B cell-targeted therapy in diseases other than rheumatoid arthritis.

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J Rheumatol 2005;73;25-28
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INTRODUCTION
Following its success as a treatment for non-Hodgkin’s lymphoma (NHL) and B cell chronic lymphocytic leukemia, rituximab (RTX) has been investigated in a broad range of diseases involving B cells. Because of its safety profile and availability, RTX has been tried in a wide variety of autoimmune diseases; its success in these open-label studies suggests the importance of B cells in these diseases. For some diseases, for example idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA), the critical role of B cells is obvious because of the demonstrated importance of pathogenic autoantibodies. In other diseases such as rheumatoid arthritis, dermatomyositis, and antineutrophil cytoplasmic antibody-associated (ANCA+) vasculitis, the importance of B cells has not been well established, and the apparent success of RTX in treating these diseases has raised interesting questions about their pathogenesis. Although it is likely that B cell depletion is the major mechanism of action of RTX in autoimmune disease, this remains to be established; RTX might also alter cell migration or interact with inhibitory receptors.

RITUXIMAB FOR CHRONIC IDIOPATHIC THROMBOCYTOPENIC PURPURA
ITP is an immune-mediated disorder during which platelets are opsonized by autoantibodies and prematurely destroyed by the reticuloendothelial system. The disease follows a chronic and refractory course in around 25% to 30% of patients, and there is a need for more effective therapeutic interventions. The efficacy and safety of RTX 375 mg/m² once weekly for 4 weeks were investigated in 25 individuals with chronic ITP that had been resistant to between 2 and 5 different prior therapies1. The overall response rate to RTX was 52%. Responses were generally seen within 4 weeks (Figure 1). Seven patients exhibited durable responses lasting for at least 6 months. The time to response varied widely between patients, suggesting that there may be 2 mechanisms of action: a rapid response as is seen with intravenous immunoglobulins (IVIG), and a delayed response such as might be seen with immunosuppressive drugs. Thus, with rituximab in ITP there may be an early response due to rapid activation of inhibitory receptors and a delayed response due to gradual elimination of autoantibody-producing cells2.

In another study involving 57 patients with refractory ITP, patients received the NHL-based dose of 4 infusions of 375 mg/m² RTX. Eighteen patients (32%) achieved a complete response, and 16 (28%) maintained this remission after a median of 49 weeks (range 16 to 136)3. The ability of a brief course of RTX to induce longterm responses has been one of the especially intriguing aspects of this therapy.

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This educational activity is sponsored by the University of Texas Southwestern Medical Center at Dallas, which is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians, through an unrestricted educational grant from Genentech, Inc. and Biogen Idec Inc.

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Key Indexing Terms:
RITUXIMAB
AUTOIMMUNE HEMOLYTIC ANEMIA
DERMATOMYOSITIS
IDIOPATHIC THROMBOCYTOPENIC PURPURA
POLYNEUROPATHIES
SYSTEMIC LUPUS ERYTHEMATOSUS
RITUXIMAB: SAFE AND EFFECTIVE IN AUTOIMMUNE HEMOLYTIC ANEMIA

AIHA must always be considered in the differential diagnosis of hemolytic anemias, especially if the patient has a concomitant lymphoproliferative disorder, autoimmune disease, or viral or mycoplasma infection. AIHA is especially problematic in children, where prolonged therapy with high-dose steroids can have a major effect on growth and development, and where the immature immune system makes them particularly susceptible to infectious complications of immunosuppression.

Zecca, et al6 evaluated RTX prospectively in 15 children (age range 3 mo to 14 yrs) with refractory AIHA who received RTX 375 mg/m² for a median of 3 weekly doses. Absolute B lymphocyte counts became undetectable after treatment in all patients and had returned to normal 6 months after treatment in 10 patients (67%). Thirteen patients (87%) responded to treatment, showing at least a 1.5 g/dl increase in hemoglobin (Hb) and a > 50% reduction in absolute reticulocyte count. Overall median Hb increased from a pretreatment value of 7.7 g/dl to 11.8 g/dl 2 months after RTX treatment (p < 0.001; Figure 2).

