




# Promising Experimental Treatments for Lupus Nephritis: Key Talking Points and Potential Opportunities

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**Abstract:** Lupus nephritis (LN) is a frequent and serious complication of systemic lupus erythematosus (SLE), impairing patients' quality of life and significantly increasing mortality. Despite optimizing the use of conventional immunosuppressants and other biological drugs, its management remains unsatisfactory. This is mainly due to the heterogeneity of SLE, but also to insufficiently effective treatment regimens and clinical trial limitations (strict criteria, low number of patients included, and side effects). Most clinical trials of new biological therapies have failed to meet their primary endpoints in both general SLE and LN, with only two biological drugs (belimumab and anifrolumab) being approved by the Food and Drug Administration (FDA) for the treatment of SLE. Recently, several Phase II randomized controlled trials have evaluated the efficacy and safety of new biologics in LN, and some of them have demonstrated an improvement in clinical and laboratory measures. Multi-target therapies are also being successfully developed and encourage a belief that there will be an improvement in LN outcomes.

**Keywords:** biological therapies, systemic lupus erythematosus, lupus nephritis, trial

## Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune rheumatic disease that can have severe and life-threatening presentations. This is explained mainly by its inflammatory activity, treatment-associated complications, concomitant diseases, and long-term sequelae. The main pathogenic feature of this disease is the presence of antibodies that bind autoantigens, forming immunocomplexes that precipitate in tissues, leading to organ damage. SLE is associated with significant morbidity and mortality rates reported to be 2- to 3-fold higher than the general population.<sup>1,2</sup>

In particular, lupus nephritis (LN) is one of the most serious complications in patients with SLE. However, definitions of LN have varied between studies. Some include all SLE patients with proteinuria, whilst others reported only biopsy-proven LN, but overall it seems to affect 30–40% of all SLE patients.<sup>3,4</sup>

Glomerular and interstitial inflammation mediated by immunocomplex precipitation lead to renal impairment, with further end-stage renal disease (ESRD), which impairs patients' quality of life and overall survival.<sup>1,2</sup> Therefore, prompt recognition and treatment are mandatory to minimize the impact of LN on these patients.

Over the past 60 years, the outlook for a patient with SLE has considerably improved, largely due to advances in diagnosis. For example, in the 1950s, the four-year survival for patients with SLE was 50%, while, currently, the fifteen-year survival is approximately 85%.<sup>5,6</sup>

However, focusing on LN, long-term dialysis became available only in the 1970s, concomitant to the introduction of better therapies and transplantation, which led to a 10% decrease in the ESRD risk at 10 and 15 years. Disappointingly, since 1990, the risk of LN patients progressing to ESRD has remained constant between 17% and 22% at 10 and 15 years, respectively.<sup>4,7–9</sup> In addition, up to 25% of patients who achieve remission have a flare within 3 to 4 years.<sup>10</sup> This reflects the need for an earlier

diagnosis and better access to therapies and, in particular, trying to ensure patient adherence. However, the need for more efficacious drugs to improve patient outcomes and quality of life remains paramount.

The development of new biological drugs to treat patients with many autoimmune rheumatic diseases has dramatically improved the outcome and quality of life of patients, especially those with rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis.<sup>11</sup> In contrast, in SLE, but especially in LN, very few therapies have been approved. B-cell targeting therapies, such as rituximab and belimumab, have proved to be effective in reducing glucocorticoid dosing, controlling disease activity, and inducing therapeutic response (especially in severe or refractory LN patients).<sup>12–14</sup> Despite its approval, renal response after belimumab treatment was only observed in a third of LN patients, and rituximab did not meet its primary endpoints in either an LN or non-nephritis SLE trial.<sup>13,15</sup> However, its utility is widely recognized and guidance on the treatment of LN from both the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) recommends its use.<sup>13,16–18</sup> However, we still need to develop new directed therapies to become part of the standard therapy for LN patients, with improved efficacy, fewer side effects, and worldwide availability.

Here, we review the approved therapies for LN patients, the results of previous clinical trials, and future potential targets for LN.

## Brief Overview of the Immunopathology of Lupus Nephritis

Understanding the immunopathology of SLE, with a special focus on LN, has led to a better understanding of this disease, and has also opened doors to the development of several new drugs, with different targets, that might potentially improve patient outcomes [Figure 1].

Autoantibodies are made by most healthy individuals and are present in patients for years before the first symptoms of SLE appear.<sup>19</sup> The ability of autoantibodies to initiate clinical SLE depends on genetic background, epigenetic changes, and environmental exposure that interfere with normal innate and adaptive immunity paths, with consequent loss of tolerance, and increasing survival of autoreactive B cells. Several mechanisms are involved in this process, including defective clearance of apoptotic cells, the inability to degrade neutrophil extracellular traps (NETs), and abnormalities in B-cell receptor signaling.<sup>20</sup>

