Published in final edited form as:
Int J Clin Rheumtol. 2012 April 1; 7(2): 159–166.

Living life without B cells: is repeated B-cell depletion a safe and effective long-term treatment plan for rheumatoid arthritis?

David R Chen and **Philip L Cohen***
Section of Rheumatology, Department of Medicine, Temple University School of Medicine, 3322 North Broad St., Room 205, Philadelphia, PA 19140, USA

Abstract

The continued efficacy of B-cell depletion in rheumatoid arthritis (RA) depends on repeated cycles of anti-CD20 treatment to maintain low levels of B cells. It is surprising that this significant manipulation of the humoral immune system is remarkably safe with repeated treatment and that rates of adverse effects remain stable, and may even decline, over subsequent courses. Although responses to vaccines and probably to new antigens are diminished, adaptive immunity nevertheless functions adequately despite markedly restricted B-cell numbers. In the 10 years or so since the widespread use of B-cell depletion, there is little to suggest that a long-term paucity of B cells puts patients at risk for malignancy or opportunistic infections, nor that it leads to treatment-resistant RA or complications. While time will tell whether this major alteration of the immune system has other consequences, it is remarkable that drastic reduction of B-cell numbers over the long term is tolerated so well, and that it maintains efficacy in RA therapy.

Keywords

adverse effects; anti-CD20; B cells; rheumatoid arthritis; rituximab; treatment efficacy

The efficacy of B-cell depletion therapy using anti-CD20 represents a major advance in rheumatoid arthritis (RA) therapy and has renewed interest in the role of B cells in RA pathogenesis. Rituximab, a chimeric monoclonal anti-CD20 antibody, causes prompt and nearly complete depletion of peripheral B cells, which do not reappear for approximately 6 months in most patients [1]. Rituximab is effective in reducing disease activity and in slowing the progress of erosions in RA [2–4]. It has also been shown to have efficacy even after patients have failed to respond to a TNF-α inhibitor, with no difference in safety profile compared with patients who have not been on prior biologic therapy [5,6].

Probably because B cells play an important role in ongoing disease, RA patients have required repeated courses of B-cell depletion to maintain control of the illness [7]. It is rather surprising that B-cell depletion is so well tolerated in most patients [8]. How long can B-cell depletion be safely used in the treatment of RA or other chronic diseases? What kind

*Author for correspondence: Tel.: +1 215 707 5660, Fax: +1 215 707 3508, philco@temple.edu.

Financial & competing interests disclosure
PL Cohen is a consultant for Janssen Biotech (Division of Johnson & Johnson, Inc.) and Cephalon, Inc. and his research is sponsored by grants from NIAID and NIDCR. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

of problems have been encountered or may be anticipated? Are there prospects for more precise markers to guide the timing for redepletion in RA patients? These are the subjects of this perspective.

How does B-cell depletion work in RA?

The mechanism of action of rituximab in RA remains controversial but is unlikely to be simply from decreased humoral immunity. Rituximab treatment results in a rapid fall in all mature B-cell subsets, with the exception of plasma cells [9]. Antibody (and autoantibody) levels are unchanged or fall modestly [10], probably reflecting an incomplete depletion of B cells in the spleen, lymph nodes and marrow [11]. Synovial biopsy studies show a poor inverse correlation of efficacy with synovial B-cell numbers, with macrophage markers serving better as a marker of response [12,13]. Furthermore, the lack of efficacy of anti-BAFF and a TACI fusion protein in RA, despite even greater effects than rituximab on parameters of humoral immunity, makes it even more unlikely that anti-CD20 treatment exerts its role by reducing antibody levels [14]. It seems probable that the mechanism of B-cell depletion in autoimmune diseases such as RA in part reflects the role of B cells as a source of cytokines, or as antigen-presenting cells [11,15]. Additional mechanisms are possible, such as a role for B cells in influencing dendritic cells or T cells [16], or effects on a small $CD20^+$ T-cell population that may be more prevalent in RA patients [17]. It has also been proposed that anti-CD20 may exert an anti-inflammatory effect due to enhanced lymphoid drainage from joints after B-cell depletion [18].

