B Cell Targeted Therapies: Safety Considerations

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ABSTRACT. Reported data from recent clinical trials have contributed substantially to our growing understanding of the potential effectiveness and safety of B cell targeted therapy in the treatment of rheumatic diseases. Trials with rituximab, an anti-CD20 monoclonal antibody that depletes mature B cells, have amassed the most data of any B cell targeted therapy to date. A number of other B cell directed therapies are under investigation. Interestingly, although they may share a common target, the different agents have quite distinct mechanisms of action, and therefore their efficacy and safety profiles may differ. A common concern with all B cell directed therapies is the potential effect these agents may have on humoral immunity. The safety profile of rituximab in the oncology setting is well known, based on a database of well over 370,000 patients. Phase II trials of rituximab in rheumatoid arthritis (RA) have begun to examine safety issues specifically in the RA population, including issues surrounding longterm and repeated treatment safety profiles. Questions about the longterm safety of B cell therapy remain to be clarified: What will be the safety profile for repeated treatment courses? What will be the safety profile when B cell targeted therapies are used in sequence or in conjunction with other agents? Answers to these important questions are likely to come from careful observations by treating clinicians, data from registries, and longterm followup of patients enrolled in clinical trials. (J Rheumatol 2006;33 Suppl 77:18-23)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
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INTRODUCTION

While efficacy is an important factor in choosing a treatment, the safety profile will strongly influence the way an agent is ultimately used clinically. Safety issues can negatively affect patient compliance and tolerability: even the most effective agent will not be used if associated with intolerable side effects. In this article, general safety issues surrounding B cell targeted therapies and safety data from clinical trials investigating these therapies will be discussed, as well as hypothetical concerns about the longterm safety of B cell targeted therapies and implications of their use. Key information now available gives some insight into the safety benefits and limitations of these drugs.

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GENERAL SAFETY ISSUES ASSOCIATED WITH B CELL DIRECTED BIOLOGIC AGENTS

A number of safety issues are associated with the use of biologic disease modifying antirheumatic drugs (DMARD) in rheumatoid arthritis (RA). These can be broadly divided into 2 categories. The first is target-related issues. Unlike anti-tumor necrosis factor (TNF) therapies, which target a single cytokine, B cell targeted therapies create a more complex safety situation, as different B cell-inhibiting agents may work by different mechanisms of action. Therefore, each may have a different safety profile, and data from clinical studies and experience with one agent or approach may or may not be strictly applicable to another.

Additionally, B cell targeted therapies may potentially affect distinct aspects of B cell function. This includes humoral immunity, or antibody production to specific antigens, as well as B cell costimulatory function and cytokine secretion. Regarding humoral immunity, one surrogate marker of this important function is vaccine response. Perhaps the most important target-related adverse effect potentially associated with B cell targeted therapies is immunodeficiency. A number of primary immunodeficiencies that primarily affect humoral immunity have been described (many arising from specific genetic defects in B cell development at different stages) that may give us a window on a "worst case scenario" for therapies that target B cell function (Figure 1).

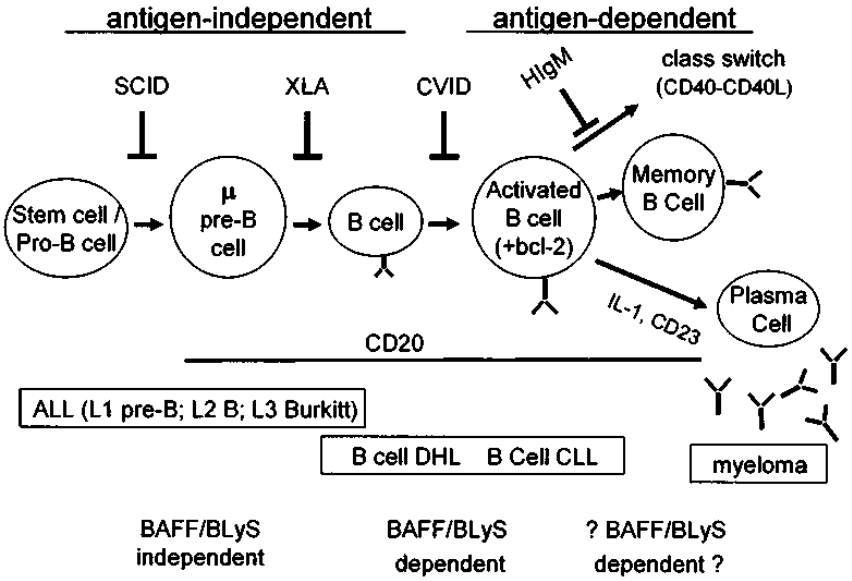

Figure 1. B cell development. Immune deficiencies of different kinds can arise at different stages of B cell development. Also depicted are tumors that arise as malignant transformations of B cells at different points in their development. SCID: severe combined immunodeficiency; XLA: X-linked agammaglobulinemia; CVID: common variable immunodeficiency; HIgM: hyper-immunoglobulin M syndrome; DHL: diffuse histiocytic lymphoma; CLL: chronic lymphocytic leukemia.

