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REVIEW

# Rituximab for Rheumatoid Arthritis

Marc D. Cohen · Edward Keystone

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## ABSTRACT

Rituximab is a chimeric monoclonal antibody directed at the CD20 molecule on the surfaces of some but not all B cells. It depletes almost all peripheral B cells, but other niches of B cells are variably depleted, including synovium. Its mechanism of action in rheumatoid arthritis (RA) is only partially understood. Rituximab was efficacious in clinical trials of patients with RA, including those who are methotrexate naïve, those with an incomplete response to methotrexate, and those with an incomplete response to tumor necrosis factor inhibitors. The need for a concomitant traditional disease-modifying drug, the optimal dose of rituximab, and the optimal interval for retreatment remain somewhat uncertain. Rituximab seems to be most efficacious in seropositive patients and those with an incomplete response to only one tumor necrosis factor inhibitor. Rituximab has a reasonable safety profile, with a small risk of serious infectious events, which is stable over time and repeat courses. Opportunistic infections are rare. Reactivation of hepatitis B remains a concern. The possible association of rituximab and progressive multifocal leukoencephalopathy may still require vigilance. Malignancies and cardiovascular events do not appear to be increased. Infusion reactions are more likely with the initial infusion, and are usually mild. Rituximab may cause hypogammaglobulinemia, but any risk of subsequent risk of increased infectious events is not yet well established. Before initiating rituximab, patient screening for hypersensitivity to murine proteins, infections, congestive heart failure, pregnancy, and hypogammaglobulinemia is imperative. Vaccinations should be administered prior to treatment whenever possible. Rituximab has been a significant addition to the rheumatologists' armamentarium for the treatment of RA.

M. D. Cohen (✉)
Professor Emeritus Mayo Clinic, Rochester, USA
e-mail: mcohen@rheumdoc.net

E. Keystone
University of Toronto, Toronto, Canada

E. Keystone
The Rebecca MacDonald Centre for Arthritis and Autoimmune Diseases, Mount Sinai Hospital, Toronto, Canada

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## INTRODUCTION

Rituximab remains a unique therapeutic option for the treatment of rheumatoid arthritis. There is now a rich literature regarding its efficacy and safety. Questions remain, however, about its exact mechanism of action in RA, the most appropriate dosing schedule, and which RA patients might benefit the most from its use. All of these aspects of rituximab for RA are reviewed in this article.

## MECHANISMS OF ACTION

Rituximab is a monoclonal antibody directed at the CD20 molecule on the surfaces of some B cells. It is a chimeric product consisting of approximately 20% mouse and 80% human protein. Rituximab depletes mature B cells and pre-B cells through memory B cell stages, but stem cells, pro-B cells, terminally differentiated plasma cells, and plasmablasts do not express CD20 and are not depleted [1, 2]. Intravenous rituximab in RA patients results in almost complete depletion of peripheral B cells and variable depletion of B cells in synovium and other sites such as lymphoid tissue and bone marrow [2, 3]. Clinical response correlates to some degree with synovial tissue B cell depletion and perhaps with peripheral B cell depletion [3–6]. Reconstitution of B cells post rituximab results in immature, naïve B cells, but in many patients it leads to relapse of clinical disease [3]. Rituximab depletes B cells by several mechanisms, including mediation of antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and B cell apoptosis [2]. Precisely how B cell depletion results in clinical efficacy in RA is incompletely understood, but the effects may be mediated via B cell antigen presentation ability, B cell production of cytokines, and B cell production of autoantibodies such as rheumatoid factor [1, 2].

### Compliance with Ethical Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

## APPROVAL

Rituximab has been approved by the US Food and Drug Administration and the European Medicines Agency in Europe for the treatment of RA in patients with an incomplete response or intolerance to tumor necrosis inhibitors (TNFi). It is licensed as two intravenous 1 gm infusions separated by 2 weeks with concomitant methotrexate (MTX) and with intravenous corticosteroid premedication [7].

