B-Cell Therapies for Rheumatoid Arthritis

Jose U. Scher, M.D.

Abstract

B cells were originally considered key mediators in the pathogenesis of rheumatoid arthritis (RA). The presence of these cells in many RA synovial tissues and the discovery of rheumatoid factor had put B cells originally at the center of disease pathogenesis. That enthusiasm vanished shortly thereafter only to resurface in the last 15 years with the appearance of highly specific anti-cyclic citrullinated protein antibodies. Rituximab, an anti-CD20 antibody that depletes mature B cells, was approved for the treatment of RA in 2006. Since then, B cell depletion strategies have proven efficacy for advanced disease, particularly in those patients that do not respond to DMARDs or TNFa inhibitors.

Rheumatoid arthritis (RA) is one of the most common autoimmune rheumatic diseases, affecting 1 in 100 individuals worldwide. It is considered a complex systemic multifactorial inflammatory process with predilection for the joints. If left untreated, RA leads to deformity, considerable disability, and major co-morbid conditions, including cardiovascular disease and increased mortality. Genes appear to be important in some patients, particularly those carrying risk alleles at the HLA-DRB1 locus (shared epitope hypothesis) and other non-HLA alleles (i.e., PTPN22). However, currently identified genetic factors only account for about 20% of the disease variance. Gene-environmental interactions are deemed, therefore, necessary for phenotypic expression of disease. For decades, multiple environmental factors have been studied in relationship to RA, including hormones, viruses, silica, and bacteria. More recently smoking and periodontal diseases have gained interest as potential triggering factors in already predisposed individuals. Multiple lines of research have also implicated tobacco and Porphyromonas gingivalis (a periodontopathic bacterium) in the activation of B cells and the consequential production of anti-citrullinated peptide antibodies (ACPAs) by plasma cells in RA. Whatever the mechanism, B cells have had a longstanding role in the pathogenesis of RA. In the 1940s, Waaler and Rose discovered rheumatoid factor (RF), an auto-antibody against the Fc portion of immunoglobulin G (IgG) that eventually lead to the categorization of RA as an autoimmune process. Although this was a great achievement into the understanding of mechanism of disease, work on B cells and autoantibodies lost momentum when it was found that RF lacked sensitivity (only 60 to 70% of RA patients were positive for the test) and specificity (many other chronic diseases lead to the production of RF). The field turned its attention to other cellular immune players such as T-cells, fibroblasts, and macrophages. An initial come back of B cells was related to the discovery that antibodies targeting citrullinated peptides (anti-citrullinated protein antibodies or ACPA) were highly specific for RA. Moreover, at the beginning of the 21st Century, rituximab was successfully utilized for the treatment of RA. Ever since, B cell depletion has led to a renaissance of B cells as key mediators of rheumatoid pathogenesis.

Although rituximab is the only B cell directed, FDA-approved molecule for the treatment of RA, several other B cell targeting therapies have emerged in the last few years. Discussing other promising B cell depleting strategies is beyond the scope of this article. This review will focus on the latest advances in the knowledge of clinical application.

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of rituximab in established RA patients (Table 1).

**Mechanism of Action for Rituximab**

Rituximab is a monoclonal, chimeric (mouse/human) anti-CD20 antibody. CD20 is a molecule only found in most mature B cells, and it is absent from either bone marrow stem cells or pro-B cells. Consequently, rituximab treatment leads to targeted depletion of mature circulating and tissue residing B cells. Because of this unique expression pattern, rituximab has a dual advantage. First, it allows for repopulation of circulating B cells once it is cleared from the system. This repopulation process occurs with a majority of antigen inexperienced, naïve B cell population, a situation analogous to a post-bone marrow transplant scenario. On the other hand, rituximab does not affect fully matured plasma cells and allows for normal levels of circulating immunoglobulins in the majority of patients throughout treatment. Beyond this evidence, the mechanisms by which rituximab is effective in RA are still not fully understood.

**Rituximab Use in the Treatment of RA**

Although initially developed for the treatment of B cell non-Hodgkin’s lymphoma, rituximab has subsequently been approved for the treatment of chronic lymphocytic leukemia (CLL), RA, and most recently, the adult forms of Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA).

The FDA has approved rituximab for its use in RA patients with moderate to severe disease who have failed other disease modifying antirheumatic drugs (DMARDs) and at least one anti-TNF inhibitor (TNFI), always in conjunction with methotrexate (MTX). In European countries, the indications are slightly different in that rituximab is approved only in severe cases of RA. The efficacy and safety of this drug was tested in early phase II randomized clinical trials leading to rituximab licensing for RA in 2006. This was followed by several studies showing both an improvement in disease activity and a decrease in joint damage by radiographic assessment.