Agent-related adverse events (AE) may vary from agent to agent and between constructs. AE are specific to the administration of the agent. Rituximab is currently the most studied B cell directed therapy in clinical trials. With rituximab, infusion reactions have been the most common agent-related AE in clinical trials. In patients with RA as compared to those with lymphoma, infusion reactions have tended to be less severe. Another agent-specific AE is immunogenicity. Although the frequency of antibodies to treatment compounds can be determined, at present the full clinical relevance of these results and their future implications are incompletely defined.

SAFETY DATA

Although safety database records relating to treatment with B cell targeted therapies are not as extensive as those for older approved therapies, data are available on about 1000 patients with RA and on over 100 patients with lupus treated with rituximab. The importance of having data on as many treated patients as possible is highlighted by recent events with natalizumab in multiple sclerosis[1-4]. Three cases of progressive multifocal leukoencephalopathy were observed when an estimated 3000 to 5000 patients had received therapy. This emphasizes the importance of pharmacovigilance and the "rule of threes": To reliably demonstrate a rare AE that occurs at the rate of about 1 in 1000, a data set of about 3000 is necessary. This formula can be extrapolated for rarer AE. For these reasons, a large data set is necessary to have a spectrum of safety information.

RITUXIMAB IN NON-HODGKIN'S LYMPHOMA

More than 370,000 patients have been treated with rituximab in the oncology setting[5]. These numbers provide some level of assurance that major safety signals have already been detected and that management protocols have been developed. While extrapolation when comparing safety may not be exact, the experience of rituximab in non-Hodgkin's lymphoma (NHL) may be a good analogy to RA for several reasons: Both diseases result in impaired immune response, clinicians have to deal with issues of multiple concomitant medications in these patients, and both diseases are associated with multiple comorbidities. Additionally, the severity of both diseases can be comparable.

The overall safety conclusions regarding treatment with rituximab in NHL are that serious adverse events (SAE) occur relatively infrequently and are associated with well-defined risk factors, such as cardiopulmonary disease or high numbers of circulating cancer cells and heavy tumor load. Patients with higher tumor loads had more problems with infusion-related events. Infusion reactions are usually associated with the first treatment

and tend to become less frequent over time. AE associated with infusion reactions include hypotension (shock), fever [> 40.0°C (> 104.0°F) for > 24 h], and nausea. Interestingly, in the NHL population, prolonged depletion of circulating B cells has not been associated with cumulative toxicity or an increased incidence of opportunistic infections[6-8].

Clinical trials in RA have demonstrated that retreatment will almost certainly be necessary. Therefore, data concerning repeated course of therapy is very important. In NHL, there are several multicenter, controlled maintenance therapy trials under way. Safety data from these types of trials are eagerly awaited.

RITUXIMAB IN RHEUMATOID ARTHRITIS

When comparing NHL and RA data, it is important to remember that there are differences in the underlying disease that may affect side-effect rates and profiles. For example, the tumor lysis syndrome noted in patients with NHL most likely will not be a large issue in the treatment of patients with RA.

The safety profile of rituximab in RA is emerging from Phase II and Phase III trial results. In the Phase IIa trial[9] discussed elsewhere in these proceedings[10], safety data through 2 years showed no apparent increase in total infections: infections and serious infections were similar in all treatment groups (Figure 2). Most frequently reported were respiratory and urinary tract infections. Infections were more likely to occur in the rituximab groups compared to placebo. However, in RA, it is perhaps to be expected that effective immunomodulatory therapies may result in a slight increase in infections[9,11]. Patients who received cyclophosphamide had more SAE; however, it is unlikely that cyclophosphamide will be part of the standard RA regimen. All in all, the AE associated with the treatment groups in this study appeared to be manageable.

