REPORT

Update on rituximab

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Rituximab is a chimeric monoclonal antibody that was developed for the treatment of B cell lymphomas.¹ It is directed against the CD20 cell surface molecule.² CD20 is a tetraspan membrane protein that is present only on B cells, and is expressed initially at the immature B cell stage, remaining until the final differentiation into plasma cells. The function of CD20 is not clear, although it may play some role in signalling or in calcium mobilisation.³ Curiously, mice that were genetically engineered to lack CD20 (CD20 knock-out mice) have not shown any clear defects in their B cells.⁴ Nevertheless, the specificity of CD20 for the B cell lineage, and its failure to be easily shed or internalised, has made it an excellent target for depletion by monoclonal antibodies. Not only does rituximab kill CD20+ lymphoma cells, but it also substantially depletes normal B cells from the peripheral blood.⁵ Tissue depletion also occurs, but is perhaps less profound, and in any case has been little documented in patients.⁶ The mechanism of B cell depletion appears to be a combination of FcγR dependent ADCC (antibody dependent cell mediated cytotoxicity), complement mediated lysis, and apoptosis,⁷ although the relative contributions of these mechanisms in vivo remains to be determined. In addition, stimulation of the inhibitory FcγRIIB may also play a role in rituximab therapeutic effects.⁸

CLINICAL DATA

In 1997, the US Food and Drug Administration (FDA) approved rituximab for the treatment of low grade non-Hodgkin's B cell lymphomas.⁹ Since that time, it has been used in over 500 000 patients with generally excellent tolerability. Largely through a series of investigator sponsored trials supported in part by Genentech (South San Francisco, CA), the use of rituximab has been extended to a much wider spectrum of B cell malignancies, and strikingly, to a variety of autoimmune diseases in which B cells have been thought to play a role (fig 1). So far, blinded, randomised controlled trials (RCTs) have been completed only for rheumatoid arthritis, with clear indications of efficacy. Published uncontrolled series for idiopathic thrombocytopenic purpura, polyneuropathy, systemic lupus erythematosus, and Wegener's vasculitis, have given very suggestive signals of potential usefulness. In all, anecdotal information is available on some 30 autoimmune conditions (box 1).

The data for rheumatoid arthritis are most extensive.¹⁰ Laboratory studies of rheumatoid synovium and mouse/human chimeras had suggested a role for B cells in this disease.^{11 12} Following the pioneering work by Jo Edwards in a small uncontrolled series of patients who had been resistant to conventional therapy,¹³ an RCT showed efficacy similar to what has been seen in the antitumour necrosis factor (anti-TNF) trials (43% American College of Rheumatology (ACR) 50 at 24 weeks with the combination of methotrexate and rituximab), and a further trial has confirmed this (unpublished).⁹ Salient features of the 2004 follow up article are:

- Only some of the efficacy was lost at 48 weeks, even though the patients were not re-treated with rituximab.

- The peripheral B cell count was predictably profoundly depressed one month after treatment, and started to recover after about four months.
- Rheumatoid factor titres fell.
- No repeated serious safety concerns emerged.

Other factors such as concomitant use of steroids, dosing, re-treatment, and patient eligibility need to be worked out further. Additional controlled trials are ongoing (box 2).

Two other recent publications show striking anecdotal data suggesting that rituximab may work in Wegener's granulomatosis¹⁴ and dermatomyositis.¹⁵ In Wegener's granulomatosis, 11 patients considered to be cyclophosphamide failures were treated with rituximab and steroids, and all responded dramatically in terms of disease activity and antineutrophilic cytoplasmic antibody (ANCA) titres. Two of these patients further responded to re-treatment when they experienced flares after six months. In dermatomyositis, six patients who had failed cytotoxic therapy responded to rituximab with increased strength, decreased rash, and improved pulmonary functions. In both these diseases, multicentre controlled trials have been initiated to establish efficacy (see box 2).

In systemic lupus erythematosus (SLE), several small uncontrolled series and case reports have suggested efficacy, and again controlled trials are currently ongoing to obtain formal proof.^{16 17} We have recently completed enrolment in a 24 patient, open label phase 1/2 trial of patients with moderately active SLE (box 3). The data will be published in detail elsewhere. In brief, patients who received the full therapeutic dose (375 mg/m² once a week ×4) showed profound B cell depletion in all cases save one. All patients showed improvement in their disease activity indices. The SLEDAI (SLE Disease Activity Index) score at four months after initiation of therapy correlated highly with the B cell level in the peripheral blood. Patients who had the full dose mostly did not make human antichimeric antibodies (HACA; antibodies to rituximab). The consistency of B cell depletion and the relatively low level of HACA formation contrast with what was seen in a similar trial conducted at the University

Figure 1 Publications in the medical literature on rituximab and autoimmune diseases, by year. PubMed was searched for "rituximab" NOT "malignant".

