent than Azathioprine as maintenance therapy [25]. In lupus nephritis, multiple dosing strategies of Rituximab have been used ranging from 2 infusions of either 500mg or 1000mg to 375mg/m2 every week for 4 weeks. Notably, regimen comprising 2 doses of 500mg showed comparability with other dosing regimens [26-28]. An observational study evaluating the impact of off-label low dose rituximab in a variety of autoimmune conditions reported decent clinical response in majority patients [29]. Few reports comparing the effectiveness of 500mg and 1000mg doses of RTX in RA patients with an inadequate response to MTX found significant clinical improvement with both regimens [19] The SERENE trial concluded that two infusions of either dose, combined with MTX, led to substantial improvement at 24 weeks, with sustained benefits at 48 weeks. Similar proportions of patients in the RTX 500 mg and RTX 1000 mg groups achieved ACR20 (54.5% vs. 50.6%) and ACR50 (26.3% vs. 25.9%) responses. Additionally, mean DAS28-ESR scores over 48 weeks were comparable between the two groups [19]. The MIRROR trial showed that escalating the dose from 500mg to 1000mg did not improve the clinical outcomes [20]. IMAGE trial demonstrated that MTX combined with 1000mg of RTX significantly reduced joint damage progression and improved clinical outcomes, while the MTX + 500 mg RTX group showed significant clinical improvement, but joint damage progression remained unchanged [22]. The DANCER trial further confirmed improvement of health-related quality of life with both doses [30]. Findings from CERERRA and a meta-analysis by Bredemeier et al. also demonstrated comparable clinical outcomes between 500 mg and 1000 mg doses [23,24]. Furthermore, lower-dose regimens (e.g,500 mg every six months) have been explored as cost-saving alternatives without compromising efficacy in select patient populations [31]. Our study data mirrors similar clinical outcomes with both low and high doses of bRTX, as seen in clinical trials of originator molecule. Parallel evaluation of CD 19 levels alongside disease activity indices, helps in depicting a clearer picture of disease control and therapeutic response. This sustained B cell depletion with clinical effectiveness was seen even at 1 year of bRTX dosing. The cost implications of such changes will be substantial, improving affordability of the molecule in Indian background and possibly beyond. Interestingly, the significantly lower CD19 counts at 12 months in the 1000 mg group suggests a dose-dependent impact on B-cell depletion, a finding consistent with previous studies [18,32]. In our study significantly higher CD19 depletion at 12 months in 1000mg bRTX group was not associated with significantly superior clinical disease control. A plausible explanation of this disparity might be that the level of CD19 depletion brought about by 500mg bRTX was sufficient for therapeutic response with no additional benefit being conferred by a greater CD19 depletion in 1000mg group in this group of RA patients. However, a more pronounced depletion may have implications for long-term disease control and relapse rates. Additional longitudinal studies are required to establish whether this translates into superior clinical outcomes over time. The high degree of correlation between CD 19 cell depletion and clinical disease remission brought about by both doses further helps to reinforce clinical confidence in utilizing lower dose of bRTX in regular practice. Notably, as most patients were on MTX while on bRTX treatment with a few continuing other DMARDs as well, the ACR 50 response was impressive. All the patients were educated individuals and thereby showed compliance and motivation towards treatment. The near complete CD 19 positive B cell depletion in all patients laid the molecular foundation of the remarkable clinical response observed.

## Limitation

However, the retrospective design, small sample size, observational nature, lack of head-to-head comparison, and absence of imaging evaluation preclude causal inference. Additionally, the 12-month follow-up may be insufficient to capture long-term differences in effectiveness and safety. Future studies with extended follow-up and larger cohorts are needed to confirm these findings and refine optimal dosing strategies for bRTX in different RA patient subgroups.

## Conclusion

The findings of this study suggest that a lower dose of bRTX may be sufficient for satisfactory disease control in real-world setting, with significant economic benefit that may transgress to better biologic penetration. Given the comparable effectiveness in disease activity control and sustained B-cell depletion for 12 months, the 500 mg bRTX regimen may offer a cost-effective alternative without compromising therapeutic benefit. The moderate-to-high degree of correlation between CD19 cell depletion and disease activity reduction establishes potential prospect of absolute CD 19 cell count assessment as a molecular marker of disease remission, guiding subsequent dosing of bRTX. Future research focusing on long-term outcomes including remission and response rates, potential differences in immunogenicity between the two-dosing regimen and ethnic difference is essential for universal recommendation of low dose bRTX in RA.

## Acknowledgement

The authors acknowledge the immense contribution of Mr Subhendu Dutta Bhowmick, data scientist, in analysing and drafting a comprehensive interpretation of the dataset

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**Citation:** Syamasis Bandyopadhyay, Aheli Ghosh Dastidar, Sandip Kumar Chandra. Different Aosing Regimens of Rituximab Biosimilar in Rheumatoid Arthritis: A Comparative Analysis of Disease Activity Control, B-cell Depletion and Adverse Effect Profile. Fortune Journal of Rheumatology. 7 (2025): 41-50.