B-lymphocyte depletion therapy in rheumatoid arthritis and other autoimmune disorders

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Abstract

B-lymphocyte depletion therapy is being explored in a wide range of autoimmune disorders. In many, there is early evidence for efficacy, and immunosuppression has not been a major problem. The mechanism of action is unclear, but appears to be consistent with the lowering of autoantibody levels, where relevant antibodies are quantifiable. An interesting finding is the persistence of clinical improvement for periods of 1 year or more after B-lymphocyte return, which supports the concept that stochastic generation of rare pathogenic B-lymphocyte subsets may be a rate-limiting step in pathogenesis.

Key words: CD20, rituximab, systemic lupus erythematosus. Abbreviations used: ITP, immune thrombocytopenic purpura; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; FcyR, Fcy receptor.

Introduction

By April 2002, over 300 individuals with autoimmune disease had received B-lymphocyte depletion therapy (Table 1). Although there may be positive reporting bias, the impression from open prospective series and case reports is of substantial benefit [1-29]. Not every subject with every disease has responded, but at least in IgM-associated neuropathies, rheumatoid arthritis (RA), immune thrombocytopenic purpura (ITP) and systemic lupus erythematosus (SLE), results look promising.

This initial success has led to the setting up of a randomized controlled trial in RA patients. It has encouraged the increasing use of B-lymphocyte depletion in life-threatening complications of less common autoimmune disorders. It has also raised a number of questions. Why are response rates higher in some conditions than others? Why do some subjects improve and others do not? Why is it that, although improvement can last for 1 year

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Table I

Published reports of the use of rituximab in autoimmune disease (further studies in progress)

C, cyclophosphamide; G, glucocorticoid; ATG, Anti-thymocyte globulin; haemolytic anaemia, 'warm', i.e. not with cold agglutinins; PRCA, pure red cell aplasia; GVHD, graft versus host disease. *Case report.

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Regulation of B-lymphocytes in Health and Disease

or more after return of circulating B-lymphocytes, most individuals relapse? What is the optimal protocol? Most critically, how does it work?

Rationale

The detailed rationale for B-lymphocyte depletion has varied for different conditions; however, the central concept has been the removal of the cellular source of pathogenic autoantibodies. Paradoxically, this should perhaps not have been expected. B-lymphocytes do not secrete large amounts of antibody. Antibody is produced in bulk by daughter plasma cells. The main agent in use at present for B-lymphocyte depletion is the anti-CD20 antibody rituximab. B-lymphocytes express CD20, but plasma cells express little or none. Many investigators may have made what now appears to be a largely erroneous assumption, i.e. that plasma cells are short-lived and dissipate rapidly. Evidence that this was not so was already available from lymphoma subjects treated with rituximab, in whom total immunoglobulin levels changed little, despite the absence of circulating B-lymphocytes for many months [30]. It seems that unclear thinking may have been felicitous, and that at least some autoantibodies do disappear relatively rapidly after B-lymphocyte depletion, which perhaps reflects an origin from a sub-population of short-living plasma cells.

Attempts to reduce autoantibody levels are easily justified in ITP, IgM-associated neuropathies, cryoglobulinaemia and SLE, in which a pathogenic role for autoantibodies is generally accepted. In dermatomyositis and RA, the role
of autoantibodies has been more contentious, but may become less so as the role of the immunoglobulin receptor FcγRIIIa comes to be appreciated.

FcγRIIIa ligation is now recognized as a key event in immune-complex-mediated inflammation. Small circulating immune complexes are well documented in RA, and the distribution and functional properties of FcγRIIIa fit well with the pathology of RA being due to an immune-complex–FcγRIIIa interaction that leads to cytokine release [31–35]. (The K/BxN transgenic mouse looks promising as a model for this effector mechanism [36].) Dermatomyositis, like ITP, responds to intravenously administered immunoglobulin, the most plausible explanation being that immune complexes based on anti-allotypic or anti-idiotypic antibodies saturate Fcγ receptor (FcγR) and thereby inhibit disease-related events. The implication is that dermatomyositis may also involve antibody–FcγR interactions.

