Commentary
SLE

Rituximab in lupus

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Abstract

B cells are essential to the development of systemic lupus erythematosus (SLE). The chimeric monoclonal antibody rituximab depletes B cells by targeting the pan-B-cell surface marker CD20. Preliminary experience with this agent in SLE and other autoimmune diseases has been encouraging. Controlled trials in SLE will be necessary to determine whether rituximab is useful therapy in this disease, and will teach us more about the roles of B cells in its pathogenesis.

Keywords: B cells, CD20, rituximab, systemic lupus erythematosus

Introduction: B cells in systemic lupus erythematosus

A central feature of systemic lupus erythematosus (SLE) is the loss of B-cell tolerance. At least some autoantibodies from a limited spectrum of reactivities against mainly intracellular antigens are usually present, and probably account for some of the pathological manifestations. Although the numbers of B cells in the peripheral blood are often decreased, those that are present have abnormal phenotypes indicative of activation [1].

In addition, substantial evidence from mouse models of systemic autoimmunity clearly implicates the central role of B cells [2]. In several spontaneous models, the genetic abnormalities that cause the loss of tolerance must be expressed in those B cells that become autoimmune [3]. A wide variety of single gene abnormalities that are largely or solely expressed in B cells also leads to lupus-like systemic autoimmunity, either by lack of function through spontaneous mutations or knockout transgenics, or through hyperexpression of exogenous transgenes [4]. If B cells are removed from lupus models by genetic manipulations or chronic antibody therapy, the syndrome is largely suppressed, including T-cell abnormalities [5].

Other studies in mice genetically without B cells also implicate B cells in a number of immunoregulatory interactions that go beyond their clear role as the precursor of antibody forming cells [6]. B cells can regulate T cells, dendritic cells and other B cells. They can produce a variety of cytokines, including IL-4 and IL-10, and even can differentiate into subtypes that secrete certain sets of cytokines, analogous to T helper type 1 and T helper type 2 cells [7]. B cells are superb antigen presenting cells, since they can express MHC class II as well as co-stimulatory molecules such as CD80 and CD86, and their cell surface immunuoglobulin antigen receptor is ideal for focusing and concentrating specific protein molecules [8].

Curiously, at present we do not know for certain what role B cells play in human SLE [9]. Some clinical manifestations appear to be antibody mediated, such as hemolytic anemia and glomerular inflammation, but the pathogenesis of many of the aspects of the disease remains obscure, and most of the disease-associated autoantibodies do not appear to have a direct pathogenic role. The potential immunopathogenic importance of B cells is implicated in the occasional case reports of SLE patients that developed common variable immunodeficiency and showed improvement in the manifestations of SLE concomitant with loss of B-cell function [10].

IL = interleukin; MHC = major histocompatibility complex; SLE = systemic lupus erythematosus.

Rituximab and B-cell depletion

It was thus a reasonable hypothesis that removing B cells in SLE might have a positive therapeutic effect [11]. The availability of Rituxan® (rituximab) (Genentech, South San Francisco, CA, USA) made it possible to test this hypothesis [12]. Rituximab is a chimeric monoclonal antibody reagent consisting of human IgG_1 and kappa constant regions, and of mouse variable regions from a hybridoma directed at human CD20. CD20 is a specific B-cell marker present in all stages of B-cell development except the earliest and the latest [13]. Its cell function is unknown (CD20 knockout mice have no obvious B-cell deficits [14]) but it is expressed at high levels, it does not shed or endocytose when exposed to antibody, and it does not exist in a soluble form [15]. These features predicted that CD20 might be an excellent target for therapy directed at B-cell malignancies. This in fact proved to be the case, and rituximab was approved in 1997 for treatment of non-Hodgkin B-cell lymphomas [12]. After four weekly intravenous doses, rituximab also depletes normal B cells from the peripheral blood almost completely in most patients, and this depletion persists for 6 months and more, well beyond the persistence of the rituximab itself. Importantly, the extent of depletion of B cells from peripheral lymphoid organs is not known. However, serum immunoglobulins do not fall substantially during treatment, and increased infections have not been found to be a complication.

After rituximab received Food and Drug Administration approval for lymphoma, several investigators began trying it in uncontrolled series of patients with a variety of autoimmune diseases. The hope was not only that the drug might be therapeutically effective, but also that through monitoring its use we would learn a great deal about the role of B cells in the pathogenesis of these conditions. Encouraging anecdotal reports have appeared for a potential response to rituximab of patients with rheumatoid arthritis, polymyositis/dermatomyositis, idiopathic thrombocytopenia purpura, essential mixed cryoglobulinemia, hemolytic anemia, myasthenia gravis, Wegener's granulomatosis, and IgM-mediated neuropathy, as well as patients with SLE [16–23]. This approach has recently received a major impetus from the preliminary report of substantial efficacy in a controlled trial in rheumatoid arthritis [24].

