

Two negative randomized controlled trials in lupus: now what?

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Abstract

Recently, two large randomized controlled trials of distinct biologic therapies in systemic lupus erythematosus, B-cell depletion with rituximab and co-stimulatory blockade with CTLA4Ig (abatacept), failed to meet primary endpoints. Given the great need for new treatments in lupus, these results were met with disappointment and have left the rheumatology and immunology community searching for an explanation. Are these experimental agents ineffective in lupus or are there trial design issues or other considerations? In this commentary, we discuss our perspective on these results within the context of current understanding of the pathophysiology of lupus and the mechanism of action of biologic therapies.

Introduction and context

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with considerable heterogeneity, characterized by dysregulation of the immune system and production of hallmark autoantibodies. Because this disease continues to be associated with significant morbidity and a three- to fivefold increased mortality compared to the general population, there is great interest in the development of new and targeted treatment approaches [1]. Current treatments are generally broadly immunosuppressive and thus fraught with complications and sometimes lack of efficacy. However, major obstacles in finding efficacious therapies for SLE include the challenges of clinical trial design given the low prevalence of disease, great clinical heterogeneity, relapsing-remitting course, and lack of well-established endpoints [2–5]. These challenges have contributed to the fact that there have been no new drugs approved for the treatment of SLE in over 50 years.

Despite these difficulties, there is reason for optimism. A great deal of effort toward improving lupus clinical trial methodology has come from OMERACT (Outcome Measures in Rheumatology) [6], the US Food and Drug Administration (FDA) clinical trial guidelines [7], the Systemic Lupus International Collaborating Clinics

conference, and EULAR (European League Against Rheumatism) [5]. Moreover, our understanding about the pathogenesis of SLE has grown substantially in the past decade, leading to an explosion of promising biologic therapies.

Although multiple immunologic abnormalities are undoubtedly important for the development and clinical expression of SLE, a large body of evidence strongly points to the B cell as a central player in the pathogenesis of this disease [8]. The disease is characterized not only by defects in B-cell development, homeostasis, signaling, and tolerance but also by abnormalities in cytokines and chemokines either produced by B cells or with important B-cell influences [8]. B cells may participate in the immune dysregulation of SLE at multiple levels; serving as the precursors of antibody-secreting cells, taking up and presenting autoantigens to T cells, helping to regulate and organize inflammatory responses through cytokine and chemokine secretion (such as interleukin-10, interleukin-6, interferon- γ , and lymphotoxin- α), and regulating other immune cells. The importance of these latter functions has been clearly demonstrated in murine SLE, where B cells have been found to be critical to the development of disease even when they are unable to secrete autoantibodies [9].

Given the large body of evidence implicating abnormalities in the B-cell compartment in SLE, a rational approach to treatment involves B-cell depletion. FDA-approved for lymphoma and rheumatoid arthritis refractory to anti-tumor necrosis factor (TNF), B-cell depletion with the anti-CD20 monoclonal antibody rituximab has also shown benefit in open-label studies and case series (often for severe, refractory cases) for many other autoimmune diseases. As for SLE, our initial phase I/II study [10] and other similar open-label trials have provided strong support for this therapy, which has become a useful tool for refractory SLE with either renal, central nervous system, or hematological involvement [11–16]. Given the growing familiarity amongst rheumatologists with using this therapy in rheumatoid arthritis, there is expanding off-label use in other rheumatic diseases including SLE.

Rituximab is by no means the only promising biologic therapy under investigation in SLE. As an alternative to selective B-cell depletion, there has been great interest in targeting co-stimulatory signaling pathways as well as antagonizing cytokines that have prominent B-cell effects. Belimumab is a fully human monoclonal antibody that neutralizes soluble B-cell activating factor of the TNF family (BAFF), a cytokine important for B-cell survival and plasma cell differentiation. Mice over-expressing BAFF develop an SLE-like phenotype [17]. Moreover, lupus-prone mice have elevated levels of circulating BAFF, and administration of soluble BAFF receptors ameliorates disease progression and improves survival [18].

