Th2 cells predominate over those of Th1 cells [2, 3]. Other reports, however, suggest a predominance of Th1 cells in SLE patients having class IV lupus nephritis as defined by the World Health Organization (WHO) [4]. We recently reported that the level of the Th1 chemokine interferon-induced protein 10 (IP-10)/CXCL10 is increased in the cerebrospinal fluid of patients with CNS lupus and demonstrated that CNS involvement in SLE is an immunological disorder of Th1 predominance [5].

Several reports have shown that both CD40/CD40L and CD80/CD82 interactions are a prerequisite for the development of Th1 lineage cells [6–8]. Therefore, rituximab-induced down-regulation of CD40 and CD80 on B cells might inhibit the activation and development of Th1 dominance by preventing CD40/CD40L and CD80/CD82-mediated downstream interactions, and thereby result in the suppression of Th1-predominant immunological disorders such as CNS lupus. Given the inhibitory effects of rituximab on interactions between CD40/CD40L and CD80/CD82, this drug is somewhat analogous to CTLA4-Ig, a human fusion protein combining the extracellular portion of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) with the Fc region of human IgG [9]. In this case, however, rituximab inhibits not only B-cell functions but also Th1-cell activation and has an advantage over CTLA4-Ig, which is reported to inhibit only CD80/CD82 interactions. A comparative clinical study between rituximab and CTLA4-Ig is needed to reveal whether rituximab is more effective than CTLA4-Ig for the treatment of lupus. Taken all the data together, rituximab is an efficient immunosuppressive strategy. As we pointed out previously, clinicians should be aware of the risk of the development of severe infections following treatment with rituximab [10]. In this regard, the strategy proposed by Tokunaga et al. is well considered since they successfully treated their patients with only a few injections of rituximab. The authors have declared no conflicts of interest.

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Accepted 5 October 2005
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Rheumatology 2006;45:122–123

doi:10.1093/rheumatology/ke1189
Advance Access publication 8 November 2005

Rituximab reduces both quantity and quality of B cells in SLE: reply

SLE is an autoimmune disease characterized by autoreactive T cells and polyclonal activation of B cells. We reported that five SLE patients with organ-threatening disorders, resistant to intensive conventional therapies, were treated by weekly use of rituximab (375 mg/m², twice), and that sufficient evidence of excellent tolerability and high efficacy of rituximab therapy was obtained. Moreover, a rapid and marked reduction in the expression of the costimulatory molecules CD40 and CD80 on B cells was found on serial phenotypic assessments of residual B cells in all five patients. Such down-regulation was seen for more than 7 months in two patients, implying that reduction of both the quantity and the quality of B cells by rituximab could improve the disease course in refractory SLE [1].

Furthermore, we have recently found that the expression of CD40L, a ligand for CD40, and inducible T cell co-simulator (ICOS), a ligand for CD80 and CD86, was also down-regulated on CD4+ T cells in some of SLE patients (unpublished data by MT and YT). Silikakis et al. [2] also reported that rituximab consistently decreased CD40L-bearing CD4+ T cells by 4-fold as early as 1 month from baseline in 10 patients with lupus nephritis, and that the expression of CD40L was almost blocked when partial remission was clinically evident. On the other hand, Anolik et al. [3] reported that rituximab improved abnormalities in B-cell homeostasis, with a decreased proportion of autoreactive memory B cells after treatment. Therefore, rituximab-induced depletion of memory B cells could also prevent the activation of autoreactive T cells through interactions with B cells, resulting in the down-regulation of CD40L and ICOS on CD4+ T cells.

Dr. Okamoto’s comments that rituximab might suppress Th1-dominant disorders by reducing interactions between CD40–CD40L and CD80–CD82 are a fascinating explanation of the dramatic efficacy of the therapy for neuropsychiatric SLE, in which Th1 dominance has been reported. However, although rituximab completely down-regulated CD40 and CD80 expression on B cells in all 10 recently assessed SLE patients, it decreased CD40L on CD4+ T cells in only half of the patients (unpublished data by MT and YT). Thus, the effects of rituximab on the Th1–Th2 balance remain unclear and further studies are required. Alternatively, rituximab might change the proportions of helper or autoreactive T cells and regulatory T cells, since following rituximab treatment some patients displayed sharp increases in their CD25+/CD4+ cell counts [2]. However, this was observed in only some SLE patients and further studies are again needed.

The CD40–CD40L pathway is known to play a central role in the B cell–T cell interactions that provide the pathological autoimmune responses, and overexpression of CD40L always correlates with disease activity of SLE. A reduction in both the quantity and the quality of B cells interacting with T cells through CD40–CD40L was observed with rituximab, implying that


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rituximab may improve the disease course of SLE by partially resetting the autoimmune responses. Thus, therapeutic B-cell depletion by rituximab has not only provided an opportunity to learn more about the biology of B cells and their roles in the pathogenesis of SLE and other autoimmune diseases, but has also brought a promising treatment a step closer to the clinic [4].

No conflict of interest has been declared.

Rheumatology

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<th>Key messages</th>
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<td>• Rituximab provides high clinical efficacy for refractory SLE.</td>
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<tr>
<td>• Since a rapid decrease in CD40 and CD80 on B cells was found in SLE treated with rituximab, the reduction in quantity and quality of B cells interacting with T cells via costimulatory molecules could improve the disease course of SLE by partially resetting autoimmune responses.</td>
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Accepted 5 October 2005

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