Does repeated B-cell depletion retain its initial efficacy?

Early observations indicated that RA patients relapsed after initial rituximab treatment, quelling hopes that pathogenic clones of B cells might have been permanently eliminated by therapy. Thus, B-cell depletion must be maintained for a sustained therapeutic effect. Rituximab is now approved with repeat dosing at 16–24-week intervals. Upon cessation of drug, the time to relapse varies yet seems specific for each patient [7]. Many relapse if treatment is not given for 6–12 months, but some clinical trials have noted averages of 20 months between retreatment [19]. The variation in time to relapse has led to the recommendation to treat-to-target rather than treating every 6 months, which may lead to over-treatment and a theoretically increased risk of adverse effects [20]. On the other hand, repeat dosing based purely on clinical recurrence of tender and swollen joints appears to reduce the efficacy. In one study evaluating predictors for response for repeat treatment, it was found that every point of deterioration of Disease Activity Score using 28 joint counts (DAS28) prior to a second course of rituximab resulted in a higher DAS thereafter [21]. This treat-to-target regimen resulted in greater mean improvement of disease activity and lower Health Assessment Questionnaire – Disability Index scores. This finding supports repeat therapy without anticipating a decrease in the DAS28 [20,22]. In another study, efficacy was maintained in 37 patients with repeated cycles over 4 years. On average, patients were treated every 20 months [23]. Here, 45% of the patients continued to respond even beyond the 5 years of the study, with over five courses in a few patients. A small study suggested that administering only 1000 mg for subsequent courses was sufficient to maintain lower DAS28 and disease activity [24].

Long-term studies show continued efficacy of B-cell depletion in most patients continuing to receive repeated courses. Is there any way to predict when patients will relapse? Neither the degree of B-cell depletion nor B-cell recovery reliably correlated with or predicted response or relapse [25]. Additionally, neither rheumatoid factor nor anti-CCP positivity, nor changes in their levels correlated with response or relapse, although seropositive patients tended to have more prolonged responses to each dose [6]. Some studies have found larger

subsets of IgD^+CD27^+ memory B cells in nonresponders [9]. A higher proportion of $CD27^+$ memory B cells was also associated with earlier relapse of disease. In the TNF-α transgenic RA model, expansion of $CD23^+CD21^{hi}$ B cells correlated with active disease, and these cells were responsive to anti-CD20 treatment [26]. In a recent study of gene dimorphisms, the VV genotype of FcγRIII was associated with better response to rituximab, while VF and FF were less responsive to therapy. These gene polymorphisms may serve to identify patients with better responses and sustained improvement with repeat courses [25,27,28].

Do adverse reactions limit repeat dosing of rituximab? Does the risk increase with repeated treatment?

The incidence of adverse effects in general across multiple studies remains fairly stable across several courses of the medication. The rates of adverse effects were the highest in the first few months of therapy; some studies even found that adverse effect incidence decreases with each subsequent course. The principal adverse effects of rituximab therapy are listed in Table 1. Serious adverse effects were not increased with multiple courses [5,20,28,29]. Some of these data are summarized in Table 2.

Infusion reactions

Infusion reactions occur in approximately 30–35% of patients on their first infusion of rituximab with concomitant coverage with intravenous glucocorticoids [20,29]. The incidence has generally been lower in RA than lymphoma patients [19]. The reactions are generally mild to moderate in severity. Headache, pruritus, throat irritation, flushing, rash, hypertension and fever are the most common. Severe reactions have been infrequent, less than 1%, and have included anaphylaxis, severe dyspnea, chest pain and rash. Subsequent infusions and courses of rituximab have decreasing incidence of infusion reactions with each treatment [29]. Thus, infusion reactions are not anticipated in patients given long-term rituximab.