Box 1: Autoimmune diseases where rituximab has anecdotal suggestions of efficacy

- Rheumatoid arthritis‡
- Systemic lupus erythematosus
- Wegener's granulomatosis
- Idiopathic membranous nephritis
- Essential mixed cryoglobulinaemia
- Dermatomyositis
- Sjögren's syndrome
- Multiple sclerosis
- Opsoclonus-myoclonus syndrome
- Multifocal motor neuropathy
- Chronic inflammatory demyelinating poly(radiculo)-neuropathy (CIDP)
- Myasthenia gravis
- Monoclonal IgM-mediated peripheral neuropathy
- Acquired Factor V, VIII, and IX inhibitors
- Evan's syndrome
- Pure red cell aplasia
- Acquired angioedema
- Idiopathic thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Autoimmune haemolytic anaemia
- Cold agglutinin disease
- Acquired insulin resistance
- Pemphigus vulgaris
- Pemphigus foliaceus
- Transplant rejection
- Chronic graft versus host disease
- Graves' disease
- Hashimoto's thyroiditis
- Antiphospholipid syndrome

‡Rheumatoid arthritis also has RCT supported data for efficacy

of Rochester, for reasons that are not apparent.^{18–21} HACA formation had been quite infrequent in the lymphoma populations surveyed, although most patients were not tested for this. In our study we measured patients' serum titres of antibodies to tetanus toxoid and to pneumococcal polysaccharides. We then gave the patients boosters for tetanus and Pneumovax® and tested again. The ability of patients to respond to antigenic re-challenges varied, and it may be that such a functional measure could be more representative of systemic B cell depletion than cell counts in samples of peripheral blood. Similar immunisation data from controlled trials will be very useful in this regard.

FUTURE DIRECTIONS (BOX 4)

It seems likely that rituximab, and other anti-B cell therapies, will play an increasingly important role in the therapeutic armamentarium for the autoimmune diseases. The proof of efficacy for rituximab in rheumatoid arthritis seems to be reasonably secure, although we wait additional results from RCTs. Rheumatologists and others are already using rituximab off-label in a variety of conditions. It would be expected that some of the upcoming RCTs will indeed demonstrate efficacy in diseases other than rheumatoid arthritis. Such proof will be very important to the further development of

Box 2: New randomised clinical trials for rituximab in autoimmune diseases

- Rheumatoid arthritis (company sponsored)
- Systemic lupus erythematosus (two company sponsored)
- Dermatomyositis/polymyositis/juvenile dermatomyositis (National Institute of Arthritis and Musculoskeletal Diseases)
- Antineutrophilic cytoplasmic antibodies + vasculitis (company + Immune Tolerance Network)

Box 3: Phase 1/2 safety and efficacy trial of rituximab in systemic lupus erythematosus

- Universities of Pennsylvania, Rochester, and Colorado
- N = 24
- Eighteen completed full dose therapy
- No clear safety signal
- Suggestion of efficacy
- All but one B cell depleted

Box 4: Future considerations

- Humanised antibody
- Redosing decisions
- Combination therapy
- Mechanistic studies
- Safety concerns

the use of biologicals in autoimmune diseases. New anti-B cell reagents that recognise CD20 (for example, a humanised anti-CD20), or other B cell determinants such as CD22, will also be developed. It is unlikely that B cell depletion will cure most patients with autoimmune diseases, and in fact, in many experiences re-treatment has been necessary and effective. How should re-treatment be handled: by a fixed regimen, say every six months? When B cells return? When signs or symptoms return? These are key questions that would be complex to resolve by controlled trials. What kind of concomitant therapies should be used? In the rheumatoid arthritis trial, the combination of rituximab and methotrexate appeared to do better than rituximab alone. Should rituximab always be combined with some cytotoxic? How about the combination of biologicals?

In all of this a further understanding of the mechanisms of B cell participation in disease and the mechanisms of action of rituximab would greatly facilitate additional development of therapeutic approaches.²² B cells play many roles in the immune response (box 5), and it is not known which of those roles are essential in different diseases. Clearly, the involvement of B cells goes beyond that of autoantibody production.

A further issue is one of safety (box 6). The most consistent adverse reactions to rituximab have the immediate infusion reactions, most often after the first dose, and are usually relatively mild.²³ These reactions have not been particularly troubling in the autoimmune disease populations. Serum sickness has been seen.²⁴ With B cell depletion so profound,

Box 5: Potential roles of B cells in autoimmune diseases

- Make autoantibodies
- Regulate autoantibody specificities
- Lose tolerance
- Regulate T cells
- Regulate other B cells
- Are regulated by T cells
- Produce cytokines
- Present antigen
- Influence dendritic cells
- Regulate lymphoid structure

the possibility of infectious complications remains a persistent concern. Although individual cases of serious infections, including hepatitis B reactivation,²⁵ have been reported, surprisingly there has not been a general experience of increased infections, even in patients who have been re-treated. However, it will be essential to remain vigilant in this regard if rituximab obtains widespread use in autoimmune populations. The occurrence of reactivated tuberculosis with the anti-TNF therapy²⁶ and, more recently, progressive multifocal leukoencephalopathy with natalizumab,²⁵ are sobering illustrations of what can happen when we use therapies with such exquisitely specific and effective targeting capabilities.

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Competing interests: Dr Eisenberg has consulted with Genentech, Inc., and Biogen Idec as part of this project.

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Box 6: Safety concerns

- Serum sickness
- Infection: hepatitis B
- Cytopenias
- Others?

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