The Phase IIa study also brought to light the issue of prolonged B cell depletion. After treatment with rituximab, B cell numbers were low and then increased to or towards the normal range over the course of months[9]. Of note, to date there has not been significant evidence of severe humoral immunodeficiency. This dissociation between biologic endpoints, such as depletion in circulating cell numbers, and functional outcomes has been observed with other therapies. For example, a number of depleting monoclonal antibodies specific for the helper T cell antigen CD4 were studied in patients with RA[12]. Although patients thus treated had extremely low counts of circulating peripheral CD4+ cells, in most studies, there was minimal if any improvement in their arthritis as assessed by synovial inflammation and clinical measures. Interestingly, despite low numbers of circulating T cells, there was also no evidence for severe impairments in cell-mediated immunity. A dissociation between a biologic endpoint and clinical outcomes was also seen in studies

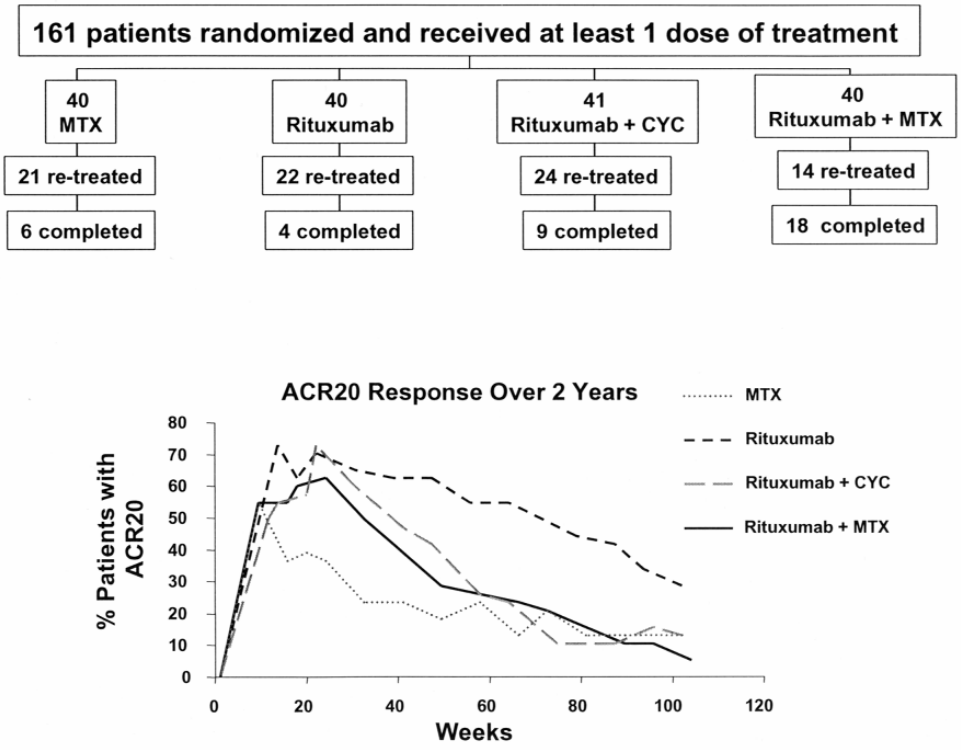

Figure 2. Efficacy and safety of rituximab at 104 weeks. MTX: methotrexate; CYC: cyclophosphamide.