Blockade of co-stimulatory interactions between B7 on antigen-presenting cells (including B cells) and CD28 on T cells can also prevent activation of B cells in SLE. A fusion protein of the extracellular domain of cytotoxic T-lymphocyte antigen (CTLA) and immunoglobulin constant regions, CTLA4Ig, binds to B7 at a much higher affinity than CD28, thus blocking CD28-mediated co-stimulation and activation of T cells. CTLA4Ig (abatacept) is FDA approved for the treatment of rheumatoid arthritis [19] and, thus, similar to rituximab, is theoretically available for off-label use in SLE. In murine SLE, CTLA4Ig has demonstrated remarkable efficacy, improving both renal disease and survival [20].

Recent advances

Randomized controlled trials evaluating either rituximab or abatacept in the treatment of SLE have not been available until the recently reported studies at the 2008 American College of Rheumatology meeting. Merrill *et al.* [21,22] reported the EXPLORER trial, a

randomized, double-blind, placebo-controlled trial comparing rituximab to placebo in a 2:1 randomization in 257 active non-renal lupus patients. Inclusion criteria required at least one organ with British Isles Lupus Assessment Group (BILAG) A (severe disease activity) or at least two organs with BILAG B (moderate disease activity) at study entry while taking immune suppressive treatment. Two doses of 1,000 mg rituximab given 2 weeks apart were administered at baseline and again at 6 months. All patients continued their baseline treatments and received a 10 week course of high dose steroids up to 0.5 to 1.0 mg/kg depending on baseline steroids and the severity of their disease, with taper over an additional 8 weeks. The proportion of subjects achieving a partial clinical response (PCR) or major clinical response (MCR) at 52 weeks, with a primary endpoint as defined in Table 1, was no different in the treatment group (24.9% PCR including MCR) versus the placebo group (27.3%). There were also no differences between the groups for any of the pre-defined, mostly BILAG-based, secondary endpoints. Both groups had significant and sustained decreases in global BILAG and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores over time. In a pre-specified subgroup analysis of black and Hispanic subjects, who overall had lower placebo responses (15.7% PCR including MCR), there was a statistically significant difference with the addition of rituximab (33.8% PCR including MCR). Additionally, the subgroup of patients receiving methotrexate began to diverge at the end of the study, with a statistically significant increase in the placebo group disease activity and sustained response in the rituximab treated group. Finally, there was a suggestion of serological efficacy given the improvement in anti-DNA titers and complement levels in both groups, but with significant separation over time favoring rituximab. Overall, we conclude that the EXPLORER trial did not demonstrate clinical efficacy of rituximab in SLE since it did not meet any of the primary or secondary endpoints. However, the outcome suggests that most SLE patients with non-renal disease respond well to high dose steroids, and other immunosuppressive agents appear to be effective in maintaining a response, making it difficult to demonstrate a benefit of drug with this study design.

Merrill *et al.* also reported on an efficacy study of abatacept (CTLA4Ig) in reducing flares in non-renal SLE patients with active polyarthritis, serositis, or discoid lesions. This double-blind, placebo-controlled phase II trial randomized 180 subjects 2:1 to abatacept (10 mg/kg every other week for three doses, then monthly) or placebo for 1 year. Prednisone at 30 mg per day was given for 1 month and then tapered per protocol. The primary endpoint was the proportion of patients with a

Table 1. Recent SLE randomized, controlled trials of biologics

Reference	Size	Study drug	Endpoint	Select findings
Merrill <i>et al.</i> [21]	257	Rituximab	BILAG MCR/PCR* at 52 weeks	No significant difference in primary and secondary endpoints; subgroup analysis suggests benefit in black and Hispanic subjects
Merrill <i>et al.</i> [22]	180	Abatacept	BILAG flare by 1 year	No significant difference in primary and secondary endpoints; <i>post hoc</i> subgroup analysis suggests higher fraction of treated subjects on low dose prednisone without flare during final 2 months of study
Chatham <i>et al.</i> [23]	449	Belimumab	SELENA-SLEDAI at 52 weeks	No significant difference in primary and secondary endpoints; <i>post hoc</i> subgroup analysis suggests benefit in seropositive subjects as measured by novel SLE responder index