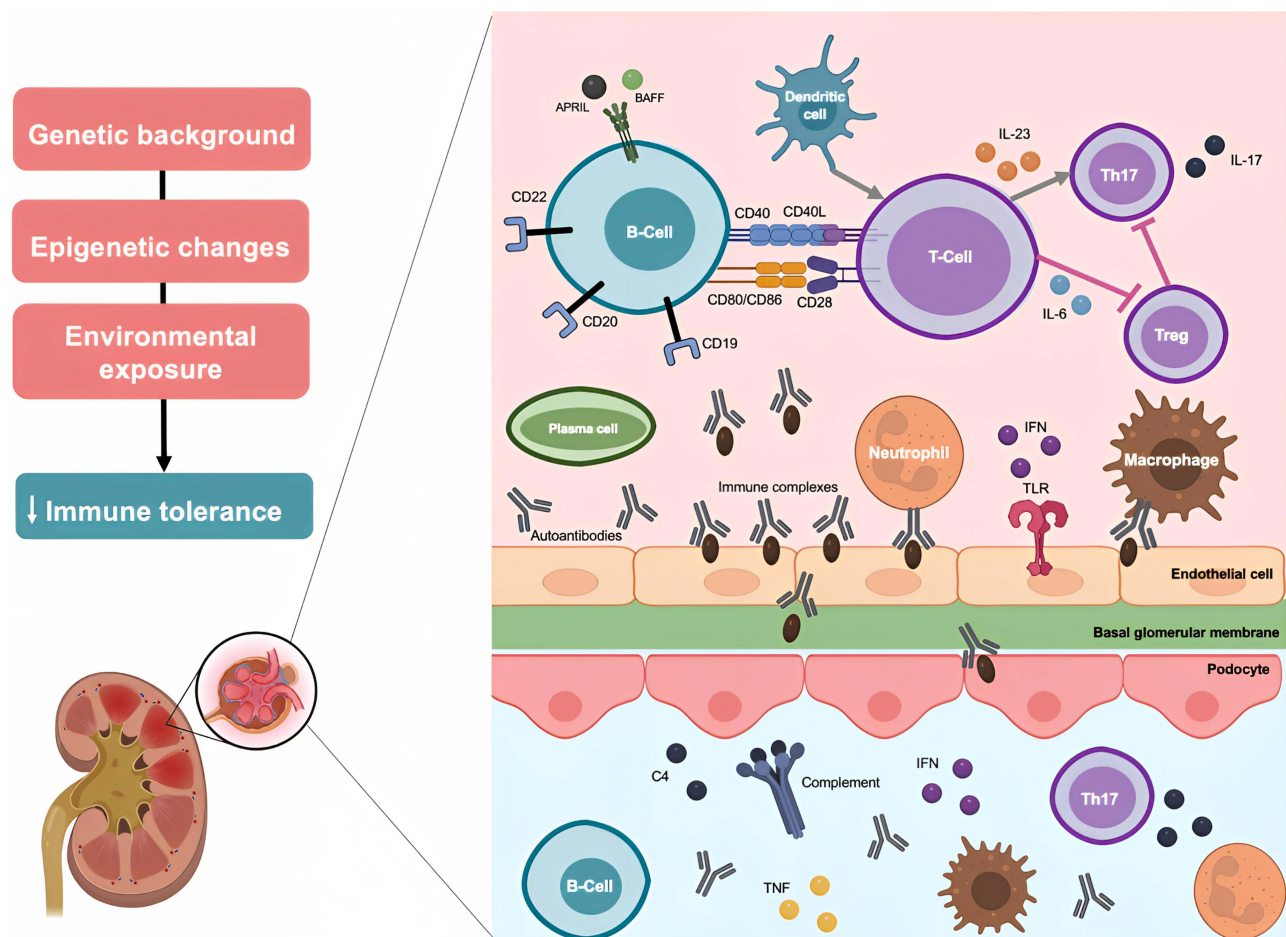
B lymphocytes from SLE patients play an important role as antigen-presenting-cells, inducing the activation of CD4+ auto-reactive T-cells, allowing the activation and differentiation of B-cells, and consequent production of high-affinity autoantibodies.<sup>21,22</sup>

As immune tolerance is lost, activation of tissue-resident phagocytic cells occurs, followed by the release of cytokines/chemokines from the fixed cells and activation of complement by the complement-binding immune complexes and autoantibodies fixed to glomeruli autoantigens. Infiltration of B, T (especially cytotoxic T cells and Th17 T cells), and dendritic cells, as well as monocytes from the peripheral blood, also occurs. Toll-like receptors (TLR) activation produces large amounts of inflammatory cytokines and IFN- $\alpha$  and IFN- $\beta$ , which also contribute to renal damage. The latter triggers the proliferation of parietal epithelial cells (and consequent glomerular crescent formation) and later production of extracellular matrix contributing to glomerulosclerosis.<sup>20</sup> Ectopic clusters of follicular Th cells are also found in LN patients, which probably contribute to the pathogenesis of this disease.<sup>23</sup>

## Measurement Tools

Different measurement tools have been in clinical trials used to ascertain SLE disease activity and response to therapies. The SLE disease activity index (SLEDAI) is a global activity index which captures disease activity in the previous 30 days. Two different versions have been used, the SLEDAI-2K and SELENA-SLEDAI.<sup>24</sup> The Physician Global Assessment (PGA) is a visual analog scale, semi-quantitative, that accesses disease activity over the past two weeks.<sup>25</sup> Although simple to use and calculate the score, it is a binary system and does not distinguish between patients who are better (but not completely recovered) from those who are worse or the same.