Immunity to the anti-CD20 chimeric antibody

Because rituximab contains murine-derived sequences, patients can develop human anti-chimeric antibodies (HACAs) directed against foreign epitopes encoded by xenogeneic V gene regions. In patients given TNF-α inhibitors, such antibodies increase the risk of infusion reaction and decrease the efficacy of therapy [30]. In a pooled safety analysis for rituximab, 11% of patients were found to be HACA positive [5]. Infusion reaction rates and severity were, however, similar in patients who were positive or negative for HACAs. The lack of clinical significance to the HACAs may represent their failure to neutralize antibody activity, or the vast antibody excess with the doses of rituximab administered. The presence of HACAs does not appear to limit long-term dosing of rituximab.

Infection

It is notable that an increased incidence of infections among treated RA patients is not demonstrable in individual studies, nor in meta- analyses when compared with placebo (primarily methotrexate with or without systemic steroids) [31]. This is in contrast to increased rates found in hematologic malignancy patient studies, where combination chemotherapy with rituximab incurred an increased risk of infection, suggesting that increased infections may be related to underlying disease or other concurrent immunosuppressant therapy. The incidence of infections of any kind is 40% and similar to placebo in trials of at least 6 months duration. Serious infections have ranged between 2 and 7%, similar to placebo groups [20]. In the Autoimmunity and Rituximab Registry, serious infections were slightly higher, with 82 infections in 78 patients out of 712 patients getting

rituximab for RA [32]. Opportunistic infections were minimal, with no cases of reactivation tuberculosis and rare cases of disseminated fungal, parasitic or protozoal infections [29]. Pneumonia and other bronchopulmonary infections were the most common overall infections [13,19,32]. Even in RA patients with a history of serious bacterial infection, rituximab treatment was well tolerated and not associated with additional infections [33].

Infections seem to be more frequent in the initial months after infusions, which may be secondary to the initial bolus of glucocorticoid given as pretreatment [5]. Subsequent courses have either similar or even lower rates of infections. Risk factors for infection identified through multivariate analysis may help to discern patients at greatest risk. Risk factors included older age, underlying pulmonary or cardiac disease/insufficiency, and previous severe infection. Patients taking higher doses of glucocorticoid therapy who had extra articular manifestions of their disease had higher risk of infections. Baseline hypogammaglobulinemia and baseline low IgG have also been associated with increased risk of infection [32].

Hepatitis B (HBV) reactivation has been frequently reported in the oncogenic literature but reports are limited in RA. In patients with hematologic malignancy, HBV and reactivation were the most frequent serious infectious complication during B-cell depletion, with high mortality rates [34]. The safety of rituximab in chronically HBV-infected RA patients is uncertain. Prophylactic antiviral therapy has been used to prevent this complication, but rituximab might be best avoided by patients with positive hepatitis B surface antigen [31]. Hepatitis C (HCV)-related hepatic failure has not been reported in either the oncologic or rheumatologic literature. There have been reports of increased levels of HCV viral load and some increased liver function tests in lymphoma patients treated with rituximab [35]. These, however, have not correlated with actual viral RNA levels and liver damage in these patients, so the clinical implication of the abnormal test is unclear. Other viral reactivations have been reported: cytomegalovirus, herpes simplex, varicella zoster and Epstein–Barr viruses. Most of these reactivations were mild to moderate in severity, although rare serious herpes zoster has been reported [31,32]. Cytomegalovirus has caused enterocolitis, pneumonitis and esophagitis, mostly reported in the oncology literature. Otherwise most viral infections have been of the upper respiratory tract [31].