*MCR = all BILAG Cs or better in every organ system at 24 weeks with maintenance of this response until week 52; PCR = all BILAG Cs or better at week 24 and maintenance for 16 weeks or at most 1 BILAG B at week 24 and maintenance until week 52. BILAG, British Isles Lupus Assessment Group; MCR, major clinical response; PCR, partial clinical response; SELENA, Safety of Estrogen in Lupus Erythematosus National Assessment; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index.

new SLE flare (BILAG A or B) after the start of steroid taper over 1 year. There was no difference in the flare rates between the treatment group (79.7%) and placebo group (82.5%) or any of the secondary BILAG endpoints. In *post hoc* analyses, the question of whether BILAG B flare might be too stringent an endpoint to distinguish between placebo and active treatment was examined. An increased trend towards efficacy was found in the polyarthritis subgroup (95 patients) when only BILAG A flares were counted (36.5% in abatacept-treated patients versus 62.5% in the placebo group). When physician assessment was used to determine flare there was a difference in overall flare endpoint (63.6% in the abatacept group versus 82.3% in the placebo group). In addition, the proportion of patients who were on less than 7.5 mg prednisone and also rated to have no flare during months 10–12 was significantly higher in the abatacept group (42.4 versus 28.1% in the placebo group). As with the prior trial, we conclude that this study did not demonstrate efficacy of abatacept in non-renal SLE since the primary and secondary endpoints were not met. However, the *post hoc* analyses suggest to us that the outcome measures used were suboptimal and also that there may be greater efficacy of abatacept in the polyarthritis subset of disease.

As a point of comparison, belimumab (fully human monoclonal antibody against BAFF) for SLE has also been evaluated in a double-blind, placebo-controlled trial. Long-term follow-up for this trial was also presented at the American College of Rheumatology 2008 meeting [23]. This study did not meet its original primary efficacy endpoint, which was the change in the Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI score at week 52. However, 28% of patients were not serologically active [serologically active patients were defined as antinuclear antibody positive (+ANA) or anti-double-stranded DNA (dsDNA) positive and represented 72% (n = 321) of

study patients]. When only the serologically active subjects were analyzed *post hoc*, there was a statistically significant improvement in disease activity using a novel responder index [the SLE responder index (SRI)] based on a SELENA-SLEDAI improvement of four or more, no new BILAG 1A or 2B flares, and no worsening on the Physicians Global Assessment. As defined by the SRI, belimumab-treated seropositive subjects achieved a 46% response at week 52 versus 29% of placebo-treated subjects ($P < 0.05$). With open-label therapy, the SRI response increased to 55% by week 76 and persisted through 160 weeks. By week 52, 62% of belimumab-treated seropositive subjects had SELENA-SLEDAI flares versus 74% of placebo-treated subjects (P -values not significant). During long-term open treatment, the frequency of SELENA-SLEDAI flares declined to 7% at 3 years, suggestive of sustained improvement of disease activity with long-term therapy. Overall, we conclude that belimumab may have efficacy in non-renal SLE, particularly over long-term treatment, results that need to be confirmed in ongoing randomized studies with appropriately selected SLE patients and refined primary endpoints.

Implications for clinical practice

There are two broad explanations for the negative results of these two recently reported major trials: either the drugs are not effective or the trial design was suboptimal for demonstrating clinical efficacy. We do concede that animal models do not always accurately reflect what will happen in humans. Moreover, there have been notable examples of therapeutics that appeared effective in open-label studies until well controlled studies provided contrary evidence [24]. Nevertheless, given the large body of pre-clinical and open-label data in refractory disease suggesting efficacy, we should consider whether trial design was optimal for demonstrating benefit. Several recent editorials have addressed the formidable challenges of trial design in SLE [2,3,25]. No drug has

been approved for SLE in the past 50 years. Therefore, we do not have established methods for determining efficacy for new drugs, especially for non-renal SLE. The discussion that follows focuses on a number of key trial design issues within the context of the expected biological action of rituximab and abatacept.