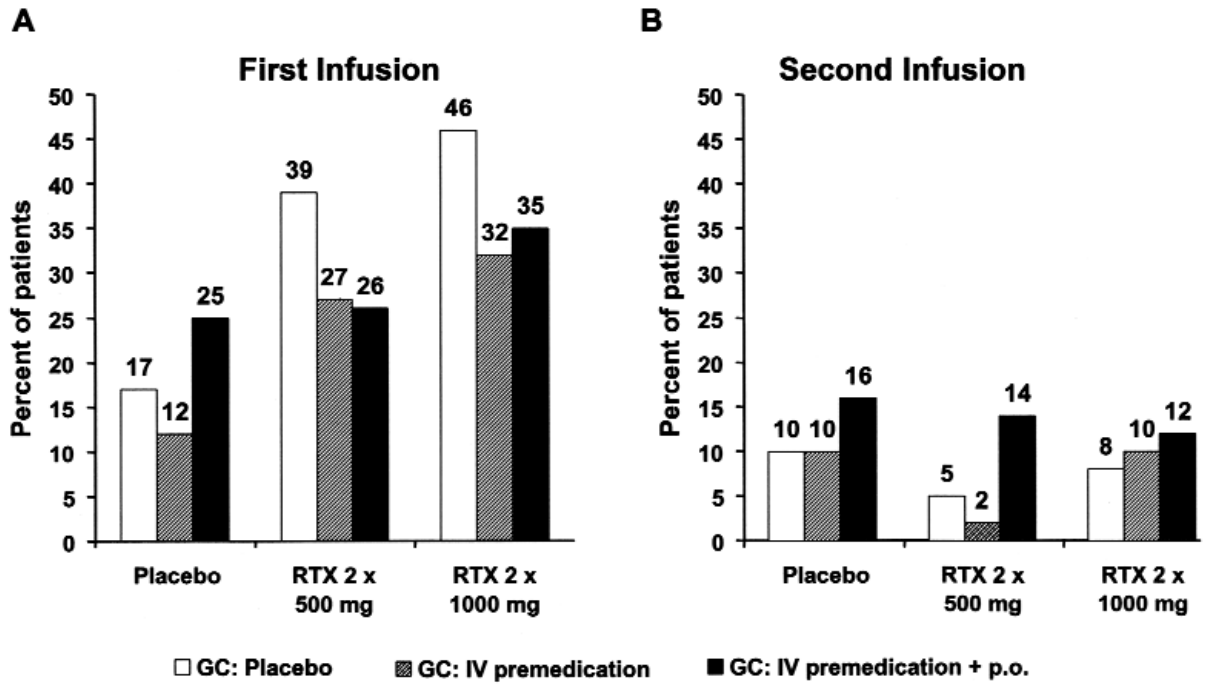

Figure 3. Infusion reactions from the rituximab Phase IIb DANCER Study[11]. A. Infusion reactions associated with the first infusion of RTX. B. Infusion reactions associated with the second infusion of RTX. GC: glucocorticoids; RTX: rituximab.

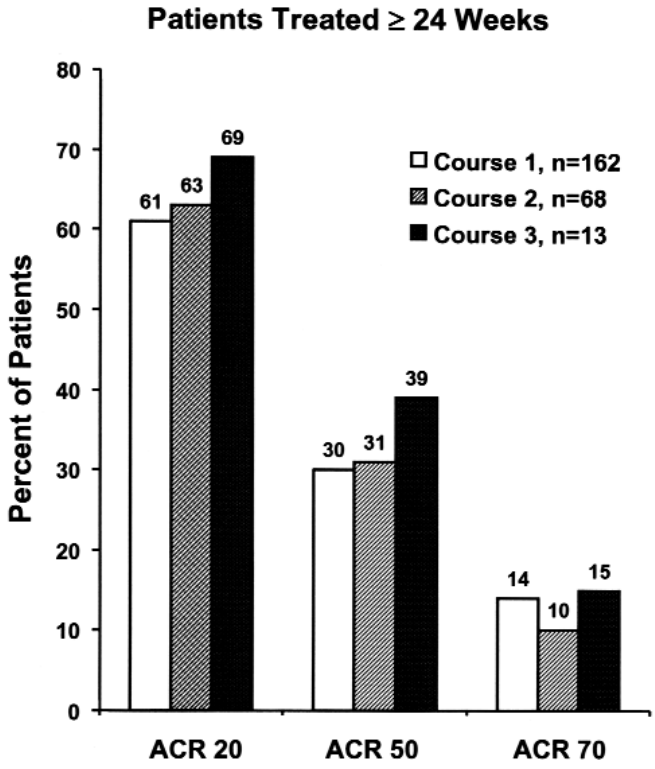

Figure 4. Efficacy following repeated courses of rituximab in patients with RA. Patients from Phase IIa and IIb studies who were in the RTX + MTX treatment groups were enrolled in this open-label extension study. Placebo patients were also eligible to enter.

targeting the cytokine interleukin 5 (IL-5) in patients with asthma. This cytokine is responsible for eosinophil survival; thus, blocking IL-5 results in eosinophil depletion. Interestingly, when patients were treated with recombinant IL-5, there was no change in their asthma disease activity[13]. Similarly, another study focused on treating patients with recombinant IL-12 in order to shift the Th2 inflammatory response characteristic of asthma[14]. IL-12 is responsible for balancing the Th1 and Th2 response. In this experiment as in the previous one, although IL-12 was successful in depleting eosinophils, there was no clinical benefit. These studies suggest that with targeted biologic therapies there can be a dissociation between biologic parameters such as circulating cell numbers and clinical outcomes.

