In AURA-LV, 33% of patients treated with voclosporin 23.7 mg twice per day reached an RR at 24 weeks compared to 19% of placebo-treated patients (OR 2.03, $P < 0.05$).[734] Similarly, in AURORA, 41% of voclosporin-treated patients achieved RR at 52 weeks, compared to 23% of placebo-treated patients (OR 2.65, $P < 0.001$).[702,754] A pooled analysis of the 2 trials showed that patients treated with voclosporin added to standard therapy had an RR rate of 44% at 1 year, compared to 23% in placebo patients ($P < 0.0001$).[755] Adverse events were similar between the placebo and voclosporin arms.

Compared to other CNIs, such as cyclosporine and tacrolimus, voclosporin has a more consistent pharmacokinetic–pharmacodynamic relationship due to enhanced binding of the voclosporin–cyclophilin complex to calcineurin and reduced drug and metabolite load. Preliminary evidence, based on data from the AURA-LV and AURORA trials, suggests that therapeutic drug monitoring may not be necessary in patients.[756]

Results from these 2 pivotal trials led to the US FDA approval of voclosporin to treat adult patients with LN in January 2021. Of note, voclosporin is not recommended for patients with a baseline eGFR $\leq$45 ml/min per 1.73 m^2, as these patients were excluded from the trials. Also, voclosporin has not been studied with cyclophosphamide.

The positive results of AURA-LN and AURORA coupled with the Asian studies of tacrolimus and cyclosporine suggest triple immunosuppressive therapy incorporating a CNI can be an effective treatment regimen for LN. An advantage of a CNI-based regimen is the more rapid reduction of proteinuria. However, more data on long-term efficacy and safety of CNI use in LN are required.

Practice Point 10.2.3.1.6: There is an emerging role for B-lymphocyte targeting biologics in the treatment of LN. Belimumab can be added to standard therapy in the treatment of active LN. Rituximab may be considered for patients with persistent disease activity or repeated flares.

Results from phase 2 and phase 3 clinical trials did not demonstrate superiority in efficacy when B cell–targeting therapies (rituximab, ocrelizumab), costimulatory blockade (abatacept), or anti-interleukin-6 monoclonal antibody were added to standard initial therapy of glucocorticoids and either MMF or cyclophosphamide.[757–762] The negative outcomes contrast with reports of case series that suggested efficacy when patients with suboptimal response to standard therapy were treated with rituximab.[763–766] Interestingly, patients treated with rituximab and abatacept in the RCTs showed more effective suppression of anti-double-stranded deoxyribonucleic acid (dsDNA) levels and complement activation, but this biological efficacy did not translate to conventional clinical indicators of treatment response.[757,759] Reasons for the apparent discrepancy between biological efficacy versus clinical observations, and between the case series versus RCT results, include the different populations of patients studied, the outcome parameters used in the trials, and the relatively short duration of observation in the trials. Some trials using biologics have yielded encouraging results. For example, in a prospective single-center pilot study to investigate whether rituximab could facilitate corticosteroid avoidance, 50 patients with active LN (22 Class V, 28 Class III/IV $\pm$ V) were treated with rituximab 1 g and methylprednisolone 500 mg i.v. on day 1 and day 15 and were maintained on MMF (maximum dose 1.5 g twice per day, target trough blood level of mycophenolic acid 1.2–2.4 μg/ml [3.7–7.5 μmol/l]) without glucocorticoids, and by 52 weeks, 52% of patients achieved complete remission and 34% achieved partial remission.[767]

The negative outcomes in previous clinical trials do not preclude a therapeutic role for some of these novel agents in selected patients, including those who have not responded well to or who do not tolerate standard therapy, or when steroid-sparing is attempted (Supplementary Tables S56–S59[718,742,757–759,764]).[767]

Ongoing clinical trials continue to investigate the role of biologics for the treatment of LN. A recent phase 2 study showed that in adult patients with active proliferative LN treated with MPAA and glucocorticoids, the addition of obinutuzumab resulted in higher complete renal response rates at week 76 (40% vs. 18%, $P = 0.007$), and at week 104 compared to placebo (54% vs. 29%, $P = 0.005$). The rate of serious adverse events and serious infections did not differ between the 2 groups.[760]

A phase 3 RCT of belimumab (10 mg/kg i.v. on days 1, 15, and 29, then every 28 days to week 100) added to standard-of-care therapy resulted in approval of belimumab for LN by the U.S. FDA in December 2020.[701] This trial, Efficacy and Safety of Belimumab in Patients with Active Lupus Nephritis (BLISS-LN), examined the 2-year primary efficacy renal response (PERR) after belimumab or placebo was added to standard-of-care therapy, which was either MMF or the Euro-Lupus reduced-dose cyclophosphamide regimen chosen by the site investigator. PERR was defined as a ratio of PCR of $<$0.7, an eGFR that was no worse than 20% below baseline or at least 60 ml/min per 1.73 m^2, and no use of rescue therapy for treatment failure. At week 104, significantly more patients who received belimumab achieved a PERR compared to the number of those who received placebo (43% vs. 32%; OR 1.60; $P = 0.03$; Supplementary Table S60[701]). Key secondary endpoints included complete renal response and the risk of renal event or death. These also favored belimumab. Subgroup analysis showed that the overall PERR response was driven by the results in the larger subgroup (73.5%) of patients who received MMF as background therapy. Belimumab treatment was not associated with excess adverse events.

In summary, there are accumulating data on the biological and clinical efficacy of various biologics. Although long-term results are awaited, results on these biologics have expanded the armamentarium of therapeutic options and potential combinations of treatments. The favorable safety profile associated with some of the new biologics presents a distinct advantage. Further investigations are necessary to define the profiles and characteristics of