Commentary

Targeting B cells in systemic lupus erythematosus: not just *déjà vu* all over again

Robert Eisenberg

Division of Rheumatology, Department of Medicine, University of Pennsylvania, School of Medicine, 756 BRBII/III, 421 Curie Boulevard, Philadelphia, PA 19104-6160, USA

Corresponding author: raemd@mail.med.upenn.edu

Published: 15 May 2006
This article is online at http://arthritis-research.com/content/8/3/108

Arthritis Research & Therapy 2006, **8:**108 (doi:10.1186/ar1967)

See related research article by Dörner *et al*., http://arthritis-research.com/content/8/3/R74

Abstract

Epratuzumab (anti-CD22) is a humanized monoclonal antibody that recognizes a pan-B-cell marker. It potentially downregulates B cell activity through negative signaling, as well as depleting B cells moderately. The uncontrolled series discussed by Dörner and colleagues in this issue of *Arthritis Research & Therapy* suggests that epratuzumab may be safe and efficacious for systemic lupus erythematosus. A randomized controlled trial is currently active to test this possibility.

The article by Dörner and colleagues in the current issue of *Arthritis Research & Therapy* describes an open-label phase I trial of the B cell-specific humanized monoclonal antibody epratuzumab (anti-CD22) in 14 patients with moderately active systemic lupus erythematosus (SLE) (one or more British Isles Lupus Assessment Group (BILAG) Bs in all patients except one) [1]. Clinical improvement was seen in all patients by 7 to 10 weeks after initiation of the 6-week course of four infusions. The infusions were generally well tolerated, and overall no repeated safety signals were seen. Other than a modest and inconsistent fall in B cell counts in peripheral blood, no laboratory parameters were affected, including autoantibodies and complement. These data are supportive of the rationale for the currently active randomized controlled trial of epratuzumab to establish efficacy in SLE.

Like the rituximab target (CD20), CD22 is a cell surface protein uniquely expressed on normal B cells from the early stages of development (pre-B) until differentiation into plasma cells [2,3]. Also like rituximab, the initial experience with epratuzumab was with B cell lymphomas, in which it has shown some suggestion of efficacy in uncontrolled series [4]. Beyond these obvious parallels, however, the stories diverge. The CD22 molecule can clearly deliver intracellular signals, either constitutively or after interaction with its ligand, which is an α2,6-sialic acid residue found in many glycoproteins, including IgM and other cell surface proteins. The effect of CD22 signaling is generally, but not entirely, negative or anti-stimulatory, both in terms of Ca^{2+} flux and protein tyrosine phosphorylation. It modifies signaling through other cell surface molecules, including the B cell receptor (BCR), CD19/21, and CD45. Mice in which the CD22 gene has been disrupted show hyperresponsiveness of B cells to BCR crosslinking, yet paradoxically a deficit in response to T cell-independent antigens. In conjunction with other genetic risks for autoimmunity, the lack of CD22 heightens the propensity to develop SLE [5,6]. In addition, mouse strains that spontaneously develop SLE on a multigenic basis preferentially express CD22 alleles that have functional deficiencies [7]. Finally, some human evidence also links CD22 polymorphisms to SLE [8]. Thus, the CD22 molecule is more than mainly just a useful target on B cells, as with CD20, but also has several functions that may be relevant to the pathogenesis of autoimmunity.

The potential efficacy of targeting CD22 in SLE might therefore not be mediated by the partial depletion of B cells observed. Epratuzumab might modify the function of B cells without killing them. It does not block interactions of CD22 with its ligand, as do some anti-CD22 monoclonal antibodies, but it does initiate signaling through the CD22 molecule [9]. Given the heterogeneity of CD22-mediated responses in experimental systems, the possible consequences of such signaling in a given patient cannot readily be predicted. In fact, the published experience with epratuzumab in lymphoma, in which cell killing is presumably necessary for efficacy, suggests that this agent has only very modest capabilities when used alone and unaltered. Because the CD22 molecule is rapidly internalized after antibody binding (unlike CD20), it has been predicted that anti-CD22 would

BCR = B cell receptor; BILAG = British Isles Lupus Assessment Group; SLE = systemic lupus erythematosus.

be an excellent vehicle for the delivery of toxic moieties to B cells. This seems to be true, because epratuzumab conjugated with toxin or radiolabel leads to substantially higher response rates in B cell lymphomas than the agent alone [10]. Such approaches also create more clinical adverse reactions and would probably not be acceptable for use in SLE. Another curious finding in the lymphoma experience is that combining epratuzumab with rituximab, although not increasing the overall clinical response rate above what is seen with rituximab alone, may lead to a substantially higher number of complete responders or persistent responders [11].

The nearly complete lack of changes in biological markers in patients treated with epratuzumab on the one hand reflects the benignity of the agent. It can be infused rapidly over less than 1 hour without serious infusion reactions, and so far no major toxicities have emerged. One trivial possibility is that the binding of CD22 changes little in the organism, and thus the current randomized controlled trial may fail to find evidence for therapeutic efficacy. Assuming, however, that epratuzumab will be shown to improve SLE clinically, then the lack of biological markers of its effects may in fact be a drawback to its rational use. Because even the fall in B cells in peripheral blood is quite modest and inconsistent (Figure 5 in [1]), there is at present no obvious way to follow patients for physiological effects of the treatment or for the need for retreatment, which will probably be required as is true of rituximab [1].