The most alarming rituximab-associated opportunistic infection is reactivation and neurologic infection by JC virus, causing progressive multifocal leukoencephalopathy (PML). There have been only limited case reports in RA patients treated with rituximab. A few of these reports are confounded by treatment with other immunosuppressive agents and, in one case, chemotherapy and radiation therapy after rituximab and a few months prior to onset of PML [36,37]. The incidence of PML in RA has been estimated at 0.4 per 100,000 versus 0.2 per 100,000 in the general population, so there is a suggestion of increased risk with rituximab-treated RA patients. There have been more cases and probably more risk of PML in systemic lupus erythematosus patients and hematologic malignancy patients treated with rituximab.

A risk factor for increased infection rate after rituximab treatment of lymphoma patients was baseline hypogammaglobulinemia and low IgG [20], with the development of hypogammaglobulinemia in a few or all immunoglobulin isotypes in a minority of patients. In these patients, a progressive decrease has been observed with repeat courses of rituximab, yet most patients maintained normal immunoglobulin levels through repeat courses. IgM in particular has been observed to fall more than the other isotypes [23,29]. There was no pattern that could help predict who developed hypogammaglobulinemia. The clinical implications of the fall in immunoglobulins, however, appear fairly limited. In the study by Popa *et al.*, hypogammaglobulinemia was not associated with any significant increase in

adverse events or infections [23]. A meta-analysis of clinical trials found similar severe infection rates before and after the fall in immunoglobulins. There was higher numerical incidence of severe infection among patients with low IgG in these trials and other studies, with a trend towards more risk despite not being statistically significant [28,29].

In summary, with the notable exception of hepatitis B, and not including the remote risk of PML, there is little evidence that patients whose B cells are chronically depleted are at any higher risk of infection.

Hematologic risks of long-term rituximab

Late-onset neutropenia, defined as an unexplained absolute neutrophil count of less than 1.5 × 10^9/l occurring at least 4 weeks after the last rituximab infusion, is widely reported in the oncology literature, occurring in 4–8% of B-cell lymphoma patients receiving mono or combination therapy with rituximab. Earlier studies had found it to be very rare in autoimmune disease, but a more recent case–control study found neutropenia in 5% of 164 patients on rituximab [38]. The rate may have been even higher, as some cases may have been missed owing to less frequent laboratory testing. The occurrence of the neutropenia varied between the first and second course and one patient had a recurrence at repeat treatment. Unfortunately the study period was only 12 months, so no assessment of risk with further repeat dosing can be made.

The patients who developed neutropenia were predominantly RA patients, but also included systemic lupus erythematosus and juvenile idiopathic arthritis patients, and had no difference in baseline immunoglobulin levels. They had no significant differences in B-cell counts, although all had lower levels of IgM post-rituximab compared with control [8,20]. Similar to hematologic malignancy patients developing this complication, these patients seemed to have a higher rate of serious infection [31,38]. The neutropenia was severe enough in a number of the patients to require granulocyte colony stimulating factor (G-CSF). In the single bone marrow biopsy carried out in the cohort, there was a reduction of granulopoiesis and maturation arrest at the promyelocyte stage, which is similar to what has been reported in the oncology literature [39].

Thrombocytopenia has also been reported in not only patients treated with rituximab but also in the oncology literature. At least 15 case reports have been reported, and nearly all had platelet counts well below 50 × 10^9/liter. Interestingly, the decrease usually occurred a few hours following the infusion, was the lowest the following day and usually resolved in the next few days. Only two of the cases had any bleeding complication [40]. No reports have been made of this adverse effect in any of the RA patients treated with rituximab, but typically RA patients do not have laboratory draws in the days immediately following treatment. It is therefore unclear whether RA patients treated with rituximab have had this adverse effect. Both of these hematologic complications, however, are transient, rare and reversible, and are not related to long-term B-cell depletion.

Development of neoplasms in long-term rituximab-treated patients

There has been no increase in solid or hematologic malignancies associated with rituximab treatment, nor to date with prolonged B-cell depletion with repeated courses. Risk of recurrence of malignancy cannot be fully evaluated, since these patients have usually been excluded from trials [20]. There were cases of skin cancers, lymphoma and breast cancer reported, but the incidence after age and sex adjustment was equal to the general population [5,29].