The inclusion of RA as an antibody-mediated disorder goes against recent attempts to classify it as a ‘Th1 disease’; however, the Th1/Th2 paradigm may prove unhelpful with regard to autoimmunity. There remains no consistent evidence of loss of T-cell tolerance in human autoimmunity, suggesting that, even though conditions such as RA are T-cell-dependent, T-cells may have no primary role in disease initiation or mediation of inflammation [35]. This paradox can be resolved by the concept that a small number of autoreactive B-cell clones can perpetuate their own existence through mechanisms that include the ability to gain help from T-cells of normal reactivities [35]. The ability of rheumatoid factor B-cells to obtain help from any T-cell is well understood [37]. Potential mechanisms in other conditions need further exploration. The implication of such self-perpetuating B-lymphocyte clones in autoimmune disease brings in a new rationale for B-lymphocyte depletion; the arguments are the same as for lymphoma. If the relevant clones can be destroyed then there is a prospect of long-term remission. This was the rationale for B-lymphocyte depletion in RA and it remains the ultimate goal [2,3,35].

Mechanics of B-lymphocyte depletion

B-lymphocyte depletion protocols for autoimmunity have all made use of the chimaeric monoclonal IgG1, anti-CD20 antibody, rituximab. Rituximab was licensed for use against lymphoma in 1997–1998 and has therefore been available for off-label use. It is given by slow infusion over several hours. The dose recommended in lymphoma, four infusions of 375 mg/m² of body surface area at 1-week intervals, has been used in many protocols, but both lower and higher doses have been tried. Rituximab has often been used alone, but it has also been used in combination with cyclophosphamide and/or glucocorticoid (see Table 1) [1–29]. In lymphoma, febrile reactions to infusions are common, but they appear to be less so in autoimmune disease. Use of corticosteroid may be partly responsible for this.

The mechanism of cytotoxicity of rituximab is not clear, but may involve antibody-dependent cytotoxicity, complement-mediated lysis and/or the induction of apoptosis. There is some evidence for synergy between rituximab and other lympholytic agents, but the contribution of different agents and optimal combinations are not known. Although circulating B-lymphopenia is usually absolute, there is no information about the level of solid tissue depletion in humans. Primate studies suggest that depletion may be substantial but not total at the doses that are used at present [38].

One of the striking findings with the use of rituximab is the lack of evidence for increased rates of infection, despite the absence of circulating B-lymphocytes for long periods. Evidence from lymphoma patients is difficult to interpret because of the high rate of infection in control groups receiving chemotherapy. Nevertheless, the experience so far with autoimmune subjects is very encouraging. Lack of infection probably reflects the lack of a major decline in total immunoglobulin levels.

Clinical outcome

An initial study in five RA patients, using rituximab, cyclophosphamide and prednisolone, revealed that all five achieved and maintained major improvement for at least 6 months, and up to a maximum of 33 months, after treatment [2]. A further 17 patients who were treated on an open basis with modified protocols showed responses related to protocol intensity with comparable results at high dosage [3]. Results were less impressive when rituximab was used at a reduced dose without cyclophosphamide, or when the total rituximab dose was reduced to 500 mg/m² of body surface area. Further dose ranging studies will be required. The phase II randomized trial of 160 patients, which is currently in progress, will go some way towards this.

In peripheral neuropathies that are associated with IgM antibodies against neural antigens, rates
of improvement were high and improvement has been maintained by repeat treatment. Systematic outcome data are only available from one study in SLE [5], in which five out of six patients showed improvement in global disease activity scores. The sixth may well have had irreversible disease.

Studies in haematological disorders suggest that although there are major benefits, the rate of response may be lower. The larger studies with ITP patients show response rates of slightly more than 50%, with only a proportion of these being major, or near complete, responses. Series in haemolytic anaemia, both with and without cold agglutinins, are still small and at least one study reported disappointing results, despite good results in others [14]. Individual case reports indicate that benefits have been observed in a range of other disorders, but this must be seen in the context of unpublished experience, which includes failure of response in several instances.

