Commentary

B cells as a therapeutic target in autoimmune disease

Jörg J Goronzy and Cornelia M Weyand

Departments of Medicine and Immunology, Mayo Clinic, Rochester, MN, USA

Corresponding author: Jörg J Goronzy (e-mail: goronzy.jorg@mayo.edu)

Received: 6 Jan 2003 Revisions requested: 5 Feb 2003 Revisions received: 17 Feb 2003 Accepted: 25 Feb 2003 Published: 19 Mar 2003

Arthritis Res Ther 2003, **5**:131-135 (DOI 10.1186/ar751)

Abstract

Depleting B cells with anti-CD20 monoclonal antibodies emerges as a new therapeutic strategy in autoimmune diseases. Preliminary clinical studies suggest therapeutic benefits in patients with classic autoantibody-mediated syndromes, such as autoimmune cytopenias. Treatment responses in rheumatoid arthritis have opened the discussion about whether mechanisms beyond the removal of potentially pathogenic antibodies are effective in B-cell depletion. B cells may modulate T-cell activity through capturing and presenting antigens or may participate in the neogenesis of lymphoid microstructures that amplify and deviate immune responses. Studies exploring which mechanisms are functional in which subset of patients hold the promise of providing new and rational treatment approaches for autoimmune syndromes.

Keywords: autoantibody, autoimmunity, B-cell depletion, rheumatoid arthritis, systemic lupus erythematosis

Introduction

The discovery of autoantibodies in chronic inflammatory diseases initiated an era of clinical investigation and established the foundation of modern clinical immunology. The original descriptions of antinuclear antibodies by Holman and Kunkel [1] and of rheumatoid factor by Rose and colleagues [2] were followed by the identification of numerous self-antigens that were recognized by autoantibodies. Antibodies to different autoantigens have remained one of the most important diagnostic tests in clinical immunology. In some diseases, these antibodies have been directly implicated in tissue damage. It is, therefore, not surprising that humoral autoimmunity was at center stage in the 1960s and 1970s and that various treatment approaches were designed to interfere specifically with autoantibody production or to remove autoantibodies from the circulation. Plasmapheresis was explored in the treatment of a variety of autoimmune syndromes, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and vasculitic syndromes. Plasmapheresis still has an accepted role in thrombotic thrombocytopenic purpura and cryoglobulinemia; however, in other chronic inflammatory diseases, plasmapheresis has had disappointing results. After 1980, treatment strategies no longer focused on the B cell and the removal of autoantibodies but, rather, focused on effector mechanisms of macrophages and the cytokines that are produced in inflammatory responses. Thus, the success of recent pilot studies that explored B-cell depletion as a therapeutic strategy came unexpectedly and has renewed interest in reconsidering the role of the B cell in these diseases [3,4].

A new therapeutic strategy – targeting CD20+ B cells

All pilot studies of B-cell-depleting treatments have targeted the CD20 antigen using a chimeric mouse/human antibody, rituximab. Expression of CD20 is restricted to B cells from the pre-B-cell stage to the immunoblast stage [5]. Lymphoid precursors and plasma cells are spared in CD20-directed depletion. CD20 is not shed from the cell surface and does not internalize upon antibody binding [6]. Rituximab binds complement and induces antibody-dependent cellular cytotoxicity, effectively depleting CD20-expressing cells. In addition, signaling via CD20

ACR 20 (50) (70) criteria = American College of Rheumatology criteria for 20% (50%) (70%) improvement; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus.

appears to activate proapoptotic pathways, further increasing the antibody's depleting activity [7]. Rituximab has been used in the treatment of B-cell non-Hodgkin's lymphoma as a single agent as well as in combination therapy, emphasizing its high B-cell-depleting potency [8]. In patients with lymphoma, rituximab infusion is frequently associated with a cytokine-release syndrome that probably results from CD20-mediated stimulation of tumor cells [9]. B-cell levels slowly recover over a period of approximately 6 months. Despite B-cell depletion, immunoglobulin levels are usually maintained, possibly as a consequence of plasma cells being spared.

B-cell depletion in antibody-mediated diseases

It is understandable that rituximab has been most frequently explored in autoimmune cytopenias, a disease group that is clearly linked to the function of pathogenic autoantibodies. The best response rates were found for hemolytic anemia in cold agglutinin disease, approaching 85% in one prospective study [10,11]. In other autoimmune cytopenias, such as other forms of hemolytic anemia or chronic autoimmune thrombocytopenia, response rates are lower and range from 30 to 50% [12–14]. These data confirm that, at least in some patients, plasma cells are not sufficient to maintain autoantibody levels and that continuous B-cell recruitment and activation are necessary to maintain autoantibody production. Some of the treated patients relapsed after the repopulation of B cells, consistent with the model that the breakdown of self-tolerance and the production of autoantibodies reflect a defect in T-cell biology and not a primary B-cell dysfunction. However, some patients have sustained remissions, suggesting that the depletion of autoimmune memory B cells can have a long-lasting effect. Loss of B-cell memory function has also been pinpointed as a cause of serious side effects in anti-CD20-directed therapy. Patients with B-cell lymphoma who received anti-CD20 antibody treatment experienced reactivated hepatitis B and parvovirus infection [15–17]. This is of particular concern in patients with hepatitis-C-associated mixed cryoglobulinemia. Preliminary data support the notion that the treatment is safe in these patients; however, larger studies with careful monitoring of hepatic outcome are awaited. A trial to be sponsored by the US National Institutes of Health is in the planning stage.