In contrast, the British Isles Lupus Assessment Group (BILAG) index evaluates, more comprehensively, disease activity over the past month in nine separate organ systems, assessing the items in each as new, same, worse, improving or never present. These data are converted into scores for each organ/system according to severity [A (severe),



**Figure 1** Immunopathology of lupus nephritis. Created with Biorender.com.

**Abbreviations:** APRIL, A proliferation-inducing ligand; BAFF, B-cell activating factor; BAFFR, BAFF receptor; BTK, Bruton's tyrosine kinase; CD40L, CD40 ligand; IFN, interferon; IL, interleukin; TLR, toll-like receptor; TNF, tumor necrosis factor; TWEAK, tumor necrosis factor-like inducer of apoptosis.

B (moderate), C (mild), D (no current activity), or E (no current or previous history)].<sup>26</sup> Unlike the SLEDAI system, the BILAG can distinguish partial improvement from no change or deterioration.

The SLE responder index (SRI) combines the SELENA-SLEDAI, BILAG and PGA. SRI responses correspond to a  $\geq 4$ -point reduction from baseline in SELENA-SLEDAI score and no new BILAG A score and no more than one new BILAG B organ domain score compared with baseline no worsening in PGA.<sup>25</sup> Some clinical trials use SRI-3, SRI-5, or SRI-6 depending on the SELENA-SLEDAI score improvement.

The BILAG-based composite lupus assessment (BICLA) is a similar index to SRI, however with more weight on BILAG instead of SLEDAI. Requirements for BICLA response include BILAG improvement (all A scores at baseline improved to B, C or D, and all B scores improved to C or D); no deterioration of disease activity (no new BILAG A scores and  $\geq 1$  new B score); no worsening of the total SLEDAI-2K score from baseline; no significant deterioration ( $<10\%$  worsening) on visual analog PGA; and no treatment failure (defined as non-protocol treatment).<sup>24</sup>

## Conventional Lupus Nephritis Treatment

Renal biopsy is the gold standard for LN diagnosis, and therapeutic decisions are often based on the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of glomerular involvement.<sup>27</sup>

Classic immunosuppressants, such as steroids, cyclophosphamide, azathioprine, and mycophenolate mofetil, remain first-line therapy for LN treatment in most cases, with very few changes over the past 25 years.

Initial immunosuppressive treatment in patients with class I or II LN is rarely required unless needed for extrarenal manifestations of SLE. However, if the patient presents with a nephrotic syndrome with confirmed podocytopathy, low-dose glucocorticoid [with or without another immunosuppressive agent such as mycophenolic acid analogs (MPPA), azathioprine or a calcineurin inhibitor (CNI)] should be considered.<sup>28,29</sup>

For patients with class III (focal proliferative) or IV (diffuse proliferative) glomerulonephritis with or without a class V (membranous) component, initial treatment includes glucocorticoids plus either MPPA or low-dose intravenous cyclophosphamide or MPPA and a CNI.<sup>18,28</sup>

Once initial therapy is complete, patients should be placed on MPAA for maintenance. Azathioprine can be considered an alternative, notably if the patient wants to get pregnant, as well as belimumab if it has already been used as part of a triple therapy plan.<sup>18,28</sup>

Evidence for the optimal treatment of Class V LN is still limited, however, given the 10–30% risk of progression to ESRD of these patients who also present with concomitant nephrotic proteinuria, immunosuppressive therapy should be considered.<sup>28,29</sup>

In the presence of a non-responding or refractory disease, therapy with rituximab (anti-CD20 molecule) should be considered, as well as adding belimumab to the previous therapy.<sup>29,30</sup>

Hydroxychloroquine (or an equivalent antimalarial) should be administered to every patient with SLE (including those with lupus nephritis), given its beneficial effects on disease control, reduction in organ damage, and vascular complications.<sup>17,18,28,29,31</sup>

Voclosporin is a new calcineurin inhibitor, structurally similar to cyclosporine, but more potent and with decreased toxicity (without requiring drug-level monitoring). It has been approved by the FDA, and very recently by NICE, for the treatment of LN in combination with MPAA, and glucocorticoids.<sup>32</sup> Exactly when to use it in LN patients has yet to be generally agreed.

## Development and Current Usage of Biological Drugs Approved for the Treatment of LN

Theoretically, drugs which block the antibody-producing B cell lineages ought to be effective in SLE. Belimumab is, currently, the only biological drug approved for LN by the Food and Drug Administration (FDA).<sup>33</sup> The use of rituximab is approved in the United Kingdom by National Health System (NHS) England and, as mentioned, is recommended by EULAR, the ACR, and the Kidney Disease Improving Global Outcomes (KDIGO) group.<sup>17,18,28,34</sup>

### Belimumab

Belimumab is a fully human IgG1 $\lambda$  monoclonal antibody that inhibits the soluble form of a B-cell survival factor, BAFF (also known as BLyS). It has been approved for LN treatment in combination with standard initial and subsequent therapy, either in intravenous or subcutaneous form, for patients 5 years or older with autoantibody-positive SLE.<sup>33</sup> However, experience with this regimen is still limited, and its role in initial therapy has not been established.<sup>35</sup>