Timing of endpoints

Steroids have a rapid onset of action but other agents may take time to become effective. Indeed, the results of the open-label extension of the belimumab trial suggest that endpoints longer than 1 year may be necessary to determine the full potential of biologic therapy. In EXPLORER, greater serological improvement (anti-dsDNA, C3, C4) was seen in patients treated with rituximab compared to placebo by the end of the trial. Although serological improvement was not associated with clinical improvement, a longer trial may have found benefit.

In the EXPLORER trial, this problem may have been compounded by re-treatment with rituximab at 6 months. One of the interesting findings from our pilot open-label trial of rituximab in SLE was the prolonged effect on the immune system with an expansion of transitional B-cells at reconstitution in patients who were good long-term responders [26]. We hypothesize that this B-cell subset may have immunoregulatory potential. If so, re-treatment with rituximab every 6 months would prevent the beneficial effects of an expanded transitional cell subset. This raises the important issue that both the timing and choice of endpoints need to be matched to the putative mechanism of action of the biologic agent. Even more, one might hypothesize that the treatment should be even more individualized, based on the degree of B-cell depletion. We have observed various degrees of residual memory B-cells in our rituximab-treated SLE patients, which we believe may adversely affect outcomes [27].

Choice of endpoints

None of the primary outcome measures used in any of the three discussed trials had been validated in clinical trials. Although a significant improvement in SLEDAI score of four points should provide good evidence of efficacy of an agent, this may not be a sensitive enough tool especially when measured against an effective 'placebo'. We believe the BILAG-based MCRs and PCRs defined in the EXPLORER study are also problematic. By these indexes, response needed to be achieved within 6 months and then maintained. However, based on the mechanism of action of rituximab in SLE, maximal response may not be achieved by 6 months. As previously discussed, we believe that depletion of B cells is responsible for only a fraction of the efficacy of

B-cell depletion therapy. Other putative critical mechanisms include the way the immune system reconstitutes (in which case long follow-up will be necessary beyond 1 year) and/or indirect effects of B-cell depletion on other arms of the immune system, like T cell subsets.

Secondary endpoints in EXPLORER (largely BILAG based), including the time to moderate or severe BILAG flare, and exploratory endpoints, including a decrease in global BILAG and SLEDAI score, were also not met. However, the abatacept study seems to suggest that outcome indicators that use BILAG flares as the measurement tool are also problematic, especially if a single BILAG B flare is counted. The novel SRI defined in the belimumab study *post hoc* analysis may provide a more sensitive and accurate measure of disease response. It notably combines the SLEDAI, the BILAG, and Physician Global Assessment, and has apparently been accepted by the FDA as an SLE disease assessment tool. Additional work is necessary in the lupus community, however, to decide upon and further validate appropriate composite outcome measures.

Another consideration is whether quantitative measures of disease activity in defined organ systems would provide more objective outcomes. Of note, ongoing trials of rituximab and abatacept in renal lupus have the dual advantage of hard outcomes in a more homogeneous population of SLE. On the other hand, outcome measures can only be part of the problem given the recent press release from Genentech that their study of rituximab in lupus nephritis, LUNAR, also failed to meet primary endpoints.

Patient population

Lupus is a very heterogeneous disease and the more targeted our therapies become, the more we will need to recognize subsets of patients who might benefit from any given targeted treatment. In the case of rituximab, disease manifestations caused directly by pathogenic antibodies produced by long-lived plasma cells are unlikely to improve with rituximab since this therapy does not have significant effects on long-lived plasma cells. Based on pre-clinical data, antibody independent mechanisms are important in renal lupus, and short-lived plasma cells may be the predominant source of anti-dsDNA. However, an important caveat to this is the demonstration in murine lupus that anti-dsDNA producing plasma cells can also be selected into the long-lived compartment [28] and may need to be eliminated for optimal efficacy. Open-label studies of B-cell depletion also suggest benefit in refractory disease that has been unresponsive to conventional treatments, including high dose steroids and cyclophosphamide. However, it will not be possible

