Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are representative inflammatory autoimmune diseases that are thought to involve disturbances in T- and B-cell functions. Immune complexes consisting of antigens and autoantibodies secreted from activated B cells cause severe inflammation in various tissues and organs. To control this inflammation, immunosuppressants, such as the corticosteroids methotrexate (MTX) and cyclophosphamide (CY), are widely used. However, we have encountered patients with RA and SLE who are refractory to these conventional treatments, and thus innovative approaches need to be developed.

CD20 is a surface molecule specific for B cells. It is expressed in most stages of B cells. Rituximab is a chimeric monoclonal antibody specific for human CD20 and is known to deplete B cells. This antibody has already been used and has demonstrated high effectiveness in the treatment of B-cell lymphomas. Recently, the potential efficacy of B-cell depletion therapy with rituximab has been reported in several autoimmune diseases.

RA is characterized by marked infiltration of the synovium by T cells. RA had traditionally been thought of as a T cell-mediated disease. However, since B cells present antigens and activate T cells in the synovium and B cell-activated T cells release proinflammatory cytokines that can promote joint destruction or stimulate other cells to release destructive cytokines, more recent research has highlighted the role of B cells in joint inflammation and led to RA trials for rituximab (Fig. 1). The phase 3 trial, known as the Randomized Evaluation of Long-Term Efficacy of Rituximab (REFLEX), evaluating the efficacy and safety of rituximab in patients with RA who experienced an inadequate response to TNF blockers, has demonstrated improvements in the signs and symptoms of active disease (1). The study also demonstrates that one dose of rituximab or two doses given once provide a significant benefit over six months. Rituximab is now approved for use in combination with methotrexate in refractory RA patients in USA.

SLE is an autoimmune disease characterized by autoreactive T cells and polyclonal activation of B cells. Recently, we and others reported the potential efficacy of B-cell depletion therapy with the anti-CD20 antibody rituximab in SLE (2, 3). We have treated 10 patients with refractory SLE [including neuropsychiatric SLE (NPSLE) and lupus nephritis, in whom conventional treatments failed] with rituximab and their clinical manifestations were evaluated. Three patients were suffered from herpes zoster, pneumonia and infection after the infusion of rituximab, but no severe adverse effects were observed. Rituximab resulted in rapid improvement of clinical manifestations, as shown by the reduction of the SLE disease activity index (SLEDAI) score at day 28 (Fig. 2). It is noteworthy that in all 10 NPSLE patients the acute confusional state, cognitive dysfunction, phychosis, seizure disorders and severe headache were improved. Urinary protein levels in lupus nephritis patients became (-) or (+/-). It took more than one month for the improvement of nephritis, whereas the acute confusional state rapidly improved within a few days after the treatment, suggesting there could be different mechanisms for rituximab for NPSLE and nephritis. Nine patients are in remission for more than 1 year.

Moreover, a rapid and marked reduction in the expression of the costimulatory molecules CD40 and CD80 on B cells was found on serial phenotypic assessment of residual B cells in SLE 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. Furthermore, we found that the expression of CD40 L, a ligand for CD40, was also down-regulated on CD4 T cells in SLE patients (3). Anolik et al reported that rituximab improved ab-
Figure 1. The role of B cells in inflammatory autoimmune diseases.

Figure 2. Improvement of SLEDAI in 10 SLE patients treated with rituximab.

Figure 3. Rituximab reduces memory B cells and induces re-constitution of B cell lineage, which leads to clinical efficacy in inflammatory autoimmune diseases.
normalities in B-cell homeostasis, with a decreased proportion of autoreactive memory B cells and reconstitution of B cell lineage after the treatment (4). 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 CD40 L on CD4 T cells, implying that rituximab may improve the disease course of RA and SLE by resetting the autoimmune responses (Fig. 3). 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 (5).

References