The addition of belimumab to standard initial and maintenance therapy appears to improve rates of renal response in patients with active LN. BLISS-LN, a Phase III trial, multinational, multicenter, randomized 448 class III to V LN patients to receive belimumab added to the initial standard therapy, or just standard therapy. In this trial, complete renal response was significantly higher in the belimumab group compared to those in the placebo (30 vs 20%, OR 1.7, 95% CI 1.1–2.7, p-value = 0.03). The risk of a kidney-related event or death was also lower in the belimumab group (there was one death in the belimumab group, compared to two in the placebo group).<sup>16</sup> A post-hoc analysis was performed and demonstrated that higher rates of complete response with belimumab were seen in patients with a urine protein/creatinine ratio <3g/g. However, belimumab treatment still reduced the annual rate of estimated glomerular filtration rate (eGFR) decline, suggesting that the addition of belimumab to standard therapy could lower the risk of LN flare and eGFR decline in these patients.<sup>36</sup> A 28-week open-label extension of BLISS-LN was undertaken, endorsing its safety and efficacy, consistent with the previous trial.<sup>37</sup>

Later, in the Italian BeRLiSS-LN cohort study, belimumab was used as an add-on therapy for LN patients with persistent disease despite initial therapy. Similar results were seen in the BLYSS-LN trial, confirming its efficacy, safety and glucocorticoid-sparing effect, reinforcing the view that belimumab can be used successfully in patients with an incomplete response or persistent disease after the initial therapy.<sup>38</sup>

## Rituximab

Rituximab is a mouse/human chimeric type I anti-CD20 monoclonal antibody that induces B-cell lysis mediated by complement and Fc receptor bearing-cytotoxic cells, and by induced programmed cell death.<sup>39</sup> B-cell depletion leads to lower production and concentration of several antibodies, for example, anti-dsDNA, anti-nucleosome, and anti-cardiolipin antibodies.<sup>40,41</sup>

Rituximab has long been successfully used in rheumatoid arthritis patients and vasculitis.<sup>42,43</sup> However, the predicted B-cell depleting therapy benefit in SLE patients has been harder to demonstrate in clinical trials.

The LUNAR trial randomized 144 class III or IV LN patients to receive rituximab plus mycophenolate mofetil (MMF) compared to MMF alone. Rituximab therapy led to more responders, but no statistically significant differences in rates of complete or partial remission were seen after a year. Complete and partial renal response rates were 45.8% for patients receiving placebo and 56.9% among patients receiving rituximab (p-value = 0.18). Despite that, rituximab therapy led to significant reductions in anti-dsDNA antibody and C3/C4 levels, which were associated with reduced proteinuria.<sup>13</sup> Many possible reasons to explain this failure have been discussed, including the heterogeneous nature of SLE patients marked by different B-cell phenotypes (especially some hematopoietic stem cells and plasma cells that do not express CD20), the higher levels of B-cell-activation factors (BAFF) following B-cell depletion, but its trial design, which allowed high levels of background medications, especially steroids for long periods, is a likely culprit.<sup>44–46</sup>

In spite of the lack of clinical trial success, many favorable results with rituximab have been reported in open-label /small-series studies and it has been increasingly used as an off-label drug, with useful efficacy and relative safety. A systematic analysis of 26 observational studies and case reports supported its use in LN patients refractory to cyclophosphamide or MMF-based therapies. In these patients, rituximab was revealed to be effective in inducing partial and, to a lesser extent, also complete remission of LN, with response rates between 67 and 87%, compared to high-dose cyclophosphamide in incident patients.<sup>14,47</sup> Further case series support the use of rituximab as an inducer of remission among patients with LN with persisting or relapsing disease, especially in Class III LN.<sup>48–51</sup>