So what about SLE? A published experience with six patients looked promising, as did a few individual anecdotes [17]. A phase I trial from Looney and colleagues showed improvement in certain subgroups in a *post hoc* analysis [25]. Our own phase I trial also has examples of patients who have improved clinically and who have decreased steroid usage after treatment (unpublished data). The safety profile has so far been good, as would have been predicted from the extensive experience (over 300,000 patients) in individuals with B-cell malignancies, although it must not be forgotten that rare cases of severe, fatal infusion reactions have been reported [26]. Surprisingly, many of the SLE patients developed human antichimeric antibody responses, perhaps in part because they did not receive the full therapeutic dose in the early dose-escalation period of the protocols.

At this point, it is essential that controlled trials be conducted to determine for certain whether rituximab has a clinically useful therapeutic effect in SLE. If efficacy could be established for one particular manifestation, such as renal disease or skin disease, or on the basis of overall disease scores, it would add an important additional drug to our approach to SLE in general. If rituximab permitted substantially lower use of steroids or cytotoxics, particularly cyclophosphamide, it would be a significant advance in patient safety.

What can we expect with rituximab treatment of SLE? The data so far indicate that autoantibodies, such as anti-DNA, are not suppressed. This is in distinction to what has been seen in the rheumatoid population, where both rheumatoid factors and anticyclic citrullinated peptide antibodies decreased [27]. Anecdotally, skin and musculoskeletal manifestations may have been particularly responsive. All of the phase I trials and case reports have so far been short term. If rituximab can be shown to be effective, how will it be appropriately used? Perhaps in conjunction with cytotoxic or steroid therapy, as in the rheumatoid arthritis trial? What about repeat dosing? Will human antichimeric antibody (HACA) development be avoided by full dosing and by combination with cytotoxic agents, in parallel with the experience with infliximab [28]? If HACA do appear, will they either cause increased complications, such as infusion reactions, or will they dampen the effect of treatment or even retreatment by blocking binding of rituximab to CD20 or by changing pharmacokinetics? In most patients treated with rituximab, the B cells return to the peripheral blood starting about 6 months after treatment. Will the return of B cells signal a recrudescence of clinical disease? When should patients be retreated, and at what doses and for how long? If prolonged B-cell suppression is necessary to maintain clinical control, will this eventually lead to an immunosuppressed state with a high risk for pyogenic infections? Will it be possible to combine rituximab with other biologicals that interfere with, for example, T cell–B cell collaboration, in order to achieve greater clinical benefit with less risk? Once efficacy is established in a controlled setting, all of these questions will have to be addressed either by additional trials or by collective experience.

From a more theoretical point of view, a major issue revolves around the role of $CD20^+$ B cells in the pathogenesis of disease. If the key cells to target are the autoantibody forming cells themselves, then the effectiveness of rituximab would depend on the extent of persistence of the CD20 marker in this population, and the

longevity of those antibody forming cells that do not express CD20 [29]. If rituximab successfully could deplete the $CD20^+$ precursors of $CD20^-$ antibody forming cells, then these cells would not be replaced when they die off. Another issue is what the B-cell repertoire will look like when it returns, and what aspects of the disease are indeed B-cell dependent.

Conclusion

Given the variety of mouse models of SLE, and the fidelity with which they reproduce the spectrum of autoantibodies seen in SLE, it is unfortunate that no method currently exists to deplete B cells from mature, diseased animals as efficiently as rituximab depletes B cells in humans. If it were possible to model this therapeutic approach in mice, then we could get preliminary answers to many of the questions raised, and design our therapeutic approaches more logically. Although our and other laboratories are trying to develop this modality in mice, for the present it remains important that the trials to demonstrate safety and efficacy of rituximab in SLE, as well as in other autoimmune diseases, be accompanied by incisive studies of B-cell function and T-cell function that will provide insights into the disease mechanism and into the therapeutic potential of B-cell depletion.

Competing interests

Dr Eisenberg has received funding from Genentech to help support a trial of rituximab in SLE, and has served as a consultant for the use of rituximab in autoimmune diseases.