## EFFICACY

Rituximab has been established as efficacious and safe in RA in combination with MTX and disease-modifying antirheumatic drugs (DMARDs) [8–14] The rituximab-MTX combination was initially demonstrated to be superior than either drug as monotherapy (DANCER), and premedication with 100 mg of methylprednisolone did not affect the achievement of the primary endpoint [9]. In two subsequent trials (SERENE, MIRROR), rituximab plus MTX was superior to methotrexate plus placebo, and two doses of 1000 mg were marginally clinically different

than two doses of 500 mg [10, 11]. Both rituximab doses were similar to MTX + placebo with regards to safety.

In patients with an incomplete response to TNFi, rituximab + MTX has also been established as safe and efficacious [12–14]. In the REFLEX trial, the rituximab-treated group (2 × 1000 mg) was clinically superior at week 24, and a significant percentage of placebo-treated patients were capable of being rescued by subsequent rituximab [12]. In addition, subsequent courses of rituximab were also safely and efficaciously administered. At 2 years, radiographic progression was significantly reduced in the rituximab-treated group compared to the placebo group [13]. In a later trial (SUNRISE), rituximab was clinically superior to placebo, and retreatment at 6 months was superior to a single course at 1 year [14].

A phase 3 trial (IMAGE) also demonstrated the efficacy of rituximab in early RA patients who were MTX-naïve [15]. Rituximab was used in 2 × 500 and 2 × 1000 mg doses in this trial, and although clinical efficacy was similar, a significant reduction in radiographic damage was only seen in the latter treatment group at 1 year. At 2 years, however, the lower-dose group also demonstrated a reduction in radiographic damage compared to the placebo group [16]. The study was insufficiently powered to differentiate statistically between the two rituximab doses.

Rituximab has been studied in combination with TNFi agents, and the numerical risk of serious adverse events was only slightly increased, but without a significant increase in efficacy [17].

Rituximab has been combined with DMARDs other than MTX to achieve clinical efficacy [18]. Certainly leflunomide seems to be a viable alternative [18, 19].

Although rituximab is approved in combination with MTX, rituximab was used as monotherapy in the original phase 2 trial, and the response was superior to placebo for ACR20 responses but not for higher-level responses. A later study also found rituximab monotherapy to be efficacious, but the authors concluded that it should only be used for selected patients [19]. A large registry review found that rituximab combined with MTX or leflunomide was superior to rituximab monotherapy, although another registry found monotherapy to be reasonably efficacious [18, 20]. Rituximab monotherapy is therefore not usually recommended except for exceptional circumstances.

Given the data cited from the DANCER, SERENE, and IMAGE trials, there has been controversy over the optimal rituximab dose. While it appeared that the 2 × 1000 mg and 2 × 500 mg doses may be equivalent with respect to improvement in signs and symptoms, the 2 × 1000 mg dose showed better "high hurdle" outcomes. The 2 × 1000 mg rituximab dose demonstrated a more rapid inhibition of radiographic damage compared to the lower dose, and there was also a trend for more radiographic inhibition with the higher dose. To date, there are no data concerning the ability of the 2 × 500 mg dose to inhibit radiographic progression in TNF-inadequate responders. Bredemeier et al. conducted a meta-analysis of four rituximab studies which utilized the two doses and concluded that there were no significant differences in the clinical responses. There were limitations in the analysis, however; the main being the comparison of heterogeneous populations, including populations in which rituximab is not licensed for use: in MTX-naïve patients. Also, in this analysis, some of the included studies were only powered to detect a

difference between the rituximab dose and placebo, not between the two drug doses, and the results of the non-inferiority analyses were not consistent for all outcomes [21]. A large registry review was somewhat less certain about any differences between doses, but in an incisive editorial there was a call for more studies to address the appropriate rituximab dose issue [22, 23]. Whether or not the higher dose needs to be continued throughout all treatment courses once a targeted response is achieved is also uncertain. With regards to the question of retreatment dosing, an open label prospective non-inferiority study by Mariette et al. revealed that, in patients who achieved a EULAR good/moderate response 6 months after an initial 1000 mg × 2 rituximab dose, retreatment with a single 1000 mg rituximab dose was non-inferior to retreatment with a 1000 mg dose × 2 dose regimen [24].

