

B cell depletion in systemic lupus erythematosus

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In the last 8–9 years B cell depletion based on the anti-CD20 monoclonal antibody rituximab has been used to treat a wide range of autoantibody-associated autoimmune diseases (Table 1). Open prospective trials and case reports have shown substantial benefit for rituximab in the treatment of patients refractory to standard therapies in most of these diseases with a generally good safety profile. However, not every patient with every disease has responded. Results suggest that there is different susceptibility to B cell depletion for different diseases and probably variation in the optimal protocol. The use of rituximab has generated considerable interest in the development of other B cell targeting strategies for treating autoimmune diseases.

A phase 2 placebo-controlled trial has proved the efficacy of rituximab in rheumatoid arthritis (RA) with a good safety profile. Rituximab has recently

been approved by the US Food and Drug Administration for the treatment of patients with active RA refractory to anti-tumour necrosis factor- α drugs. Randomised controlled trials are in progress for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and systemic lupus erythematosus (SLE).

In SLE, the rationale leading to the use of B cell depletion therapy was based on:

- the presence of autoantibodies demonstrated to be pathogenic
- evidence of B cell hyperactivity, and
- studies in animal models of SLE suggesting a pathogenic role for B cells independent of their production of autoantibodies.

B cell depletion therapy based on rituximab has been used to treat patients with active, usually severe, disease refractory to conventional therapy. Recent reviews have covered published small series and case reports but important questions regarding the use of rituximab in this and other autoimmune diseases remain.^{1–3} This article will focus mainly on the use of rituximab for B cell depletion in SLE, with particular emphasis on the experience at University College London (UCL).

Therapeutic protocols

Patients reported in the literature have been treated with different protocols. Predominantly, rituximab has been used as monotherapy, as approved, for lymphoma (4 weekly infusions 375 mg/m² of body surface area) or combined with cyclophosphamide.

University College London protocol

At UCL most patients have been treated with a combination protocol: two 1 g intravenous (iv) infusions of rituximab two weeks apart, plus 750 mg cyclophosphamide and 250 mg methylprednisolone iv with each rituximab infusion.^{4,5} Cyclophosphamide is omitted from the protocol if contraindicated or the patient refuses it. Reasons for this combination protocol have been discussed elsewhere.⁴ Premedication with paracetamol and an antihistamine, in addition to corticosteroids, is used to decrease the risk of serious infusion reactions. Patients continue oral corticosteroids and hydroxychloroquine, but other immunosuppressive drugs are usually stopped to reduce the incidence of serious infections.

Clinical efficacy

Most patients reported in the literature have improved following rituximab therapy. Considerable clinical benefit in different disease manifestations has been observed, including arthritis, serositis, nephritis, autoimmune cytopenias, vasculitis and central nervous system vasculopathy. Clinical improvement is frequently associated with changes in laboratory indices of disease activity. Total immunoglobulin (Ig) serum levels usually remain within the normal range following B cell depletion treatment while changes in anti-dsDNA antibody serum levels vary but frequently decrease, particularly in patients whose response to therapy lasts longer.^{5,6} Repeated biopsies have documented major improvement in disease activity in some patients with nephritis.⁷ Good results have also been described in children.⁸

Several studies in patients with SLE show that with currently used protocols B cell depletion is less predictable and frequently of shorter duration than in patients with lymphoma or RA. It is possible that the mechanisms by which rituximab depletes B cells (mainly antibody-dependent and complement-dependent cytotoxicity) are impaired in some patients with SLE. In a phase 1/2 dose escalating trial Looney and

Table 1. Some of the autoantibody-associated autoimmune diseases for which B cell depletion based on the anti-CD20 monoclonal antibody rituximab has been used.