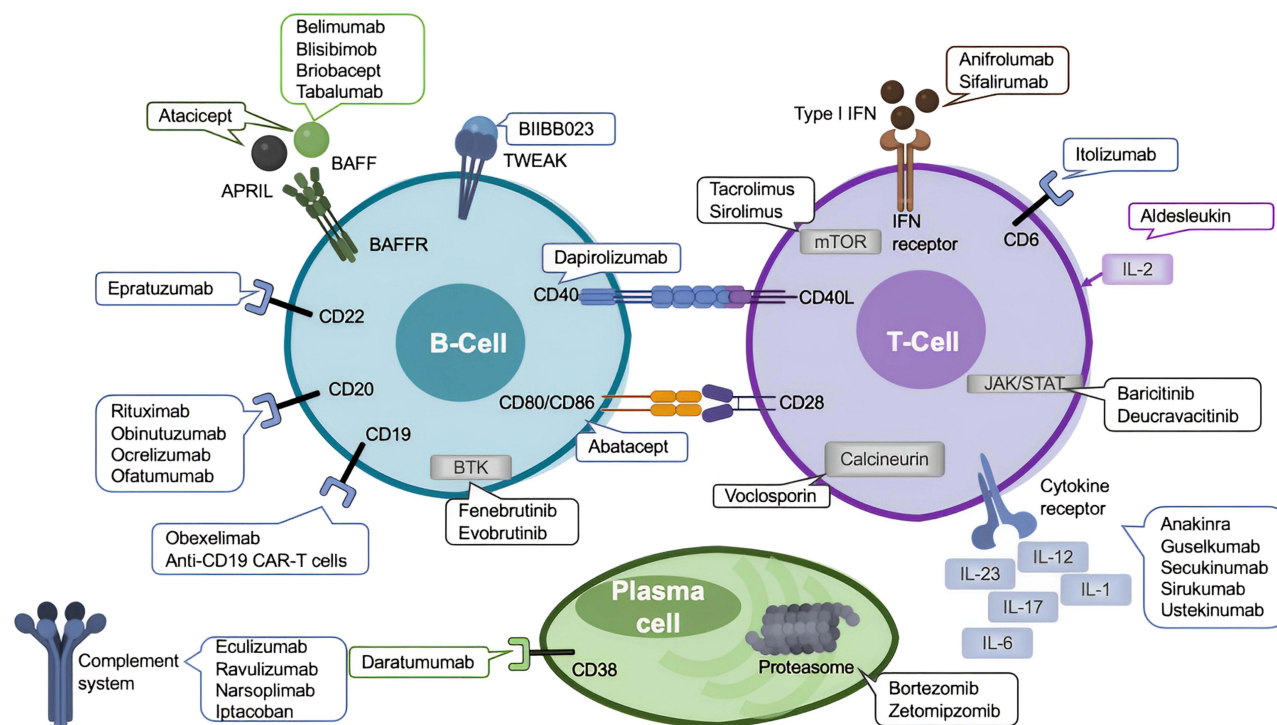
Rituximab use has also shown efficacy in reducing glucocorticoid dosing, especially if used at the time of diagnosis.<sup>12,52–55</sup> In a prospective cohort study 50 class III to V LN patients were treated with 2 doses of rituximab and methylprednisolone on days 1 and 15, and maintenance treatment of MMF and hydroxychloroquine with no steroids. Ninety percent of the patients achieved complete or partial renal response at one year, with only two patients requiring 2 weeks of oral corticoids.<sup>55</sup> Another group, in a study of 16 patients (each matched to 3 controls) followed for up to 6 years showed early treatment of patients with SLE with rituximab (followed by azathioprine and hydroxychloroquine) was safe, effective and enabled a striking reduction in steroid use.<sup>54</sup> These results suggest that LN patients given rituximab treatment at/soon after diagnosis can safely avoid/minimize oral steroids.

However, rituximab infusion-related reactions can occur in up to 15% of patients.<sup>13</sup> Nevertheless, its use has been already approved in the United Kingdom by NHS England, and, as above, it is recommended by EULAR, ACR and KDIGO.<sup>17,18,28</sup>

## Novel Therapeutic Approaches

Despite the increasing development of several new biological drugs for autoimmune diseases in the past 20 years, little has changed in the prognosis of LN patients. However, several therapeutic targets and drugs are currently being investigated for LN and might eventually provide a better outcome for these patients [Figure 2].





**Figure 2** Immunological targets of novel therapeutic agents in lupus nephritis. Created with Biorender.com.

**Abbreviations:** APRIL, A proliferation-inducing ligand; BAFF, B-cell activating factor; BAFFR, BAFF receptor; BTK, Bruton's tyrosine kinase; CAR-T, chimeric antigen receptor T; CD40L, CD40 ligand; IFN, interferon; IL, interleukin; JAK-TYK2, Janus tyrosine kinase 2; TWEAK, tumour necrosis factor-like inducer of apoptosis.

## Further Anti-CD20 Targeting Therapies

B-cell depletion therapy has already been proved to be effective, inducing B-cell lysis mediated by complement and Fc receptor bearing-cytotoxic cells, and by induced programmed cell death, leading to a lower production and concentration of several antibodies.<sup>40</sup>

Three fully humanized anti-CD20 monoclonal antibodies have been developed: obinutuzumab, ocrelizumab, and ofatumumab. They have increased affinity for FcγRIII, reducing redistribution and internalization, and enhancing its anti-CD20 therapeutic properties.<sup>46,56,57</sup>

Obinutuzumab, already approved for hematological malignancy treatment, has been shown to be better able to achieve B-cell depletion better in tissues in SLE patients and have a greater affinity for the FcγRIII on effector cells.<sup>58,59</sup> A phase II randomized controlled trial (NOBILITY) in which 125 proliferative LN patients were treated with MPAA and glucocorticoids, the addition of obinutuzumab resulted in higher complete renal responses at week 76 (40 vs 18%,  $p = 0.007$ ) and, at week 104 (54 vs 29%,  $p = 0.005$ ), compared to placebo. Obinutuzumab treatment was also associated with a potent depletion of CD19+ B cells, without an increased incidence of adverse effects.<sup>56</sup> Based on this study, obinutuzumab has already granted a breakthrough therapy designation by the FDA, while phase III trials are ongoing (NCT04702256).