Cardiovascular events in B-cell depleted patients

Cardiovascular risk and myocardial infarction were not increased in patients given repeated doses of rituximab [29]. Nearly all patients in trials who did suffer from cardiovascular complications had one or more cardiac risk factors, and the incidence at 6-month follow-up was similar in the placebo and rituximab groups. There is little to suggest that chronically B-cell depleted patients are at increased risk for cardiovascular events, and there might even be beneficial effects [41].

Can we expect new risks in patients undergoing long-term B-cell depletion?

Given the importance of adaptive humoral immunity, the thought of patients living their lives with vastly reduced numbers of B cells is a bit daunting. Yet data have repeatedly shown that repeated courses of rituximab are well tolerated, including experience in approximately one million lymphoma patients. No trends have emerged suggesting that patients given repeated courses of depletion therapy are at greater risk for infection, cancer, or immune-mediated injury than patients given single doses. As RA runs a course of decades, what risks may emerge in time? A potential problem may be the long-term effects on immunity to new antigens, as indicated by rituximab-treated patients' decreased responses to vaccines [10,29]. Over the long run, the failure to mount adequate responses to variants of current pathogens or to new pathogens may put chronically B-cell depleted patients at risk for infection.

Another potential concern is alteration of the B-cell repertoire during depletion. The reconstitution of the B-cell compartment following each cycle of depletion may not fully recapitulate the previous repertoire (although memory cells and long-lived plasma cells are mostly spared from depletion). It is possible that long-term perturbation of the immune system in this fashion might lead to impaired host defense, or even to emergence of self-reactive or otherwise deleterious clones of B cells. Data so far, however, have supported the notion that the reconstituted B-cell compartment is similar in V gene usage to the pretreatment compartment [42,43].

Rituximab depletion of B cells leads to a sharp and sustained rise in BAFF levels, and it is this anti-apoptotic cytokine that acts to restore B-cell numbers by increasing the survival rate of immature B cells [23,44]. It is possible that sustained levels of BAFF may lead to alteration in the finely tuned processes acting to maintain self-tolerance by eliminating self-reactive B cells, and that long-term anti-CD20 depletion might lead to emergence of autoantibody-producing B cells. There is no indication so far that this will be so, but we are at an early point in experience with rituximab. A parallel thought is that B-cell lymphomas might be more prone to develop in an environment rich in BAFF.

Could long-term B-cell depleted individuals develop abnormalties in other compartments of the immune system? T cells rely on B cells for antigen presentation, so it is possible that the T-cell repertoire, at least for CD4 cells reactive to exogenous antigens, might show alterations in individuals with chronic low B-cell numbers. Abnormalities in Th17 cells, already shown in one study of rituximab-treated patients, might also emerge with unknown consequences in the long term [11]. Regulatory T cells may also be influenced by depletion of B cells [45].

Is it possible that a resistant form of RA might develop after years of B-cell depletion? B cells are thought to be important in the pathogenesis of synovitis, so it is conceivable that clones resistant to anti-CD20 might develop over long periods of time with adverse consequences. This notion is entirely speculative at this point.

Are there improved ways to decide when to retreat B-cell depleted RA patients?

Current approaches to the retreatment of RA patients on rituximab are largely empirical. It is to be anticipated that increased use of biomarkers will help us to determine at what point patients can be most effectively retreated. One approach would be to perform serial B-cell subset analysis. Transitional B cells are the earliest population in the blood as repletion proceeds. Although expensive, quantitation of these cells may enable clinicians to choose just the right moment to intervene with another course of anti-CD20.