Although autoantibodies in autoimmune cytopenias and some other diseases, such as pemphigus and myasthenia gravis, have a direct role in tissue injury through the recognition of their antigen, their pathogenic roles in diseases such as Wegener's granulomatosis and SLE are less well defined. Experiences with B-cell depletion in these diseases are based on a few uncontrolled case reports. Specks and colleagues reported one patient with Wegener's granulomatosis who responded twice to B-cell depletion [18]. Treatment responses correlated with the diminution of antineutrophil cytoplasmic autoantibodies. Most of the initial case reports in patients with SLE involved patients with autoimmune hemolytic anemia. In a recent report, Leandro and colleagues described six patients with a variety of SLE manifestations who were treated with rituximab [19]. These six patients included three with WHO class IV nephritis at the time of treatment. Five of the six responded to varying degrees, the median BILAG (British Isles Lupus Assessment Group) global scores dropped from 14 (range 9–27) to 6 (range 3–8) at 6 months. All the patients continued to have fluctuations in disease activity and two had major relapses at 7 to 8 months, at a time when the B cells started to repopulate the immune system. Of interest, titers of double-stranded DNA antibody showed a variable response – all the patients had elevated titers, and a convincing titer decrease was seen in only two. Although encouraging, the overall results do not allow for any conclusions as to whether autoantibody production in patients with SLE is dependent on continuous recruitment and activation of B cells and whether transient B-cell depletion has an ameliorating effect on disease manifestations.

B-cell depletion in patients with rheumatoid arthritis

Most data on the effects of B-cell depletion in autoimmunity are available from patients with RA. Initially, Edwards and Cambridge reported on five patients with refractory RA, all of whom had major improvement in disease activity and achieved responses meeting ACR 70 criteria (American College of Rheumatology criteria for 70% improvement) [20]. These results were surprising because the prevailing paradigm of RA pathogenesis emphasizes the role of macrophage and fibroblast activation and the production of inflammatory mediators in the synovial tissue. Therapeutic effects of B-cell depletion obviously support the concept that cellular immune mechanisms and autoantibody production are critically involved in the disease process. The initial case reports were difficult to interpret, because all patients undergoing B-cell depletion also received high doses of steroids and intravenous cyclophosphamide, which are able to suppress cells of the innate immune system and to affect the production of inflammatory cytokines on their own. It was, therefore, very encouraging that DeVita and colleagues, who treated five patients, could confirm the initial observation [21]. Clinical responses were less impressive: only one patient achieved an ACR 70 response and another one an ACR 50 response. However, all five patients had failed to respond to previous treatments and did not receive concomitant immunosuppressive therapy. At the 2002 American College of Rheumatology meeting, Edwards reported preliminary results on 122 patients of a prospective randomized trial with 160 patients [22]. Thirty-two percent of the rituximab-treated patients with RA met the ACR 50 criteria, compared with 10% in the control group, further

supporting the notion that anti-CD20 treatment is beneficial in at least a subset of patients with RA.

Mechanisms of anti-CD20 treatment in rheumatoid arthritis

The question of which patients with RA respond to anti-CD20 treatment and whether the response is transient or long-term is directly linked to the role of B cells in the pathogenesis of RA [23,24]. One obvious possibility is that CD20 depletion suppresses the production of rheumatoid factor or other autoantibodies that have been described in RA. Indeed, decreased titers for rheumatoid factor were found in some patients after rituximab treatment, again supporting the notion that plasma cells are not sufficient and that active B-cell responses are needed to maintain these autoantibodies [25]. K/BXN mice, transgenic for a T-cell receptor specific for a widespread autoantigen, develop aggressive joint inflammation in strict dependence on autoantibodies [26]. Rheumatoid factors have been shown to enhance the activation of complement, and immune complexes containing IgG rheumatoid factor can crosslink Fcγ (crystallizable fragment gamma) receptors. However, in contrast to the animal model, neither for rheumatoid factor nor for any of the other autoantibodies in RA has an effector function been demonstrated that could be linked to joint inflammation. Disease activity in RA is usually not correlated with rheumatoid factor titers, and previous therapeutic attempts to reduce rheumatoid factor load have not yielded convincing clinical results [27]. One possible explanation is that it is not the removal of autoantibody but the depletion of B cells that is pivotal for treatment success in RA.