Another anti-CD20 monoclonal antibody, ocrelizumab, has shown in vitro enhanced antibody-dependent cell-mediated cytotoxicity and reduced complement-dependent cytotoxicity versus rituximab. In rheumatoid arthritis (RA) trials, this therapy has significantly reduced progressive joint damage, as well as improved RA's signs and symptoms. However, higher doses were associated with severe infectious events.<sup>60</sup> The phase III BELONG study was conducted to determine the efficacy and safety of ocrelizumab in 381 patients with active LN. However, 28.3% of patients reported a serious adverse effect until the 48th week and 16.9% reported a serious infection. Thus, this study was interrupted due to the rate of serious infections associated with ocrelizumab treatment.<sup>57</sup>

Ofatumumab is also being studied as an alternative B cell-depleting agent in patients who are rituximab-intolerant and for whom B-cell depletion is deemed as an appropriate therapeutic strategy, since it binds to a distinct extracellular

epitope of CD20, with a slower dissociation kinetics.<sup>61</sup> Two case series with 12 and 4 active LN patients suggested ofatumumab as an alternative to rituximab in LN patients.<sup>62,63</sup>

## B-Cell Signaling Targeted Therapies

B-cell-activating factors, such as BAFF, a member of the tumor necrosis factor family (also known as BLyS) are one of the most important factors associated with the survival of peripheral self-reactive B-cells. Higher levels of BAFF are also seen after rituximab B-cell depletion in some patients, and seem to be associated with higher levels of anti-dsDNA antibodies, and an increased relapse rate after rituximab therapy.<sup>44,64,65</sup> Other B-cell activating factors, such as A proliferation-inducing ligand (APRIL), have been reported to be increased in LN patients.<sup>21,66</sup> Fc fragment of IgG receptor IIb (FcγRIIB) can also increase the threshold for B-cell activation.<sup>67</sup>

Tabalumab is a fully human monoclonal antibody binding membrane and soluble BAFF. Two phase III trials studied its therapeutic effects on moderate-to-severe SLE patients, ILLUMINATE 1 and 2, which randomized 1138 and 1124 patients, respectively. However, the first trial did not meet the primary endpoint (proportion of patients achieving SRI-5 response at week 52) almost certainly because of a stipulation that any alteration in steroids meant the patient had failed and was withdrawn from the study. This was illogical as a reduction in steroids implies the patient was improving, so why prevent them from continuing with the study? The second trial did not have this stipulation and did meet its primary endpoint (SRI-4) but its secondary endpoints with a (time to severe flare, corticosteroid-sparing and fatigue) were not met. Eli Lilly<sup>®</sup> chose to halt further trials.<sup>68–70</sup>

Atacept is a human recombinant fusion protein that binds to two B-cell activating factors BAFF and APRIL. ADDRESS II, a phase IIb trial, assessed atacept in moderate-to-severe SLE patients but excluded those with severe LN. Only patients on atacept 150mg were associated with a lower SRI-6 score at week 26 [54.9% (adjusted OR 3.31; 95% CI 1.44–7.61),  $p = 0.005$ ] versus placebo (28.8%). Atacept also decreased the risk of flare in patients with more serologically active disease, although there was no difference in corticosteroid dosing.<sup>71</sup> The higher dose arm of this trial was terminated prematurely as two patients died. In retrospect, this seems an unreasonable decision by the safety committee as, sadly in most clinical SLE trials, a small number of deaths are noted. APRIL-LN, a phase II/III trial of atacept in combination with MMF in patients with LN, was terminated earlier due to an unexpected decline in serum immunoglobulin G on the first day in three patients. Two of them developed severe respiratory infections.<sup>72</sup> Subsequently, it was recognized it was the use of MMF (before the atacept was injected) that was linked to the fall in the immunoglobulin G levels, and integrated analysis of atacept trials is reassuring about the safety of atacept.<sup>73,74</sup> Vera Therapeutics<sup>®</sup> recently acquired atacept from Merck Serono<sup>®</sup> and are undertaking a new trial on LN (NCT05609812). Telitacept, another fusion protein that binds both to BAFF and APRIL, has met its primary endpoint in a recent phase III trial for SLE patients, with a sustained SRI4 response at week 52 and a rapid and sustained increase of C3 and C4.<sup>75</sup> Telitacept is currently under phase II clinical trials for LN (NCT05680480).

Blisibimod is a molecule with features peptide and antibody, inhibiting both membrane and soluble BAFF. The CHABLIS-SC1 study, a phase III trial, enrolled 442 SLE patients to receive blisibimod versus placebo. It excluded patients with severe active LN, but 29.9% of patients had renal involvement. This study did not meet its primary endpoint, but blisibimod treatment has demonstrated a corticosteroid tapering effect, and, also, in patients with renal disease, a reduction of over 50% in urinary protein/creatinine ratio between the 24 to the 52 weeks, suggesting that this drug could have benefits in LN patients.<sup>76</sup> Another phase III trial – CHABLIS7.5 to address the efficacy and safety of blisibimod in patients with and without LN is ongoing (NCT02514967).

Briobacept is another BAFF-binding protein. Studies in SLE induced-mice demonstrated its effectiveness in inhibiting anti-dsDNA antibody development, reducing proteinuria, and improving glomerular changes.<sup>77</sup> Despite these promising results, its efficacy and safety in human SLE have not been studied yet.