to study this in a randomized fashion. These results do raise the additional question as to whether a synergistic effect exists between biologic agents and cyclophosphamide, a point further highlighted by the recently reported failure of LUNAR, where rituximab was combined with mycophenolate mofetil. An ongoing trial of humanized anti-CD20 (ocrelizumab) in lupus nephritis may address this issue given that a subset of patients will receive B-cell depletion therapy combined with cyclophosphamide.

Control regimen

In both the rituximab and abatacept studies, patients had active disease requiring treatment with moderate to high dose steroids in both the experimental and placebo arms. This is a reasonable design if your experimental therapy has a very strong therapeutic effect, but could miss effects that are still important when tested against an effective treatment. It has been suggested by others that the use of concomitant steroids be restricted as much as possible in future studies and a rapid taper devised [2]. In contrast, the belimumab study did not give a course of steroids at study entry, possibly explaining its relative success – that is, patients were not as sick and there was no course of steroids to obscure the effects of the experimental drug.

Conclusions

Because of these problems, we believe the door should not be closed on additional studies of B-cell depletion or co-stimulatory blockade in SLE. Based on our current knowledge future studies of biologics could include the following: first, trials with careful attention made to immunological biomarkers of response that allow for treatment modifications if suboptimal effects are seen. In particular, we are concerned about the adequacy of depletion of memory and pathogenic B-cell subsets in SLE after rituximab. The use of biologics needs to be refined and optimized. If B-cell depletion is inadequate in the majority of patients, especially in tissue sites, how can the clinical efficacy of B-cell depletion really be addressed? Second, additional trials of organ specific disease where there may be less heterogeneity and better outcome measures, for example, immune-mediated thrombocytopenia, cutaneous lupus, and central nervous system manifestations of lupus. Third, trials selecting patients based on pathophysiology that might be more responsive to the particular biologic, for example, rituximab treatment may be particularly efficacious for disease manifestations predominantly mediated by B cells and/or short-lived plasma cells (for example, cytopenias) but not those mediated by antibodies produced by long-lived plasma cells. The failure of rituximab in both general and now renal lupus does raise the question of whether reducing pathogenic

autoantibodies is key to maximal treatment efficacy. Abatacept may be particularly efficacious for T-cell driven disease manifestations. Of course, in many cases it may be difficult to separate disease subsets cleanly on this basis, and there is mechanistic cross-over (for example, indirect effects of B-cell depletion on T cells). Fourth, long-term trials designed to test whether rituximab or abatacept can prevent flares. Fifth, early intervention trials designed to prevent evolution of the autoimmune response perhaps before selection of autoreactivity into the long-lived plasma cell pool. Lastly, combining rituximab or abatacept with other therapies that might be synergistic, such as low dose cyclophosphamide. Indeed, open-label data in human SLE suggest potential synergy between cyclophosphamide and rituximab, while pre-clinical data in murine lupus nephritis suggest the same for cyclophosphamide and abatacept [20].

In conclusion, we believe that B-cell depletion and co-stimulatory blockade remain promising approaches to the treatment of at least a subset of SLE. Recent randomized clinical trials provide important information regarding optimizing study design and upon further analysis will hopefully yield clues regarding subsets of disease that may be responsive to distinct biologic approaches so that future trials may yield evidence-based proof of efficacy.

Abbreviations

BAFF, B-cell activating factor of the TNF family; BILAG, British Isles Lupus Assessment Group; CTLA, cytotoxic T-lymphocyte antigen; dsDNA, double-stranded DNA; EULAR, European League Against Rheumatism; FDA, Food and Drug Administration; MCR, major clinical response; OMERACT, Outcome Measures in Rheumatology; PCR, partial clinical response; SELENA, Safety of Estrogen in Lupus Erythematosus National Assessment; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SRI, SLE responder index; TNF, tumor necrosis factor.