- Immunoglobulin M-associated polyneuropathies
- Cold agglutinin disease and other haemolytic anaemias
- Autoimmune thrombocytopenia
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Antiphospholipid antibody syndrome
- Antinuclear cytoplasmic antibody-associated vasculitis
- Dermatomyositis
- Sjögren's syndrome

colleagues found that clinical improvement correlated with the extent of B cell depletion in the peripheral blood.⁶

Disease flare

Experience at UCL is that in patients who respond to treatment the disease does not flare before B lymphocyte repopulation of the peripheral blood. This highlights the importance of measuring CD19 in the peripheral blood at regular intervals after rituximab therapy. Patients can either flare at the time of peripheral B cell repopulation or at a variable time afterwards (up to more than four years). A small number of patients have relapsed after treatment and their disease is well controlled on low-dose oral prednisolone without further immunosuppression. In others, a retreatment of conventional immunosuppressive therapy (previously ineffective) has sometimes been controlled disease activity following relapse after B lymphocyte depletion.

Repeat treatment

Several patients have been retreated with B cell depletion with good results if re-treatment depletion is effective and, in the case of nephritis, the damage is not extensive.⁹ Sustained clinical benefit following the second cycle of treatment lasted longer than after the first in some patients. One patient failed to deplete on retreatment due to a human antichimeric antibody (HACA) response. At UCL retreatment is given only after disease flare but two patients reported in

the literature received rituximab as part of a maintenance protocol similar to that in some lymphoma patients, with good results.¹⁰ It is not known whether this approach will result in clinically significant immunosuppression.

Side effects

B cell depletion protocols based on rituximab have generally been well tolerated. Severe infusion reactions, frequently similar to type III hypersensitivity reactions, have been described despite the recommended use of premedication,^{1,4} but these have responded to appropriate treatment. Unusually high haematological toxicity has been described in a series of paediatric patients.¹¹ Infusion reactions are similar to those described in patients with lymphoma.

Adverse events during the period of B cell depletion have been uncommon. At UCL an increased incidence of infections, particularly opportunistic infections, has not been noted. Total serum Ig levels frequently fall following treatment but usually remain within the normal range. Some severe infections have been reported in the literature but it is not known whether there is a causal link with rituximab. The risk of infection may be increased in patients who have continued other immunosuppressives.¹¹

In RA patients treated with rituximab there is evidence that antibodies to microbial antigens such as tetanus toxoid or pneumococcal capsular polysaccharides remain within the protective range following treatment.¹² There is a case for

immunising patients against these and other antigens before treatment if their levels are below the protective range and the clinical situation allows it.

Whether repeated courses of treatment upon disease flare or the use of long-term maintenance therapy with rituximab will lead to clinically significant cumulative immunosuppression is not known but it has not been observed so far. There is some indication that total Ig levels may decrease below the normal range after repeated cycles of treatment. One of the patients treated at UCL remained B cell depleted for more than five years with no side effects.

The development of HACA specific to rituximab has been described in patients with SLE treated with this drug and can interfere with retreatment.^{6,13} It is not known whether it increases the risk of infusion reactions. Preliminary data from open-label studies suggest that SLE patients may be more susceptible to develop HACA to rituximab than those with RA or lymphoma, particularly if treated with lower doses.

Conclusions

Several prospective small open-label studies and case reports suggest that B cell depletion therapy based on rituximab is a promising treatment for SLE. Its use in patients with severe active disease refractory to standard therapy is becoming relatively common in many rheumatology units. Properly controlled trials are needed to:

- determine its true clinical efficacy and side effects profile
- try to establish the optimal protocol for rituximab use in SLE
- determine whether certain SLE clinical subsets may respond better than others.

Other B lymphocyte targeting therapies are under development, several at the clinical trial stage. These include humanised anti-CD20 antibodies, anti-CD22 antibodies and B-lymphocyte-modulating agents (Blys)/B cell activating factor (BAFF) and APRIL (a proliferation-inducing ligand) targeting agents.

Key Points

A popular view until recently has been that B cells would not represent a useful target for the treatment of autoimmune diseases

B cell depletion using rituximab has shown clear potential in the treatment of patients with autoantibody-associated autoimmune diseases

B cell depletion therapy has proven efficacy in rheumatoid arthritis

In systemic lupus erythematosus, small series and case reports suggest efficacy with a good safety profile but controlled trials are needed

Other strategies to target B cells are in development

KEY WORDS: autoimmune diseases, B cell depletion, rituximab, systemic lupus erythematosus

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