REVIEW

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# B-cell-depleting Therapy in Systemic Lupus Erythematosus

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**ABSTRACT**

The emergence of a new class of agents (B-cell-depleting therapies) has opened a new era in the therapeutic approach to systemic lupus erythematosus, with belimumab being the first drug licensed for use in systemic lupus erythematosus in more than 50 years. Four agents deserve specific mention: rituximab, ocrelizumab, epratuzumab, and belimumab. Controlled trials have shown negative results for rituximab, promising results for epratuzumab, and positive results for belimumab. Despite these negative results, rituximab is the most-used agent in patients who do not respond or are intolerant to standard therapy and those with life-threatening presentations. B-cell-depleting agents should not be used in patients with mild disease and should be tailored according to individual patient characteristics, including ethnicity, organ involvement, and the immunological profile. Forthcoming studies of B-cell-directed strategies, particularly data from investigations of off-label rituximab use and postmarketing studies of belimumab, will provide new insights into the utility of these treatments in the routine management of patients with systemic lupus erythematosus.

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Systemic lupus erythematosus, a disease that predominantly affects young women and that may cause severe organ impairment and even death, is considered paradigmatic of systemic autoimmune diseases.[1] The treatment of systemic lupus erythematosus remains a challenge because a balance must be sought between the demonstrated efficacy of immunosuppressive agents (mostly used off-label) and the adverse effects of immunosuppression. For the first time in more than 50 years, the United States Food and Drug Administration and the European Medicines Agency have licensed a new drug for use in systemic lupus erythematosus: belimumab, a biological therapy targeting B lymphocytes. This suggests that a new era may be opening in our therapeutic approach to systemic lupus erythematosus, based on new drugs with more specific mechanisms of action.[2] It seems an opportune moment for a practical update on this new class of drugs in systemic lupus erythematosus.

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## B-CELL DEPLETION IN LUPUS TODAY

### Current Agents

B-cell therapies are designed to eliminate either the majority of B cells (general depletion) or only some B-cell populations (selective depletion)[3] (**Table 1**). In both cases, depletion is achieved through 2 principal mechanisms:

1) Direct killing by monoclonal antibodies against B-cell surface molecules CD19, CD20 (rituximab, ocrelizumab), and CD22 (epratuzumab). The most widely

tested category of anti-B-cell agents is anti-CD20 antibodies, which induce a broad and deep B-cell depletion.

2) Attrition due to inhibition of B-cell survival factors BLyS (belimumab) and APRIL (atacicept). Belimumab has a significantly more restricted and attenuated B-cell effect[4,5] by blocking the essential survival effect of BLyS. Atacicept induces the depletion of a significantly larger swathe of B cells and plasma cells, although this powerful effect also may increase the risk of severe infections.

## CLINICAL SIGNIFICANCE

- Belimumab is the first drug licensed for use in systemic lupus erythematosus (SLE) in more than 50 years.
- The use of B-cell-depleting agents in clinical practice is centered on SLE patients with refractory/life-threatening disease.
- Careful evaluations of the risk/benefit profiles of biologic agents in SLE are essential.
- Biological agents will be increasingly used in the near future and will have a significant impact on the management of SLE patients.

## Results of Controlled Trials

**Rituximab.** Two randomized controlled trials (RCTs) have evaluated the use of rituximab in patients with systemic lupus erythematosus (**Table 2**). The Study to Evaluate the Efficacy and Safety of Rituximab in Patients With Severe Systemic Lupus Erythematosus (EXPLORER) trial included 257 patients with moderate-severe nonrenal systemic lupus erythematosus.[6] Patients were randomized to the addition of rituximab (n = 169) or placebo (n = 88) to the baseline immunosuppressive agents, together with a 10-week course of high-dose glucocorticosteroids. The 2 arms of the trial showed no statistically significant reduction in clinical activity compared with baseline, and the hypothesized superiority of rituximab plus standard of care (SOC) over SOC alone was not demonstrated. The second RCT was the Study to Evaluate the Efficacy and Safety of Rituximab in Subjects With ISN/RPS Class III or IV Lupus Nephritis (LUNAR) trial, a phase III trial that included 144 patients with proliferative lupus nephritis. The definitive results are not yet published, but preliminary results[7,8] show that the trial did not achieve its primary and secondary endpoints (**Table 1**). The failures of EXPLORER and LUNAR taught the community of lupus investigators valuable lessons about clinical trial design in this condition and influenced the development of subsequent lupus trials.

**Ocrelizumab.** The Study to Evaluate Ocrelizumab in Patients With Nephritis Due to Systemic Lupus Erythematosus (BELONG) trial tested ocrelizumab in patients with lupus nephritis with a design similar to that of the LUNAR trial. In March 2010, Roche (Basel, Switzerland) and Biogen (Cambridge, Mass) decided to suspend the ongoing trials of ocrelizumab in patients with rheumatoid arthritis and systemic lupus erythematosus following the recommendations of an independent monitoring board. The board had detected an infection-related safety signal (including severe and opportunistic infections), several of which were fatal, among the 2400 patients from more than 30 countries. The recently reported details of the BELONG trial[9] showed a trend to a better response in the ocrelizumab 400 mg (62%) and 1000 mg (64%) arms in comparison with the placebo arm (51%, $P = .075$). The percentage of patients experiencing serious infections was twice as high in patients who received concomitant mycophenolate (32% vs 16% in the placebo arm). A specific geographical distribution of severe infections was detected in Asian patients.[9]

**Epratuzumab.** The first trials of epratuzumab in systemic lupus erythematosus were terminated early due to difficulties in supplying the active agent. However, the results from 55 patients enrolled showed that epratuzumab-treated patients required smaller quantities of glucocorticosteroids when compared with placebo-treated patients over 24 weeks.[10,11] Preliminary results of the 12-week Epidemiology of Burkitt Lymphoma in East Africa Children or Minors (EMBLEM) trial, a phase IIB RCT including 227 patients, have shown a clinical response of 38% (epratuzumab 600 mg weekly) and 35% (epratuzumab 1200 mg weekly) in comparison with the placebo arm (22%).[12]

**Belimumab.** Clinical trials of belimumab in systemic lupus erythematosus began inauspiciously, with failure of a dose-ranging phase II trial of 449 patients to achieve its primary outcome.[5] However, the trial included 30% of patients who had no antinuclear antibodies at baseline, raising questions about the validity of their systemic lupus erythematosus diagnoses. A subsequent analysis of a continuation trial in 296 of these 449 patients found that immunologically positive patients treated with belimumab showed sustained improvement in disease activity and a decrease in flares over 6 years of follow-up, accompanied by a reduction in glucocorticosteroid use.[13]

The recently published results of the Study of Belimumab in Subjects With Systemic Lupus Erythematosus (BLISS-52) trial marked the first positive RCT of a biologic agent in systemic lupus erythematosus (**Table 2**). This trial included 865 patients with positive immunological markers and moderate-severe disease.[14] A clinical response at 52 weeks was achieved by 44% of placebo-treated patients compared with 51% of those receiving belimumab 1 mg/kg and 58% of those treated with belimumab 10 mg/kg ($P = .013$ and .0006, respectively), with modest but consistent improvements across a range of clinical outcome measures. A second trial (BLISS-76) included 819 patients with a similar design, although patients and investigators re-