It is unfortunate that there is only limited preclinical information available on the signaling mediated by epratuzumab binding to CD22 on various subsets of B cells [9]. Several monoclonal antibodies against mouse CD22 have been available for several decades, yet no studies of using these reagents in mouse SLE models have appeared. In our own unpublished experience, we have found that at least two of the anti-mouse CD22 monoclonal antibodies do not deplete B cells *in vivo.*

The failure to find evidence for an immune response by the treated patients to the administered epratuzumab (human anti-humanized antibody or HAHA) is very reassuring, and contrasts with the rituximab experience, in which in SLE (as opposed to rheumatoid arthritis or lymphoma) a substantial fraction of patients responded to the agent with human anti-chimeric antibodies or HACA [12]. Presumably, this result depends partly on the lesser degree of 'foreignness' of the humanized reagent versus a chimeric one.

So what might be the future for epratuzumab in SLE or perhaps other autoimmune diseases? In part, the rituximab experience will determine the way, because development of that drug is much further advanced, with 9 years of approved use in lymphoma and recent approval in rheumatoid arthritis. However, it seems unlikely that epratuzumab will be just a weaker cousin of rituximab. Its mechanisms of action are probably quite distinct, and therefore its spectrum of clinical usefulness should not be completely overlapping. Perhaps it will synergize with rituximab or other biologicals, as is suggested in the lymphoma experience.

Competing interests

RE has received support from Genentech for investigator and industry sponsored clinical trials, basic laboratory work and consultations regarding the development of rituximab for use in autoimmune diseases. RE has been involved with the development of anti-CD20 for SLE

References

1. Dörner T, Kaufmann J, Wegener WA, Teoh N, Goldenberg DM, Burmester GR: **Initial clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy of systemic lupus erythematosus.** *Arthritis Res Ther* 2006, **8:**R74.
2. Tedder TF, Poe JC, Haas KM: **CD22: a multifunctional receptor that regulates B lymphocyte survival and signal transduction.** *Adv Immunol* 2005, **88:**1-50.
3. Eisenberg R, Looney RJ: **The therapeutic potential of anti-CD20 'what do B-cells do?'.** *Clin Immunol* 2005, **117:**207-213.
4. Leonard JP, Coleman M, Ketas JC, Chadburn A, Ely S, Furman RR, Wegener WA, Hansen HJ, Ziccardi H, Eschenberg M, *et al.*: **Phase I/II trial of epratuzumab (humanized anti-CD22 antibody) in indolent non-Hodgkin's lymphoma.** *J Clin Oncol* 2003, **21:**3051-3059.
5. Otipoby KL, Andersson KB, Draves KE, Klaus SJ, Farr AG, Kerner JD, Perlmutter RM, Law CL, Clark EA: **CD22 regulates thymus-independent responses and the lifespan of B cells.** *Nature* 1996, **384:**634-637.
6. O'Keefe TL, Williams GT, Batista FD, Neuberger MS: **Deficiency in CD22, a B cell-specific inhibitory receptor, is sufficient to predispose to development of high affinity autoantibodies.** *J Exp Med* 1999, **189:**1307-1313.
7. Mary C, Laporte C, Parzy D, Santiago ML, Stefani F, Lajaunias F, Parkhouse RM, O'Keefe TL, Neuberger MS, Izui S, *et al.*: **Dysregulated expression of the Cd22 gene as a result of a short interspersed nucleotide element insertion in Cd22a lupus-prone mice.** *J Immunol* 2000, **165:**2987-2996.
8. Hatta Y, Tsuchiya N, Matsushita M, Shiota M, Hagiwara K, Tokunaga K: **Identification of the gene variations in human CD22.** *Immunogenetics* 1999, **49:**280-286.
9. Carnahan J, Wang P, Kendall R, Chen C, Hu S, Boone T, Juan T, Talvenheimo J, Montestruque S, Sun J, *et al.*: **Epratuzumab, a humanized monoclonal antibody targeting CD22: characterization of *in vitro* properties.** *Clin Cancer Res* 2003, **9:**3982S-3990S.
10. Postema EJ, Raemaekers JM, Oyen WJ, Boerman OC, Mandigers CM, Goldenberg DM, van Dongen GA, Corstens FH: **Final results of a phase I radioimmunotherapy trial using ^{186}Re-epratuzumab for the treatment of patients with non-Hodgkin's lymphoma.** *Clin Cancer Res* 2003, **9:**3995S-4002S.
11. Leonard JP, Coleman M, Ketas J, Ashe M, Fiore JM, Furman RR, Niesvizky R, Shore T, Chadburn A, Horne H, *et al.*: **Combination antibody therapy with epratuzumab and rituximab in relapsed or refractory non-Hodgkin's lymphoma.** *J Clin Oncol* 2005, **23:**5044-5051.
12. Looney RJ, Anolik JH, Campbell D, Felgar RE, Young F, Arend LJ, Sloand JA, Rosenblatt J, Sanz I: **B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab.** *Arthritis Rheum* 2004, **50:**2580-2589.