A number of studies have demonstrated that rituximab is more efficacious in seropositive (rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) RA patients [25–27]. Data from large registries also suggest superior clinical efficacy [28–32]. In the REFLEX trial, a response was seen in seropositive (rheumatoid factor) and to a lesser extent in seronegative patients, but a significant reduction in radiographic patients was only seen in the seropositive group [11, 30]. In the REFLEX SERENE, and IMAGE studies, seropositivity for RF and ACPA was associated with a superior clinical response to rituximab [31]. A vigorous analysis of the question of antibody status and response was carried out in a meta-analysis of four trials (REFLEX, DANCER, IMAGE, and SERENE) by Isaacs et al. [25]. When a fixed-effect model was used, the results indicated a benefit with rituximab in seropositive patients compared to seronegative patients, but with a modest reduction in DAS28-ESR of 0.35 units, although heterogeneous indices suggested significant uncertainty in the overall-effect model.

Response to rituximab has also been reported to be more efficacious in patients who have failed only one TNFi, as opposed to those who have failed more than one [28, 30]. A number of studies have attempted to compare the use of rituximab in TNFi-incomplete responders versus switching to another TNFi, and although the results of many of these studies favor rituximab, they have not all been large, blinded, or direct comparisons and have not led to an accepted consensus [32–37]. Given the pending patent expiration, any further, more rigorous studies are unlikely to be conducted.

Biomarkers and genetic markers have also been postulated to affect the clinical response to rituximab. Among others, these include Fc-gamma receptor type IIIA polymorphism, promoter polymorphism of the B-cell activation factor gene, baseline numbers of CD27+ memory cells, and levels of B cell chemokines [38–41]. B cell subset numbers have been reported to predict responsiveness to rituximab, but whether or not any of these factors will ultimately be widely available or practical remains to be determined [42, 43].

## RETREATMENT WITH RITUXIMAB

In clinical trials (SERENE, MIRROR, DANCER), repeat rituximab dosing was allowed every 6 months [9–11]. Typical clinical responses from rituximab are usually seen 3–4 months after the initial infusions, although the concomitant corticosteroids may provide a very early, transient effect [7]. The duration of the effect is quite variable, so the optimal timing for retreatment is difficult to predict. Repopulation of B cells after rituximab usually requires 6–9 months, but is also variable [1, 4].

The US package insert for rituximab suggests that rituximab can be given not sooner than every 4 months according to clinical evaluation. Several retreatment options have been studied. A review of retreated patients from the clinical trials suggested that the fixed-interval (24 week) treat to target strategy was superior to one which retreated patients at the discretion of the physician (prn) [44]. In this retrospective pooled analysis, baseline disease characteristics were thought to be generally well balanced, but those patients receiving prn retreatment were more likely to have established RA with a median 8.5 years of disease and were more likely to be TNF-inadequate responders, while those patients retreated using a treat to target approach were more likely to have a shorter disease duration with a median of 3.6 years of disease and to be biologic-naïve. That the differences between the two groups may have influenced the results remains a significant possibility. A prospective study demonstrated that rituximab retreatment was deemed necessary at around 8 months [45]. The latest European consensus statement suggests that retreatment in initial responders should be considered at 24 weeks in patients who do not achieve low disease activity or remission, and that it should be delayed otherwise until disease activity flares [7].