Competing interests

JHA has received grants from Amgen Pharmaceuticals and Genentech for mechanistic studies in the context of lupus clinical trials, as well as grants from Proteolix and Vaccinex for drug development in murine models of lupus. She has served as a consultant for Genentech, Roche, Biogen, Proteolix, and Wyeth.

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References

- Bongu A, Chang E, Ramsey-Goldman R: **Can morbidity and mortality of SLE be improved?** *Best Pract Res Clin Rheumatol* 2002, **16**:313-32.
- Isenberg D, Gordon C, Merrill J, Urowitz M: **New therapies in systemic lupus erythematosus – trials, troubles and tribulations - working towards a solution.** *Lupus* 2008, **17**:967-70.
- Dall'Era M, Wofsy D: **Clinical trial design in systemic lupus erythematosus.** *Curr Opin Rheumatol* 2006, **18**:476-80.
- Bertsias G, Gordon C, Boumpas DT: **Clinical trials in systemic lupus erythematosus (SLE): lessons from the past as we proceed to the future – the EULAR recommendations for the management of SLE and the use of end-points in clinical trials.** *Lupus* 2008, **17**:437-42.
- Gordon C, Bertsias GK, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostál C, Font J, Gilboe IM, Houssiau F, Huizinga TW, Isenberg D, Kallenberg CG, Khamashta MA, Piette JC, Schneider M, Smolen JS, Sturfelt G, Tincani A, Van Vollenhoven R, Boumpas DT: **EULAR points to consider in conducting clinical trials in systemic lupus erythematosus.** *Ann Rheum Dis* 2009, **68**:470-6.
- Strand V, Gladman D, Isenberg D, Petri M, Smolen J, Tugwell P: **Endpoints: consensus recommendations from OMERACT IV. Outcome measures in rheumatology.** *Lupus* 2000, **9**:322-7.
- US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER): **Guidance for Industry: Systemic Lupus Erythematosus – Developing Drugs for Treatment.** March 2005. [www.fda.gov/cder/guidance/6496dft.pdf].
- Chan OT, Madaio MP, Shlomchik MJ: **The central and multiple roles of B cells in lupus pathogenesis.** *Immunol Rev* 1999, **169**:107-21.
- Shlomchik MJ, Madaio MP, Ni D, Trounstein M, Huszar D: **The role of B cells in lpr/lpr-induced autoimmunity.** *J Exp Med* 1994, **180**:1295-306.
- Looney RJ, Anolik JH, Campbell D, Felgar RE, Young F, Arend LJ, Sloan 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**:2580-9.
- Isenberg DA: **Treating patients with lupus with B-cell depletion.** *Lupus* 2008, **17**:400-4.
- Lindholm C, Borjesson-Asp K, Zendjanchi K, Sundqvist AC, Tarkowski A, Bokarewa M: **Longterm clinical and immunological effects of anti-CD20 treatment in patients with refractory systemic lupus erythematosus.** *J Rheumatol* 2008, **35**:826-33.
- Tokunaga M, Saito K, Kawabata D, Imura Y, Fujii T, Nakayamada S, Tsujimura S, Nawata M, Iwata S, Azuma T, Mimori T, Tanaka Y: **Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system.** *Ann Rheum Dis* 2007, **66**:470-5.
- F1000 Factor 3.0 Recommended
Evaluated by Gyorgy Nagy 31 May 2007
- Podolskaya A, Stadermann M, Pilkington C, Marks SD, Tullus K: **B cell depletion therapy for 19 patients with refractory systemic lupus erythematosus.** *Arch Dis Child* 2008, **93**:401-6.
- Jónsdóttir T, Gunnarsson I, Risselada A, Henriksson EV, Klareskog L, van Vollenhoven RF: **Treatment of refractory SLE with rituximab plus cyclophosphamide: clinical effects, serological changes, and predictors of response.** *Ann Rheum Dis* 2007, **67**:330-4.