**Monotherapy vs. Combination Therapy and Durability Questions**

Rituximab monotherapy has shown efficacy in early studies. However, the strength and durability of clinical benefits were more pronounced when rituximab was used in combination regimens with MTX. The overall response duration of a single course of rituximab, typically two-1,000 mg intravenous injections separated by 2 weeks, is longer than 6 months. The IMAGE study, for instance, has recently demonstrated the clinical and radiographic superiority of the combination therapy vs. MTX alone in early, MTX-naïve RA patients.

Intriguingly, there have not been any randomized clinical trials (RCTs) looking at the combination of rituximab with other DMARDs. However, there is no evident reason that would prevent its use along with other agents, particularly leflunomide, as suggested by observational data.

**Evidence for Optimal Rituximab Dose**

Rituximab has been approved as two infusions of 1,000 mg (separated by two weeks interval) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. However, there has been some discussion regarding the use of an alternative regimen, namely 500 mg at weeks 0 and 2. Although ACR20 and 50 responses appeared equivalent in the initial trials, ACR70 responses (or EULAR moderate to good response) were higher in the 1,000 mg x 2 regimen. At the same time, both serious adverse events or infusion reactions were significantly more prevalent in the higher dose group. The IMAGE trial, looking at MTX-naïve RA patients, did not find meaningful clinical differences between the two regimens. Nonetheless, radiographic progression

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**Table 1** Treatment of Rheumatoid Arthritis with Rituximab: Mode of Action, Indications, and Risks

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Monoclonal anti-CD20 Antibody</th>
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<tbody>
<tr>
<td></td>
<td>Targeted depletion of mature B cells</td>
</tr>
<tr>
<td></td>
<td>No effect over immature B cells or plasma cells</td>
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<tr>
<td></td>
<td>Other yet unidentified actions</td>
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<tr>
<td>Indication in RA</td>
<td>Moderate to Severe RA patients with prior failure to at least one TNFi and in combination with MTX</td>
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<tr>
<td></td>
<td>Equally effective when compared to second TNFi</td>
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<tr>
<td>Approved Regimen in RA</td>
<td>1,000 mg IV days 0 and 14 (plus 100 mg of IV methylprednisolone prior to infusions)</td>
</tr>
<tr>
<td></td>
<td>500 mg regimen used successfully in many patients</td>
</tr>
<tr>
<td></td>
<td>Retreatment typically at month 6, but no sooner than month 4; also adjusted to clinical response</td>
</tr>
<tr>
<td></td>
<td>Precise timing appears patient-dependent; personalized approaches needed</td>
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<tr>
<td>Potential Side Effects</td>
<td>Infusion reactions (common)</td>
</tr>
<tr>
<td></td>
<td>Secondary hypogammaglobulinemia (common, IgM)</td>
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<tr>
<td></td>
<td>Bacterial and fungal infections (common URI and UTI; uncommon severe infections such as pneumonia, sepsis)</td>
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<tr>
<td></td>
<td>TB reactivation</td>
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<tr>
<td></td>
<td>Progressive multifocal leukoencephalopathy, PML (rare)</td>
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<td></td>
<td>Hepatitis B virus reactivation (rare)</td>
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<tr>
<td></td>
<td>Cardiovascular events (rare)</td>
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</table>
was significantly less in the 1,000 mg group compared to the 500 mg and placebo groups (at week 52).14

**Controversies in Retreatment Schedule**
Accumulated data is currently insufficient to guide rheumatologists and patients in the precise timing of retreatment interval. Although response is typically seen after 3 months of first infusion, the durability of this response is variable and often times unpredictable. The latest guidelines are also inconclusive and somewhat not helpful for the daily clinical practitioner. The rituximab insert package in the United States asserts that retreatment can occur every 6 months or according to “clinical evaluation” but not sooner than every 4 months.19 For its part, the updated EULAR consensus statement on rituximab use in RA recommends retreatment after 6 months if patients did not reach at least low disease activity.17 This leaves the decision on the side of the treating physician who usually maintains a fixed infusion schedule (i.e., 6 months apart). On the other hand, when response is insufficient or there is flaring before that time period, patients may get retreatment at shorter intervals. This “art of rituximab infusion” creates some confusion, and it is not fully evidenced-based guided. As a result, markers of response are necessary to adjust the benefit-risk equation for many of these patients.