Whether or not initial nonresponders should be retreated remains somewhat uncertain [46, 47]. While data from the SUNRISE study demonstrated a low response overall to repeat treatment in initial rituximab nonresponders, repeat treatment was superior to a single course [14]. Analysis of data from the MIRROR study demonstrated that 46% of patients failing to achieve an ACR20 response after initial treatment achieved at least an ACR20 response at 48 weeks following their second treatment course [11]. In the analysis by Vital et al., a proportion of the patients not responding to an initial rituximab course exhibited improvement following an additional course [46]. These data suggest that an additional course of treatment within 24 weeks might be carefully considered in initial rituximab nonresponders, in contrast to the published guidelines which state that alternative treatment agents should probably be considered in initial nonresponders [7].

## SAFETY OF RITUXIMAB

In two of the clinical trials, a numerically higher rate of serious inferctions, but not opportunistic infections including tuberculosis, was reported in patients receiving the $2 \times 1000$ mg dose compared to placebo, 4.7 compared to 3.2/100 patient years in DANCER and 5.2 compared to 3.7 patient years in REFLEX [8, 11]. In the IMAGE trial, however, the rate of serious infections was lower in both of the rituximab treatment arms compared to placebo [15]. In addition, a meta-analysis did not report an increased risk of serious infections in rituximab-treated patients compared to placebo-treated patients [48]. Data from a large French registry observed a slightly increased rate of serious infections in rituximab-treated patients in the first 6 months of treatment, comparable to the rate reported in randomized clinical trials [49]. With regards to serious infections requiring hospitalization, a study concluded that the rate of such infections with rituximab was comparable to that seen with the TNFi infliximab [50].

Van Vollenhoven et al. have recently reported a pooled analysis of the long-term safety of rituximab in global clinical trials over 9.5 and then 11 years [51, 52]. The initial published data included 3194 patients and 11,962 patient years. Overall, infections (in >5%) reported in the rituximab-treated

patients were upper respiratory infections, nasopharyngitis, urinary tract infections, bronchitis, sinusitis, diarrhea, and gastroenteritis. The most common serious infection was pneumonia, with an overall serious infection rate of 3.94/100 patient years, and this was comparable to the rate of patients treated with MTX + placebo at 3.79/100 patient years. Importantly, the risk of serious infections was stable over time, even with multiple courses of treatment. There were two cases of tuberculosis (TB), no cases of extrapulmonary TB, no cases of atypical TB, and other opportunistic infections were very rare. There were no cases of hepatitis B reactivation, but one case of de novo hepatitis B. Rates of herpes zoster infection were 9.0/1000 patient-years, but this was comparable to the MTX + placebo-treated patients (11.7/1000 patient-years) and the general RA population (11.5 patient-years).

Another paper reported three cases of TB and five cases of non-TB mycobacterial infections in a survey of rituximab-treated RA patients [53]. A previously mentioned report included patients with TB treated with rituximab without reactivation [49]. A recent study of 56 rituximab-treated patients at high risk for TB did not report any reactivation [54]. The risk of hepatitis C reactivation seems uncertain [55].

Progressive multifocal leukoencephalitis (PML) is a progressive infection caused by the JC virus, and cases of PML have been reported in RA patients treated with rituximab [56–59]. A recent review in abstract form cited a total of 11 cases of PML in RA patients treated with all biologics, with rituximab being the most recently administered biologic in most of these [58]. In many of the reported cases, there had been previous treatment with immunosuppressive medications. The true incidence of PML in RA is still uncertain, but a large registry reported on 66,278 RA patients, with a rate of PML of 1.0/100,000 person-years as compared to that for the general population, 0.3/100,000 person-years [59]. In the European consensus statement regarding the use of rituximab in RA, the risk of PML was judged as small, but without an identified risk profile for the development of PML, vigilance was advised [7]. Given the relative paucity of PML cases in RA despite the increasing numbers of patients receiving rituximab in surveillance databases, the concern regarding PML may be waning.