One important immunological function of B cells is their ability to capture and take up antigen via their antigen-specific receptor and present the processed antigen in the context of MHC class II antigens to stimulate $CD4^+$ T cells [28]. The selective uptake by antigen-specific B cells is far superior to the nonspecific uptake by other professional antigen-presenting cells. Thus, the repertoire of B cells determines which antigen is efficiently presented, particularly at low antigen doses. The B-cell repertoire is grossly abnormal in patients with RA: Chiorazzi and colleagues have shown that it is markedly contracted [29]. Whether this contraction is reversible with B-cell depletion remains to be explored. The chances of restoring a highly diverse B-cell repertoire are certainly higher for B cells than for T cells, whose repertoire is also markedly contracted in patients with RA [30]. However, attempts to restore diversity by T-cell depletion have fundamentally failed, most likely due to lack of thymic competence [31,32]. In contrast, the ability to generate new B cells appears less compromised with advancing age and disease. In addition, rituximab spares precursor B cells and thus should not compromise the host's ability to regenerate a healthy and diverse B-cell pool.

The antigen-presenting function of B cells is of particular relevance for those that produce rheumatoid factor. Cell-surface immunoglobulins with rheumatoid factor specificity enable the B cell to capture and ingest IgG immune complexes, which can contain a variety of different exogenous and endogenous antigens. Such antigens are presented to T cells and initiate a T-cell response. Carson and colleagues have hypothesized that this is the main function of physiological rheumatoid-factor-producing B cells, which are preferentially found in the mantle zones of lymphoid follicles [33]. Expansion of a B-cell subset specialized in the uptake and presentation of immunocomplexed antigens could shift the balance between T-cell tolerance and T-cell immunity, providing a unique pathomechanism for RA. Depletion of such B cells with rituximab could possibly restore this balance.

A second important regulatory role of B cells relates to their contribution to lymphoid follicle and germinal center formation [34]. B-cell differentiation and B-cell memory formation are critically linked to cell–cell interactions that occur in these specialized microstructures. Complex three-dimensional arrangements of lymphocytes optimize the capture and presentation of antigen and are excellent facilitators of T-cell stimulation [35]. The formation of ectopic lymphoid microstructures is one of the characteristic findings for the synovial lesions in RA [24]. Several molecular pathways have been implicated in regulating the generation of functional germinal centers. The most important were CXCL13, a chemokine determining the recruitment of B cells, and lymphotoxin-β [34,36]. The requirement for CXCL13 and lymphotoxin-β may be related to the formation of follicular dendritic cell networks, essential structural elements of germinal centers. Ectopic lymphoid follicles are formed in the synovial tissue in about 40% of all patients with RA. In about one-half of these patients, follicles have an established network of follicular dendritic cells and show characteristic features of germinal center transformation [37,38]. These synovial tissues are characterized by high production of CXCL13 and lymphotoxin-β [39,40]. Several cellular sources for CXCL13 have been identified, including endothelial cells and synovial fibroblasts. Lymphotoxin-β was typically found on mantle-zone B cells. In such synovial tissues, the T-cell responses are B-cell-dependent. Depletion of B cells with rituximab in severe combined immunodeficiency mice that were engrafted with human synovium from patients with RA significantly suppressed the production of interferon-γ and several macrophage-derived cytokines such as tumor necrosis factor-α and interleukin-1β [41]. Synovial lesions from rituximab-treated patients have not been recovered for studies. However, the experiments in the human-synovium–severe-combined-immunodeficiency-mouse model bear close resemblance to the human disease, and similar molecular pathways can be expected to be affected.

Conclusion

The treatment studies with rituximab have created a new treatment strategy that apparently acts upstream of the current treatment regimens employing cytokine blockage and that may be well suitable for a subset of patients. Identifying the mechanisms by which B cells control disease activity will be necessary to determine who will benefit most from this treatment approach. RA currently offers the best model for study. In applying this strategy, one needs to discern which patient cohort would be best served. Are the responder patients those 20% who have germinal centers in the inflamed tissue; are the best candidates those who have a severely contracted B-cell repertoire; or do patients who have high titers of rheumatoid factors benefit the most? A second important question is how long-lasting the response is. Patients with lymphoma who have undergone rituximab treatment start to repopulate the B-cell compartment about 6 months after the treatment ends. The kinetics appears to be similar in patients with autoimmune diseases. On the positive side, immunocompetence seems to be regained with the generation of new B cells. However, it is possible that B-cell recovery coincides with disease relapse. Because antibody responses to rituximab itself occur infrequently, retreatment is an option in most patients. However, repeated cycles of B-cell depletion may seriously compromise protective humoral immunity [42]. Other treatment strategies targeting B cells are currently in development. An interesting avenue is the disruption of cytokine networks that regulate B-cell development and survival, such as the blockade of the cytokine, B lymphocyte stimulator [43]. Understanding precisely how rituximab suppresses autoimmunity holds promise for deciphering the role of autoantibodies in human diseases and will be helpful in identifying new therapeutic targets.

Competing interests

None declared.

Acknowledgements

Supported in part by grants from the National Institutes of Health (AR 42457, AR 41974 and AI 44142) and by the Mayo Foundation. We thank James W Fulbright for assistance in preparing this manuscript and Linda H Arneson for secretarial support.

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Correspondence

Jörg J Goronzy, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel: +1 507 284 1650; fax: +1 507 284 5045; e-mail: goronzy.jorg@mayo.edu