Rates of response in different conditions may relate both to the protocol used and the nature of the disease. There are indications from studies of RA and SLE that inclusion of cyclophosphamide may increase response duration, but this remains unproven and should be clarified by the RA phase II trial. It seems likely that different diseases are differentially susceptible to B-lymphocyte depletion.

**Mechanism of therapeutic action**

The simplest explanation for the benefit of B-lymphocyte depletion therapy, and for the variation in response seen, remains the degree to which levels of pathogenic autoantibodies are decreased. In IgM-associated neuropathies, RA, myasthenia gravis and Wegener’s granuloma, decay of autoantibody levels appears to match clinical response reasonably well [1,2,19,20]. In SLE, anti-DNA antibodies are not related closely to clinical improvement, but the pathogenicity of these antibodies is uncertain. In other conditions, it is generally difficult to quantify relevant autoantibodies.

The apparent benefit of B-lymphocyte depletion in RA has spurred T-cell enthusiasts to suggest that benefit is due to removal of antigen-presenting cells involved in T-cell effector mechanisms. The most obvious of several problems with this view is that even in the few situations where B-lymphocytes are present at sites of pathology they usually form a tiny minority of antigen-presenting cells. Improvement after B-lymphocyte depletion often occurs over a period of several months, despite a more or less immediate reduction in B-lymphocyte numbers. The kinetics of relapse are also hard to reconcile with an action chiefly on antigen presenting function.

What has become clear, following the use of rituximab, is that our understanding of human B-lymphocyte and plasma cell kinetics is rudimentary. We have no explanation for the prolonged absence of circulating B-lymphocytes following the use of rituximab, sometimes for over 1 year, which is much longer than following high-dose cytotoxic therapy. It is not known how low circulating levels relate to B-lymphocyte numbers in secondary lymphoid organs. There is a significant possibility that depletion of developing B-cells is easy to achieve, but that depletion of memory B-cells is much more difficult, perhaps because of sequestration in micro-environments such as the follicle centre where cells are protected from killing by CD55 and CD59. Rates of disappearance of a range of different subsets of both protective and autoantibodies in patients with RA following B-lymphocyte depletion indicate wide heterogeneity (M. J. Leandro, J. C. W. Edwards, G. Cambridge, M. Ehrenstein, M. Salden and D. A. Webster, unpublished work). The contributions of B-lymphocyte and plasma cell survival to these changes remain to be established.

Perhaps the most important question with regard to kinetics at this stage of investigation of B-lymphocyte depletion for autoimmunity, is why patients relapse, but in many cases not for many months after circulating B-lymphocyte return. As indicated above, it may be that pathogenic B-lymphocyte clones have not been fully ablated. Alternatively, it may be that the continued production of autoantibodies by plasma cells is important. There is a suggestion that, with several conditions, partial responses tend to be followed by relapse at the time of B-lymphocyte repopulation, whereas complete responses are more likely to be maintained for longer.

The delay of several months in relapse after B-lymphocyte repopulation in about half of cases may be a critical clue to the mechanism of relapse. Our usual understanding of the immune response is that once antigen has been encountered, the process evolves to completion over a period of only approx. 3 weeks. An immune response that takes 1 year to re-evolve must have unusual rate-limiting steps. This may not be so surprising in the light of evidence that RA often initially evolves over a period of several years [39]. There is a strong suggestion that both initiation and reac-
tivation of disease may be dependent on infrequent stochastic events. The best candidate for this type of event is the chance generation of B-lymphocyte clones with immunoglobulin genes that encode a very small subset of autoantibody species that are capable of engaging the autocrine proliferation loop that is normally restricted to clones that recognize foreign antigens [35].

No firm conclusion can yet be drawn, but there are several lines of evidence to suggest that long-term remission in autoimmune disease may only be achievable if B-lymphocyte depletion is combined with some form of plasma cell depletion strategy. At present, no safe and effective antiplasma cell agents are available, but increased understanding of the survival signals required by plasma cells may lead to new therapeutic avenues. In the interim, B-lymphocyte depletion alone promises to be an important option for severe autoimmune disease that are refractory to standard therapies, even if treatment needs to be repeated at regular intervals.

References

Received 10 April 2002

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