Combining a B-cell activation inhibitor to rituximab could prevent the expansion of autoreactive B cells by high levels of a BAFF resulting from B-cell depletion.<sup>78</sup> Thus, the CALIBRATE trial, a phase II trial, studied the outcome of 43 patients with recurrent or refractory LN at 24–48 weeks of a regimen that included cyclophosphamide, prednisone, and rituximab, followed by maintenance therapy with belimumab, compared with the same regimen, but without

belimumab. This was a safety trial, not powered to look critically at clinical benefit, but reduced maturation of transitional to naïve B cells and enhanced censoring of autoreactive B-cells were noted.<sup>79</sup>

BEAT-Lupus, a phase II 52-week clinical trial with 52 patients demonstrated that belimumab following rituximab in SLE patients (including 38% with LN) significantly reduced anti-dsDNA antibody levels by 70% and reduced the risk of severe flare by week 52.<sup>80</sup>

BLISS-BELIEVE trial, a phase III 104-week trial, compared belimumab therapy with placebo, belimumab plus rituximab and belimumab added to the standard of care therapy in patients with non-renal SLE. However, at week 52, the association between rituximab and belimumab did not improve disease control or remission. Despite the fact that severe active LN patients were excluded from this trial, greater reductions in proteinuria levels were observed in the belimumab plus rituximab group.<sup>81</sup>

SynBioSe – a phase II single-arm study with 16 patients with refractory disease and 12 with LN at the baseline treated with belimumab plus rituximab as induction therapy and with belimumab as maintenance showed a long-lasting reduction of anti-dsDNA and anti-C1q autoantibodies and prevention of B-cell repopulation for the 2-year follow-up, as well as a 60% complete renal response in this period.<sup>82</sup>

These findings provide some support for further investigation on the simultaneous use of B-cell targeted therapies with different mechanisms. SynBioSe-2, a phase III trial, comparing standard of care LN treatment versus rituximab and belimumab association, is currently recruiting patients (NCT03747159).<sup>83</sup>

## TNF-Like-Molecule Targeting Therapies

BIIBB023, a monoclonal antibody targeting a TNF-like inducer of apoptosis (TWEAK) that promotes renal inflammation, mesangial proliferation, tubular cell death and fibrosis, was studied in a phase II trial in 276 class III and IV LN patients after induction treatment with MMF and steroids. However, no difference was found in renal response rates, or in the renal response duration. In addition, treatment-emergent adverse effects were reported in 85% of treated patients (versus 76% of patients on placebo), which led to this trial being stopped at week 44.<sup>84</sup>

## Co-Stimulatory Blockade

B-cell depletion therapy is also associated with a reduced expression of CD40L, and other T-cell activation markers. Interactions between CD40L on T cells and CD40 on B cells in the renal interstitium are critical for the local expansion of autoantibody-producing B-cells in LN. Therapies that target this CD40-CD40L and its inducible co-stimulatory molecule (ICOS-ICOSL) ligation pathways may also improve LN management.<sup>85,86</sup>

Dapirolizumab is a polyethylene glycol-conjugated antigen-binding fragment targeting CD40L. A 24-week phase II study randomized 182 SLE patients to receive dapirolizumab. Patients with stable LN were permitted entry, whereas patients with class III or IV LN, proteinuria >2g/day, estimated glomerular filtration rate <45 mL/min/1.73 m<sup>2</sup>, and serum creatinine >2.5 mg/dl were excluded. Although the primary endpoint of this study BICLA response rates were not met, several clinical measures of disease activity generally improved from baseline in dapirolizumab-treated patients. Furthermore, greater reductions in anti-dsDNA levels and increases in C3 and C4 levels were observed in these patients, with an acceptable safety profile and tolerance. No renal endpoints were evaluated.<sup>87</sup>

Abatacept is CTA-4 agonist that interrupts CD80/CD86 interaction with CD28, modulating T-cell co-stimulation, and inhibiting T-cell proliferation and cytokine production. It has been approved for RA, and its co-stimulation inhibition has been found to be effective in LN mice.<sup>88,89</sup> The ACCESS trial – a 52-week phase II trial randomized 134 patients with class III or IV LN (with or without class V) and urine protein-to-creatinine ratio >1 to receive either abatacept or placebo added to low-dose cyclophosphamide followed by azathioprine. This trial showed no differences with respect to primary outcomes (complete response at week 24), secondary outcomes or safety issues.<sup>90</sup>

Another phase II/III trial randomized 298 class III or IV LN patients to receive either abatacept (10mg/kg or 30mg/kg) or placebo but this time in association with MMF. The primary endpoint (maintenance of glomerular filtration rate, minimal proteinuria, and inactive urinary sediment over the 52-week treatment time) was not achieved. However, renal improvement response rates at week 51 were higher in both of the abatacept groups (22.2% in the abatacept 30mg/kg group, 27.3% in the abatacept 10mg/kg group versus 20% in the placebo group). In a subgroup analysis, patients with nephrotic-range proteinuria



had a 20–30% greater reduction in urine protein-to-creatinine ratio versus placebo, from week 24 until the end of this study. Abatacept also showed greater improvements in serological activity.<sup>91</sup> However, the complete renal response criteria were more strict than in other LN trials, which may have led to the failure to achieve its primary endpoint.<sup>88</sup>

A phase III trial with abatacept versus placebo with similar primary outcomes as the previously described also showed no differences with abatacept treatment. However, abatacept-treated patients demonstrated a more rapid improvement in proteinuria and earlier sustained complete response.<sup>92</sup> Despite these discouraging results, abatacept may still have a place in LN treatment but also in articular and cutaneous involvement of SLE.<sup>93</sup>

Some phase II clinical trials are ongoing evaluating the safety and efficacy of molecules interfering with B- and T-cell interaction, for example with CD40 antagonists such as iscalimab (NCT03610516), BI 655064 (NCT03385564, NCT02770170 and VIB4920 (NCT05201469)).