The risk of malignancy does not appear to be increased in the clinical trials with very small numbers of cases, although patients with a known previous malignancy are usually excluded and the trials are of relatively short duration. In the pooled analysis, rituximab was not associated with an increased risk of any malignancy when compared to age- and sex-matched standard incidence ratios [51]. The calculated incidence rate of any malignancy was 0.69/100 patient-years. The most common solid malignancy was breast cancer. In addition, there was no evidence of an increased risk of malignancy with cumulative exposure to rituximab. Other reviews have also not found an increase in malignancies [60, 61]. A French registry review also reported no significant increase in malignancies in a rituximab-treated RA patient cohort [62]. A recent comparative effectiveness study comparing the potential risk of cancer across biologic and non-biologic DMARDs reported that the risk of any cancer with rituximab was similar to that with methotrexate [63]. In a recent abstract, the German registry reported that RA patients with a history of lymphoma, solid malignancies, or skin cancer do not have higher rates of recurrence when treated with rituximab in comparison to non-biologic DMARDs [64].

With regards to cardiovascular risk, which is increased in patients with RA regardless of treatment, myocardial infarction was the most frequent cardiovascular event reported in the pooled analysis of long-term safety data [47]. The event rate was 0.41/100 patient-years compared to 0.27/100 patient-years in the MTX + placebo-treated patients. This rate was similar to that reported in other RA patients treated with DMARDS and TNFi [65, 66]. The risk of stroke was similar in both groups and also similar to other published data [67]. Currently, there are no data showing that rituximab is associated with deterioration of cardiac function. Patients with significant uncontrolled cardiac disease were excluded from the major clinical trials in RA because of concerns about potential cardiac complications associated with infusion reactions.

Infusion-related reactions (IRR) have been reported in all of the clinical trials of rituximab in RA. In the pooled analysis of long-term safety, the rate of IRR was 23% during the first infusion of the first course and decreased with each subsequent infusion [51]. Most of the IRR were judged as mild to moderate and were rarely serious (<1%). The most common reactions included headache, pruritis, throat irritation, flushing, rash, changes in blood pressure, and fever. The DANCER trial included premedication with 100 mg of intravenous methylprednisolone, which was concluded to reduce the frequency and severity of the initial infusion reactions without contributing to the primary clinical endpoint [8]. This premedication is now part of the approval for each cycle of rituximab, although whether or not it is required for all late cycles has not been determined [7]. The routine use of antihistamines and/or paracetamol is not required, but may be useful for mild IRR [7].

Although rituximab does not affect immunoglobulin-secreting plasma cells, repeated courses of rituximab in RA have caused hypoglobulinemia [51]. A registry review demonstrated that a low IgG level before rituximab treatment was a risk factor for serious infections [49]. In the clinical trials, a low IgG level was an exclusion criterion and prohibited trial entry, but low immunoglobulins, IgM > IgG, were observed. An analysis of three randomized controlled trials of rituximab included 1039 patients, and 10.3% had a low IgM at week 24, but this increased to 18.5% with a second cycle and 23.5% after a third cycle of therapy [68]. Similarly, 1.5% had a low IgG at week 24; 4.3% and 5.9% with subsequent cycles of therapy. Despite these findings, the rates of serious infections were 5.6 and 4.8/100 patient-years for IgM and IgG respectively, and the rate in patients with normal immunoglobulins was comparable at 4.7/100 patient-years [6]. In the pooled analysis of long-term rituximab safety, 22.4% developed a low IgM level and 3.5% a low IgG level [51]. No increases in overall infection rates were observed in patients during or after the development of low IgM or IgG levels, but for IgG these rates were higher than in patients who never developed a low IgG. With the small numbers of patients with low IgG levels, no placebo comparator, and difficulties determining when immunoglobulin levels decreased, analysis of the data was thought to be limited [51]. The European guidelines regarding rituximab treatment suggest monitoring of immunoglobulin levels, with close monitoring for infection in those patients with low IgG levels [7].

## ANTI-RITUXIMAB ANTIBODIES

In the randomized, controlled trials, the incidence of human anti-chimeric antibodies (HACA) varied from 2.7% to 7.1% [9–15]. In the pooled analysis of long-term rituximab safety,

11% of rituximab-treated patients were found to have HACAs during at least one visit [51]. These and other studies have found no relationship between HACA and the dose of rituximab administered, any specific clinical manifestations, the ability to deplete B cells, the frequency of infusion reactions, the clinical efficacy of the initial dosing, or the efficacy of retreatment [51, 68, 69].