Another approach that holds promise is gene profiling. Preliminary data have been presented indicating that a characteristic gene signature may emerge upon repletion of B cells, and the prognostic value of these measurements may be of value. Protein biochip array technology is a parallel approach that may help to predict response and to guide therapy [46]. Quantitation of $CD27^+$ B cells, CD19 expression, BAFF levels and other parameters of the recovering B-cell compartment may all yield important information to guide optimal retreatment. A much-desired, but so far elusive, source of information would come from *in vivo* quantitative imaging of the B-cell compartment and subcompartments in patients, as has been carried out in early studies for T cells [46]. This information would be of potentially great value than what can be gleaned from the peripheral blood.

Future perspective

We can expect increasing numbers of RA patients on long-term B-cell depletion therapy in the coming years, given the generally favorable experience with both efficacy and safety, and considering the convenience of twice-yearly infusions over other treatment regimens. Time will tell if this sustained significant modification of the humoral immune system will give rise to increased susceptibility to infections, or to fundamental changes in the B-cell repertoire or susceptibility to lymphoma or other malignancy. To date, no signals of these dangers have arisen, and it appears to be safe and effective to continue indefinite administration of anti-CD20 to RA patients. Only through continued use and monitoring as we use rituximab beyond 10 years can it be known if repeated B-cell depletion is as safe as it now appears.

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Executive summary

- B-cell depletion needs to be given repeatedly to maintain control of rheumatoid arthritis disease activity.
- Patients receiving long-term rituximab tend to have lower autoantibody levels and lower total IgG levels.
- Except for patients with active hepatitis B (who should not receive rituximab), rheumatoid arthritis patients given repeated courses of rituximab do not seem to be at increased risk for infections.
- Progressive multifocal leukoencephalopathy in rheumatoid arthritis patients is an exceedingly rare event and occurs in patients who have received concomitant immunosuppressive therapy.
- Rituximab-treated patients have significantly impaired vaccine responses and immune responses to neoantigens, a fact that clinicians should take into account when caring for these patients.
- Studies are underway to optimize which patients to treat, and when retreatment should be given.

Table 1

Adverse effects of rituximab.

Adverse effect	Manifestations	Incidence	Ref.
Infusion reactions	Headache, pruritis, flushing rash, fever	30–35% (on first time infusion)	[20,29]
Serious infusion reactions	Anaphylaxis, severe dyspnea, chest pain, rash	<1%	[20,29]
Infection	Upper respiratory infections/nasopharyngitis, bronchitis, urinary tract infections	40%	[29,32]
Serious infections	Pneumonia	5–11%	[19,29,31]
Reactivation/neurologic infection of JC virus	Progressive multifocal leukoencephalopathy	0.4 per 100,000	[20,36]
Hypogammaglobulinemia	Low IgM levels Low IgG levels	23–32% 5–18%	[23,29]
Cytopenia	Late-onset neutropenia Transient thrombocytopenia	5% Limited data in RA	[38]

RA: Rheumatoid arthritis.

Table 2

unds of B-cell depletion.

n	Number of patients	Number of courses					IR	Serious IR	Infections	Serious infections	Opportunistic/PML	Low IgM	Low IgG	Ref.
		>1	*>2*	*>3*	*>4*	*>5*								
	37	37	28	15	7	2	Four (fevers; 10.8%)	One (urticarial rash third cycle; 2.7%)	16 (all lower respiratory infections; 43.2%)	None (0%)	None (0%)	12 (32.4%)	7 (18.9%)	[23]
	712	712	466	176	45	25	Not reported		Total not reported	82 (11.5%)	1 (fungal septic arthritis; 0.14%)	Post-treatment not reported	Post-treatment not reported	[32]
ata	2578	2578	1890	1043	425	133	915 (25% during first course)	14 (0.5%)	1663 (65%)	170 (7%)	49 (2%) VZV 1 PML (but post-cancer treatment 18 months post-RTX)	602 (23%)	141 (5%)	[29]

awal from study. Serious infection: requiring intravenous antibiotics.

Progressive multifocal leukoencephalopathy; RTX: Rituximab; VZV: Varicella zoster virus.