In an earlier study of 5 children with AIHA who were treated with RTX therapy, immunoglobulin levels fell below normal values for age5. In contrast, adults treated with RTX experience little or no decrease in IgG levels, presumably because RTX does not affect long-lived plasma cells. Therefore, to prevent therapy-induced hypogammaglobulinemia and to decrease the risk of infection, patients in the study by Zecca, et al6 also received replacement doses of IVIG (400 mg/kg every 3 weeks for 6 mo). With this precaution even young children tolerated RTX well. One child had a primary varicella zoster infection 2 months after receiving RTX, which was successfully cured with acyclovir.

RTX IN IgM ANTIBODY-ASSOCIATED POLYNEUROPATHY AND DERMATOMYOSITIS

Polyneuropathies with associated IgM antibodies are often difficult to treat. Pestronk and colleagues8 have reported their experience with RTX in 21 patients evaluated over a 2-year period. A control group of 13 untreated patients receiving standard clinical care was also followed up for 2 years. In 21 patients treated with RTX, the mean improvement in muscle strength at 1 year was 13% (p < 0.001 vs untreated patients), and 23% (p < 0.001 vs untreated patients) after 2 years. None of the 13 control patients improved by 12% of normal strength at any time during the 2 year followup; mean change in strength in the control patients was 3% at 1 year and 0% at 2 years (Figure 3).

In RTX-treated patients, disease-specific IgM and total IgM decreased at 1 and 2 years of therapy, but there were no changes in either total IgG or anti-tetanus IgG titers. In contrast, there was no change in any of these variables in control patients. RTX treatment was associated with very little morbidity. Occasional episodes of lightheadedness, chills, and transient hypotension occurred with the initial treatment, but did not recur with subsequent infusions.

A case series of 5 patients with dermatomyositis treated with RTX was reported by Levine5. Within 1 to 3 months, all patients experienced sustained improvement in muscle strength. Two adults who had failed previous therapies demonstrated 60% and 20% improvement; a previously untreated adult had a 55% improvement; and 2 children experienced improvements of 30% and 45%.

RTX: ACCUMULATING EVIDENCE OF EFFICACY IN SYSTEMIC LUPUS ERYTHEMATOSUS

RTX as monotherapy: A Phase I/II open-label, dose-escalation trial of RTX in 16 patients with systemic lupus erythematosus (SLE) has recently been completed8. Six patients showed poor depletion of B cells and 10 showed good depletion. Those patients with good depletion achieved a statistically significant improvement in Systemic Lupus Activity Measure (SLAM) score by 3 months, whereas the poor depleters showed no improvement (Figure 4). When analyzed separately, the joint and skin components of the SLAM scores both improved significantly in patients with good depletion of B cells.

Another Phase I trial has found RTX to be effective and well tolerated in SLE5. Six patients showed B cell depletion > 99% for at least 3 months and an associated clinical response. Three of these patients had a prolonged remission lasting 6 to 9 months. RTX in combination therapy: Six female patients with SLE received two 500 mg infusions of RTX and two 750 mg infusions of cyclophosphamide and high-dose oral corticosteroids10. One patient was lost to followup after
response was really a delayed response to the cyclophosphamide. Subsequently, 2 small series of ANCA+ vasculitis have recently been reported. Eriksson administered RTX to 4 patients with WG and one with microscopic polyarteritis nodosa who were resistant to other therapies. Four complete responses and one partial response were observed, and RTX was well tolerated.

Jayne and co-workers gave RTX plus cyclosporine 500 mg to 6 patients with refractory vasculitis (4 with microscopic polyarteritis nodosa and 2 with WG). All patients completed treatment and demonstrated B cell depletion. Mean Birmingham Vasculitis Activity Score declined from 9.8 at baseline to 3.8 after 3 months (p < 0.01). There were 4 complete responses and 2 partial responses.

CONCLUSIONS
Overall, RTX shows great promise in the treatment of a number of autoimmune diseases, including AIHA, SLE, and IgM-associated neuropathies. RTX is generally well
tolerated, both as monotherapy and in combination with immunosuppressive drugs such as cyclophosphamide. In adults, total IgG and IgG anti-tetanus antibody levels are unaffected, even after 2 years of therapy with RTX. IgM levels are reduced to the lower end of the normal range. Further studies are under way to determine optimum dose and treatment schedules for rituximab in autoimmune diseases.

REFERENCES