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References

1. Odendahl M, Jacobi A, Hansen A, Feist E, Hiepe F, Burmester GR, Lipsky PE, Radbruch A, Dorner T: **Disturbed peripheral B lymphocyte homeostasis in systemic lupus erythematosus.** *J Immunol* 2000, **165**:5970-5979.
2. Chan OT, Madaio MP, Shlomchik MJ: **The central and multiple roles of B cells in lupus pathogenesis.** *Immunol Rev* 1999, **169**:107-121.
3. Sobel ES, Katagiri T, Katagiri K, Morris SC, Cohen PL, Eisenberg RA: **An intrinsic B cell defect is required for the production of autoantibodies in the lpr model of murine systemic autoimmunity.** *J Exp Med* 1991, **173**:1441-1449.
4. Lawman S, Ehrenstein MR: **Many paths lead to lupus.** *Lupus* 2002, **11**:801-806.
5. Chan OT, Madaio MP, Shlomchik MJ: **B cells are required for lupus nephritis in the polygenic, Fas-intact MRL model of systemic autoimmunity.** *J Immunol* 1999, **163**:3592-3596.
6. Chan OT, Hannum LG, Haberman AM, Madaio MP, Shlomchik MJ: **A novel mouse with B cells but lacking serum antibody reveals an antibody-independent role for B cells in murine lupus.** *J Exp Med* 1999, **189**:1639-1648.
7. Lipsky PE: **Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity.** *Nat Immunol* 2001, **2**:764-766.
8. Rivera A, Chen CC, Ron N, Dougherty JP, Ron Y: **Role of B cells as antigen-presenting cells in vivo revisited: antigen-specific B cells are essential for T cell expansion in lymph nodes and for systemic T cell responses to low antigen concentrations.** *Int Immunol* 2001, **13**:1583-1593.
9. Youinou P, Lydyard PM, Mageed RA: **B cells underpin lupus immunopathology.** *Lupus* 2002, **11**:1-3.
10. Swaak A, van den Brink HG: **Case report: common variable immunodeficiency in a patient with systemic lupus erythematosus**. *Lupus* 1996, **5**:242-246.
11. Looney RJ: **Treating human autoimmune disease by depleting B cells [comment].** *Ann Rheum Dis* 2002, **61**:863-866.
12. Grillo-Lopez AJ, White CA, Varns C, Shen D, Wei A, McClure A, Dallaire BK: **Overview of the clinical development of rituximab: first monoclonal antibody approved for the treatment of lymphoma.** *Semin Oncol* 1999, **26**:66-73.
13. Tedder TF, Engel P: **CD20: a regulator of cell-cycle progression of B lymphocytes.** *Immunol Today* 1994, **15**:450-454.
14. O'Keefe TL, Williams GT, Davies SL, Neuberger MS: **Mice carrying a CD20 gene disruption.** *Immunogenetics* 1998, **48**:125-132.
15. Riley JK, Sliwkowski MX: **CD20: a gene in search of a function.** *Semin Oncol* 2000, **27**:17-24.
16. Leandro MJ, Edwards JC, Cambridge G: **Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion.** *Ann Rheum Dis* 2002, **61**:883-888.
17. Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA: **An open study of B lymphocyte depletion in systemic lupus erythematosus.** *Arthritis Rheum* 2002, **46**:2673-2677.
18. Stasi R, Pagano A, Stipa E, Amadori S: **Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura.** *Blood* 2001, **98**:952-957.
19. Levine TD, Pestronk A: **IgM antibody-related polyneuropathies: B-cell depletion chemotherapy using Rituximab.** *Neurology* 1999, **52**:1701-1704.
20. Weide R, Heymanns J, Koppler H: **The polyneuropathy associated with Waldenstrom's macroglobulinaemia can be treated effectively with chemotherapy and the anti-CD20 monoclonal antibody rituximab.** *Br J Haematol* 2000, **109**:838-841.
21. Specks U, Fervenza FC, McDonald TJ, Hogan MC: **Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy.** *Arthritis Rheum* 2001, **44**:2836-2840.
22. Zaja F, Russo D, Fuga G, Perella G, Baccarani M: **Rituximab for myasthenia gravis developing after bone marrow transplant.** *Neurology* 2000, **55**:1062-1063.
23. Treon SP, Anderson KC: **The use of rituximab in the treatment of malignant and nonmalignant plasma cell disorders.** *Semin Oncol* 2000, **27**:79-85.
24. Edwards JCW, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Close D, Stevens RM, Shaw TM: **Efficacy and safety of rituximab, a B-cell targeted chimeric monoclonal antibody: a randomized, placebo-controlled trial in patients with rheumatoid arthritis [abstract].** *Arthritis Rheum* 2002, **46**:S197.
25. Anolik JH, Campbell D, Felgar R, Rosenblatt J, Young F, Looney RJ: **B lymphocyte depletion in the treatment of systemic lupus (SLE): phase I/II trial of rituximab (Rituxan®) in SLE [abstract].** *Arthritis Rheum* 2002, **46**:S289.
26. Kunkel L, Wong A, Maneatis T, Nickas J, Brown T, Grillo-Lopez A, Benyunes M, Grobman B, Dillman RO: **Optimizing the use of rituximab for treatment of B-cell non-Hodgkin's lymphoma: a benefit-risk update.** *Semin Oncol* 2000, **27**:53-61.
27. Cambridge G, Leandro MJ, Edwards JCW, Ehrenstein M, Salden M, Webster D: **B lymphocyte depletion in patients with rheumatoid arthritis: serial studies of immunological parameters [abstract].** *Arthritis Rheum* 2002, **46**:S506.
28. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, Antoni C, Leeb B, Elliott MJ, Woody JN, Schaible TF, Feldmann M: **Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis.** *Arthritis Rheum* 1998, **41**:1552-1563.
29. Slifka MK, Ahmed R: **Long-lived plasma cells: a mechanism for maintaining persistent antibody production.** *Curr Opin Immunol* 1998, **10**:252-258.

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