- Amoura Z, Mazodier K, Michel M, Viallard J-F, Huong D, Chalumeau N, Cacoub P, Harle JR, Pellegrin JL, Kaplanski G, Godeau B, Piette JC: **Efficacy of rituximab in systemic lupus erythematosus: a series of 22 cases.** *Arthritis Rheum* 2007, **56**:S458.
- Mackay F, Woodcock SA, Lawton P, Ambrose C, Baetscher M, Schneider P, Tschopp J, Browning JL: **Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations.** *J Exp Med* 1999, **190**:1697-710.
- Gross J, Johnston J, Mudri S, Enselman R, Dillon SR, Madden K, Xu W, Parrish-Novak J, Foster D, Lofton-Day C, Moore M, Littau A, Grossman A, Haugen H, Foley K, Blumberg H, Harrison K, Kindsvogel W, Clegg CH: **TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease.** *Nature* 2000, **404**:995-9.
- Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, Russell A, Dougados M, Emery P, Nuamah IF, Williams GR, Becker JC, Hagerly DT, Moreland LW: **Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig.** *New Engl J Med* 2003, **349**:1907-15.
- Daikh DI, Wofsy D: **Cutting edge: reversal of murine lupus nephritis with CTLA4Ig and cyclophosphamide.** *J Immunol* 2001, **166**:2913-6.
- Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, Utset TO, Gordon C, Isenberg DA, Hsieh HJ, Zhang D, Brunetta PG: **Efficacy and safety of abatacept in patients with moderately to severely active systemic lupus erythematosus: results from the randomized, double-blind phase II/III study EXPLORER.** Presented at 72nd Annual Scientific Meeting of the American College of Rheumatology; October 24–29, 2008; San Francisco, CA. Abstract L12.
- Merrill JT, Burgos-Vargas R, Westhovens R, Chalmers A, D'Cruz D, Wallace D, Bae SC, Sigal L, Becker JC, Kelly S, Raghupathi K, Peng Y, Kinaszchuk M, Nash P: **The efficacy and safety of abatacept in SLE: results of a 12-month exploratory study.** Presented at 72nd Annual Scientific Meeting of the American College of Rheumatology; October 24–29, 2008; San Francisco, CA. Abstract L15.
- Chatham W, Furie R, Petri M, Ginzler EM, Wallace DJ, Stohl W, Strand V, Weinstein A, Zhong J, Hough D, Freimuth W: **Belimumab (fully human monoclonal antibody to BlyS) improved or stabilized systemic lupus erythematosus (SLE) disease activity over 3 years of therapy.** *Arthritis Rheum* 2008, **58**:S1088.
- Wegener's Granulomatosis Etanercept Trial (WGET) Research Group: **Etanercept plus standard therapy for Wegener's granulomatosis.** *N Engl J Med* 2005, **352**:351-61.
- Yuen SY, Pope JE: **Learning from past mistakes: assessing trial quality, power and eligibility in non-renal systemic lupus erythematosus randomized controlled trials.** *Rheumatology* 2008, **47**:1367-72.
- Anolik JH, Barnard J, Owen T, Zheng B, Kemsheiti S, Looney RJ, Sanz I: **Delayed memory B cell recovery in peripheral blood and lymphoid tissue in systemic lupus erythematosus after B cell depletion therapy.** *Arthritis Rheum* 2007, **56**:3044-56.
- Anolik JH, Barnard J, Cappione A, Pugh-Bernard AE, Felgar RE, Looney RJ, Sanz I: **Rituximab improves peripheral B cell abnormalities in human systemic lupus erythematosus.** *Arthritis Rheum* 2004, **50**:3580-90.
- Hoyer BF, Moser K, Hauser AE, Peddinghaus A, Voigt C, Eilat D, Radbruch A, Hiepe F, Manz RA: **Short-lived plasmablasts and long-lived plasma cells contribute to chronic humoral autoimmunity in NZB/W mice.** *J Exp Med* 2004, **199**:1577-84.
- F1000 Factor 3.0 Recommended
Evaluated by Ken Smith 17 Jun 2004