### Biologic DMARD Therapy Post-Rituximab

In a study concerning patients in whom an insufficient response was obtained with rituximab, switching from rituximab to a TNFi was relatively safe and not associated with an increase in infections [70]. In this study, the TNFi were initiated at least 4 months after rituximab, and the rate of serious infections was similar to that expected when TNFi are initiated in biologic-naïve DMARD RA patients. Similarly, the pooled analysis of long-term rituximab safety data concluded that the use of subsequent biologics was not associated with an increase in the serious infection rate [51].

### Other Treatment Considerations

Given all of these safety concerns, prior to initiating rituximab in RA patients, a careful medical history and physical examination should be undertaken to determine potential contraindications. Some of these include hypersensitivity to murine proteins, serious active infection, significant congestive heart failure, and pregnancy [7]. In addition to routine laboratory testing, baseline immunoglobulin levels should be measured, since low IgG levels are associated with a higher risk of infection, and the use of rituximab in patients with existing hypogammaglobulinemia should be considered with caution or avoided [7]. Hepatitis B and C serologies should be undertaken, because reactivation of hepatitis B surface Ag negative but hepatitis B core Ab positive disease has been rarely reported [71, 72]. Those patients who are HBsAg and anti-HBc negative should consider vaccination before rituximab is initiated, and those patients who are HBsAg and/or anti-HBc positive should not be given rituximab or they should be referred to a hepatologist for consideration of prophylactic treatment before rituximab is considered. HBsAg-negative but anti-HBc-positive patients should have HBV DNA titers and, if undetectable, rituximab might be considered, particularly after a hepatologist administers prophylactic antiviral therapy and with close monitoring of HBV DNA levels [7]. With regards to hepatitis C (HCV), rituximab has been used successfully to treat HCV-induced cryoglobulinemia, suggesting its safety with HCV. Rheumatologists should screen for HCV only to refer patients to hepatologists for treatment using interferon-free regimens [55].

Patients who have been treated with TNFi should have previously been evaluated for TB, but due to the observation that there is no evidence for an increased frequency of TB in RA patients treated with rituximab, screening patients for tuberculosis is not currently thought to be necessary [7].

Vaccinations in RA patients should be considered before rituximab, including pneumococcal, influenza, tetanus toxoid, and hepatitis B, and these are recommended at least 4 weeks before the initiation of rituximab [7]. Diminished humoral responses to influenza and pneumococcus have been reported in RA patients on rituximab + methotrexate, so immunization while on rituximab therapy may not be effective [73–75]. Live vaccines are not recommended.

Lastly, as currently recommended, rituximab infusion requires 4.25 h for the initial infusion and 3.25 h for subsequent infusions. This regimen is based on the rituximab usage in non-Hodgkins lymphoma, where the incidence of IRR is much higher than that observed in RA [76]. Long infusion times and frequent infusion rate changes are not only inconvenient but increase infusion center costs. Several studies have attempted to increase the rate of rituximab infusion after the initial infusion, with reported success [76–80]. In a recent study, infusion over 2 h was well tolerated and not associated with an increased rate of IRR [76]. Rapid infusion protocols, however, require further testing before general acceptance will be achieved.

## CONCLUSION

Rituximab has been a significant addition to the shortlist of biologic agents approved for the treatment of RA. It has a unique mechanism of action, it has been established as relatively safe, and the details regarding screening, dosing, and follow-up are becoming better understood. Rituximab is an important option for selected RA patients, and is most effective in those who are seropositive and have been exposed to one TNFi. As with all biologics for RA, further information regarding the safety of rituximab over longer periods of time will be critical. Future studies will hopefully determine exactly where rituximab will be placed in the evolving treatment paradigm for rheumatoid arthritis.

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