

B Cell-Targeted Therapy in Diseases Other Than Rheumatoid Arthritis

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ABSTRACT. There are now numerous case reports and small series using rituximab in autoimmune diseases. While these data must be interpreted with caution, they suggest that rituximab (RTX) may be a promising addition to the therapeutic armamentarium. In patients with refractory chronic idiopathic thrombocytopenic purpura, treatment with RTX was effective in inducing complete responses in a significant proportion of patients, and these responses were usually durable. RTX has also been shown to be effective and well tolerated in children with refractory autoimmune hemolytic anemia. In patients with IgM antibody-associated polyneuropathy, RTX improved muscle strength, and repeated treatments over 2 years were well tolerated. In several case series of patients with systemic lupus erythematosus, depletion of B cells during RTX therapy was associated with improvement in global disease activity. Based on these reports, further controlled studies are warranted to optimize RTX as monotherapy and to develop combination therapies in patients with refractory autoimmune diseases. (J Rheumatol 2005;32 Suppl 73:25-8)

Key Indexing Terms:

RITUXIMAB

AUTOIMMUNE HEMOLYTIC ANEMIA

DERMATOMYOSITIS

IDIOPATHIC THROMBOCYTOPENIC PURPURA

POLYNEUROPATHIES

SYSTEMIC LUPUS ERYTHEMATOSUS

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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Looney: Therapy in non-RA diseases

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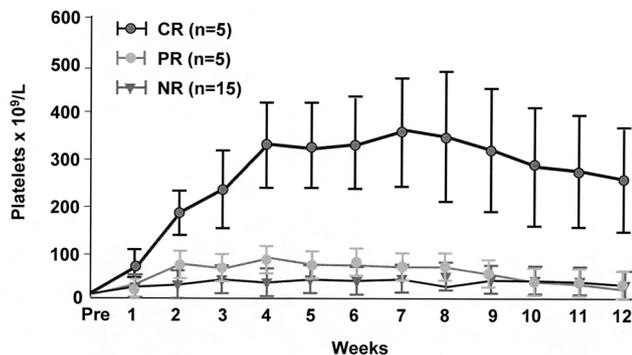


Figure 1. Platelet response to rituximab in idiopathic thrombocytopenic purpura¹. CR: complete response; PR: partial response; NR: no response. From: Stasi R, *et al*. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. *Blood* 2001;98:952-7. Copyright American Society of Hematology, with permission.

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 al*⁴ 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 al*⁴ 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 colleagues⁶ 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 Levine⁷. 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 SLE⁹. 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

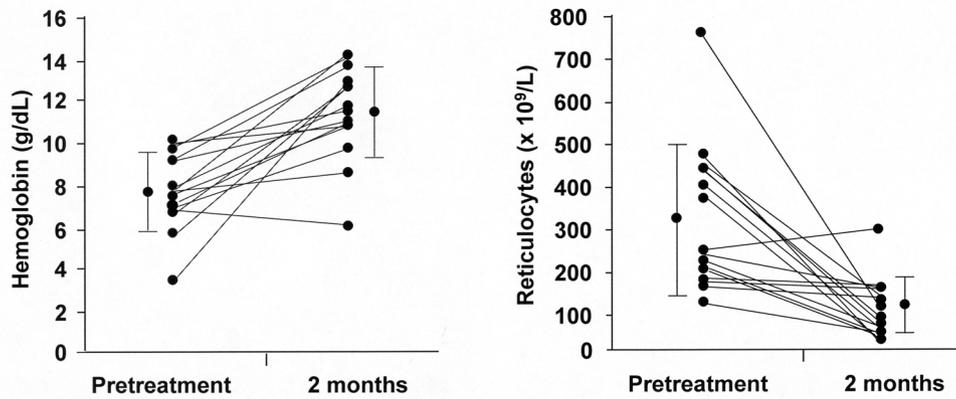


Figure 2. Hemoglobin and absolute reticulocyte counts in children with refractory autoimmune hemolytic anemia treated with rituximab⁴. The difference between pretreatment and post-treatment values is statistically significant ($p < 0.001$). From: Zecca M, *et al.* Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. *Blood* 2003;101:3857-61. Copyright American Society of Hematology, with permission.

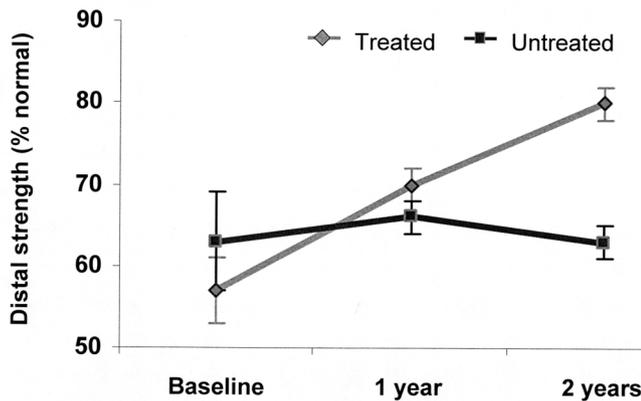


Figure 3. Changes in quantitative strength testing in rituximab-treated and control polyneuropathy patients. Error bars: SEM; $p < 0.001$, treated vs untreated.

3 months. At 6 months, all remaining patients had improved as shown by decreases in British Isles Lupus Assessment Group (BILAG) scores — from a median of 14 at baseline to a median of 6 at 6 months. No significant adverse events were observed during followup¹⁰.

A further group of 6 patients with refractory lupus nephritis received two 1 g infusions of RTX and two 750 mg infusions of cyclophosphamide¹¹. An improvement in BILAG scores was noted in all patients. Further, some improvement in renal function was noted.

RTX: A NOVEL TREATMENT FOR ANCA+ VASCULITIS

The initial case report using RTX in ANCA-positive vasculitis¹² described a patient with very refractory Wegener's granulomatosis (WG). There was an apparent response to the addition of RTX to cyclophosphamide and high-dose steroids, but it was not clear whether this

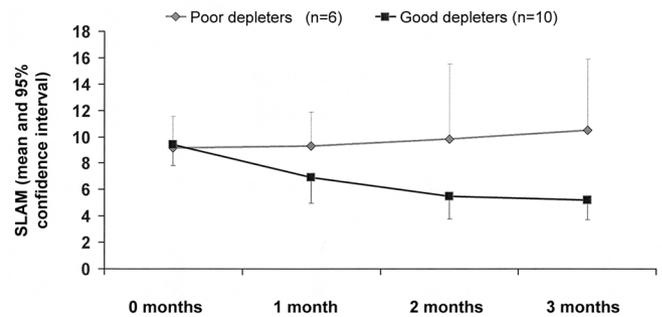


Figure 4. Changes in Systemic Lupus Activity Measure (SLAM) score in rituximab-treated patients who showed good ($n = 10$) or poor ($n = 6$) depletion of B cells.

response was really a delayed response to the cyclophosphamide. Subsequently, 2 small series of ANCA+ vasculitis have recently been reported.

Eriksson¹³ 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-workers¹⁴ 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.

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