Safety results from the rituximab DANCER trial confirmed previous findings from the Phase IIa trial: the majority of AE were mild to moderate and included headache, nausea, and rigors. Consistent with previous experience in RA, AE reported in the rituximab groups were primarily infusion-related and were largely associated with the first infusion, occurring in 18% (rituximab 500 mg), 31% (rituximab 1000 mg), and 38% (placebo) of patients[15]. The incidence decreased during the second infusion to 11% (rituximab 500 mg), 7% (rituximab 1000 mg), and 10% (placebo) (Figure 3). Two serious infusion reactions occurred on Day 1 (drug hypersensitivity and generalized edema). Pretreatment with methylprednisolone on Day 1 appeared to reduce the incidence and severity of infusion reactions by about one-third[16,17]. Infections (primarily upper respiratory tract infections) were reported in 28% of patients treated with placebo and 35% of patients treated with rituximab. There were 6 serious infections, 2 in patients treated with placebo (one pneumonia and one respiratory tract infection) and 4 in patients treated with 1000 mg (one epiglottis, one bronchitis, and 2 pyelonephritis). There were SAE in 7% of patients in both the rituximab 500 mg and 1000 mg groups and in 3% of the placebo group. One fatality due to a cerebrovascular event was reported in the rituximab 500 mg group; however, it was considered unrelated to treatment. No serious infections were reported in patients receiving rituximab 500 mg. No opportunistic infections or tuberculosis reactivations were reported. These numbers may be difficult to interpret due to the relatively small number of patients treated; however, they are encouraging. Immunoglobulin levels were slightly decreased at 24 weeks in patients who received rituximab, but they remained well within normal limits. Human anti-chimeric antibody rates at Week 24 were 0.7% (placebo), 4.9% (rituximab 500 mg), and 2.7% (rituximab 1000 mg). As mentioned, the significance of these data is difficult to determine until longterm safety and retreatment data become available. Antibody titers to common recall antigens (e.g., tetanus toxoid) appeared unaffected by rituximab treatment[15].

An extension study with rituximab retreatment has been performed (Figure 4) and is discussed in Dr. Cohen's article[10]. Safety data from that study suggest the overall adverse event profile was similar to that seen with a single treatment.

RESEARCH AGENDA

In addition to depleting CD20+ B cells with rituximab, there are a variety of other potential mechanisms for inhibiting B cells. Some agents currently in trials for various rheumatic diseases include: epratuzumab, a monoclonal antibody directed against the B cell antigen CD22;

Table 1. Safety considerations in B cell targeted therapies.

Optimal Treatment Paradigms	Immune Function with Repeated / Chronic Administration	Stratification of Patients for Safety / Efficacy	Sequential and Combination Therapy with Other Agents
• At regular intervals vs. on increased disease activity • On change in peripheral B cell numbers	• Infection • Ig levels • Vaccination response	• FcγRIIIA polymorphisms	• T cell directed therapies CTLA-4-Ig CsA LEF others • Cytokines TNF inhibitors IL-6 inhibitors IL-4 others • Others

CSA: Cyclosporin A; LEF: leflunomide; TNF: tumor necrosis factor; IL-6: interleukin 6.

several soluble inhibitors that target the B cell-activating factor/B lymphocyte stimulator (BAFF/BLyS) or its receptors, which are molecules important for B cell survival and activation or function; and belimumab, a monoclonal antibody that binds soluble BLyS[19,20]. A number of other approaches are in development. These various agents demonstrate the differing mechanisms by which B cell function may be targeted. As noted, the efficacy, as well as the safety profiles, may vary from agent to agent.

New research on common variable immunodeficiency (CVID) further stresses the importance of analyzing B cell-targeted therapies separately based on their individual mechanisms of action. There is new information about the delineation of pathways that contribute to CVID, and this implies that various B cell agents may have variable safety and efficacy[21]. Their use must be carefully monitored and followed.

CONCLUSIONS

Questions remain about the treatment strategy with B cell agents, such as optimal treatment intervals, and significance of peripheral B cell depletion, among others (Table 1). One of the most important safety issues concerns immunity and infections. Recent data published on patients with NHL treated with rituximab who were vaccinated with tumor-specific antigens showed that while T cell responses were intact, there was delayed humoral immunity that correlated with B cell number, suggesting that vaccination strategies might have to be reworked in such patients[22]. Once again, this information may not be directly applicable in patients with RA, but may indicate what to expect in this population.

A tremendous amount has been learned from TNF inhibitors in recent years. With the advent of B cell-targeted therapies and other cytokine inhibitors, combination therapy with these agents is already starting to be explored. What are the consequences of modulating 2 different immune pathways? What is the impact on safety of targeting different molecules at the same time? These are questions that will be answered as new research reveals the roles and mechanisms of each component of the immune system.

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