**Predictive Biomarkers for Rituximab Response**

As mentioned before, there is considerable efficacy variability in the way patients respond to alternative doses of rituximab. Therefore, multiple recent studies were designed to establish specific biomarkers that may help predict who will benefit from rituximab (and at which doses). One recent study employing fluorescent-activated cell sorting (FACS) showed that efficacy and clinical response were largely dependent on the degree of B cell depletion rather than actual dose. This was mostly evidenced in those seropositive patients in whom complete depletion was achieved 2 weeks after the very first rituximab dose.18

Other recent efforts have also been informative. These include: a) the observation that low memory B cell frequency (i.e., proportion of CD27+ cells by FACS) is a possible indicator of better clinical response to rituximab in RA patients already receiving MTX or TNF-α,19 and b) a related study showing that four baseline factors correlate with good-EULAR response to rituximab in seropositive chronic RA patients: absence of steroid therapy, low lymphocyte count, high IgG-RF titers, and low levels of circulating BAFF.20

Other baseline factors have been associated with a decreased response to rituximab. These include the absence of auto-antibodies (ACPA and RF), high DAS scores, and rituximab use after failing other biologics.

This body of evidence, paired with the fact that the current dosing for RA is an extrapolation of the lymphoma literature, raises the question of whether higher doses of rituximab for initial non-responders (and without complete B cell depletion) are warranted. More work is clearly needed to address this possibility, particularly to avoid potential extra safety risks.

**Switching to a Second TNF-inhibitor or to Rituximab?**
Because Rituximab can only be used on those patients with inadequate response to “one or more” anti-TNF inhibitors (TNFi), the clinically relevant argument is whether rituximab is more effective than a second TNFi after initial failure. This was addressed in two prospective cohorts. Finkch and colleagues found that switching to rituximab after initial failure (inefficacy) to one TNFi was significantly better (67% of responders by DAS28 scores) than switching to a second TNFi (37% responders).21 In the MIRA registry (MabThera in RA), those patients receiving rituximab who had already failed more than one TNFi were less likely to respond compared to those who had only failed one TNFi.22

**Use of Rituximab Before TNFi**
Although not directly from RCTs, the use if Rituximab has been routinely recorded in observational studies and registries, mostly in those patients with contraindications for TNFi use. One lesson learned from this data is the fact that rituximab durability (measured as time to retreatment) seems to be longer in those patients that were TNFi naïve.

**Warnings, Precautions and Adverse Reactions**

As with the other biologic agents utilized in the treatment of RA, rituximab use carries potential risks. The most common side effects include non-life threatening infusion reactions (nausea, hypertension, pruritus, chills, rigors, etc.) in up to a third of patients following their first dose and infections in up to 39% of treated patients (vs. 34% of placebo-treated controls). The majority of infections were due to upper-respiratory tract and urinary tract infections, possibly associated with secondary hypogammaglobulinemia. The incidence of serious infections (pneumonia, cellulitis, and sepsis) was reported in approximately 2% of rituximab treated patients (vs.1% of controls).

Much less frequently, although of greater concern, are potential severe infusion reactions (including cardiac arrhythmias, myocardial infarctions, cardiogenic shock, and death), progressive multifocal leukoencephalopathy (PML) due to JC virus infection (less than 10 patients reported in the literature at the time of this review) and reactivation of Hepatitis B.

Finally, the safety of immunization with live virus vaccines in rituximab-treated patients has not been adequately studied, and their use is currently contraindicated. Recombinant and dead virus vaccines, on the other hand, are recommended at least 1 month prior to rituximab infusion.

**Summary and Recommendations**
The role of B cells in the pathogenesis of RA has recently re-emerged due to both the discovery of ACPAs as specific
diagnostic tools and the response to depletion in some RA patients. Since its approval for use in RA 6 years ago, rituximab has also expanded the therapeutic options and increased the chances of any given patient to improve synovitis, erosive disease, deformity, and long-term consequences of inflammatory arthritis. It has also provided an alternative to those who fail oral DMARDs, TNFi, and other immunosuppressant medications.

Many questions are still in need of better answers, such as the precise dosing, the right interval for retreatment, whether there are predictive biomarkers of response, and how to prevent severe reactions or side effects. While these scenarios are being addressed at the bench and in the clinic, other B cell depletion strategies are currently being developed which may help elucidate the pathogenesis and therapeutic alternatives in RA.

Disclosure Statement
The author has no financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References