## Anti-CD19 Targeted Therapies

CD19, as a B-cell surface marker, can also be a therapeutic target in order to increase B-cell depletion in patients with SLE, especially LN. However, obexelimab (XmAb5871) is a humanized monoclonal antibody with increased affinity to FcγRIIb, a reversible B-cell inhibitor. One hundred and four moderately active SLE patients were randomized to receive obexelimab vs placebo. However, the primary endpoint, the proportion of patients with no loss of improvement (defined by improvement of at least 4 points in SLEDAI score or more than one-grade decrease in one or more BILAG index A or B scores) by day 225, was not met in the obexelimab cohort, not even in the subpopulation with seropositive disease. These results lead the manufacturer to decide not to proceed to phase III trials.<sup>94</sup>

## Anti-CD22 Targeted Therapies

CD22 is expressed on the surface of B-cells and modulates B-cell activation and migration. Epratuzumab is a humanized anti-CD22 monoclonal antibody that inhibits B-cell activation. The first phase II/III trials were interrupted due to an interruption in drug supply, however exploratory pooled analyses described a 44.1% (15 out of 34 patients) response with epratuzumab 360/m2 versus placebo (30% - 9 out of 30 patients).<sup>95</sup> EMBLEM – another phase IIb trial was conducted with 227 patients. Responder rates between epratuzumab and placebo groups were not significant. However, in a post-hoc analysis, epratuzumab 600mg weekly showed reductions in musculoskeletal, mucocutaneous, cardio-respiratory, neuropsychiatric, constitutional and renal BILAG systems compared to placebo.<sup>96</sup> EMBODY 1 and 2, two phase III trials, enrolled 786 and 788 patients to receive epratuzumab vs standard of care therapy. Unfortunately, the primary endpoint, defined as improvement at week 48 based on the BICLA, was not achieved. 265 and 258 patients, respectively, prematurely discontinued due to lack of efficacy. All trials demonstrated a B-cell reduction of 30–50%; however, complement and autoantibody levels remained constant.<sup>97</sup> LN patients were excluded from these studies. Later, a post-hoc analysis suggested that SLE accompanied by Sjögren syndrome seems to benefit from epratuzumab.<sup>98</sup> Despite this, UCB® decided not to proceed with further studies.

## Anti-CD38 Targeted Therapies

Daratumumab is a human monoclonal antibody that targets CD38, a glycoprotein that is highly expressed in plasma cells, already approved for multiple myeloma treatment. Two cases were reported in 2020 where it was used to treat two very active SLE patients, one of them with class III and V LN, already treated with MPAA, cyclophosphamide, and bortezomib. Treatment with daratumumab (followed by maintenance with belimumab) was associated with a significant reduction in pathogenic anti-dsDNA antibodies, as well as overall improvement, with proteinuria lowering and LN improvement.<sup>99</sup> A phase II trial evaluating the efficacy and safety of daratumumab in 12 patients with LN for 24 months is currently recruiting (NCT04868838).

## Anti-CD6 Targeted Therapies

CD6 is a costimulatory receptor expressed on T-cells, and, together with activated leukocyte cell adhesion molecule (ALCAM), regulates T-cell activation and function. The presence of soluble ALCAM in SLE patients is associated with active renal involvement, suggesting CD6/ALCAM pathway as a disease biomarker and a therapeutic target.<sup>100</sup>

The EQUALISE study is a phase Ib multiple ascending-dose study of Itolizumab (a humanized monoclonal antibody that binds CD6 and blocks ALCAM interaction) in 55 patients with SLE with or without active class III or IV LN. Results are still awaited (NCT04128579).

## Bruton's Tyrosine Kinase-Targeted Therapies

Another potential therapy target is Bruton's tyrosine kinase (BTK), which is a cytoplasmic tyrosine kinase present in cells of hematopoietic origin, essential to intracellular signaling in the development, survival, and activation of B-cells. BTK+ cells in SLE patient's blood seem to correlate with disease activity.<sup>101,102</sup> BTK inhibitors have been shown to limit the development of nephritis in SLE-prone mice; however, no benefit was yet identified in human SLE patients.<sup>102</sup>

Fenebrutinib, an oral highly selective BTK inhibitor, was studied in 260 SLE patients in the ATHOS phase II trial. Patients with proliferative LN were excluded. In this trial, clinical efficacy was not achieved, although a sustained strong BTK inhibition was demonstrated. However, fenebrutinib treatment significantly reduced CD19+ B-cells, immunoglobulins, and increased complement C3 and C4, with an acceptable safety profile.<sup>103</sup> As well as fenebrutinib studies, phase II trial with evobrutinib (with no LN patients) demonstrated no clinical differences versus placebo.<sup>104</sup> Other BTK inhibitors, such as ibrutinib, branebrutinib, elsubrutinib (alone or in combination with upadacitinib), orelabrutinib, TAS 5315, have already shown efficacy in SLE animal models, and are currently in clinical trials.<sup>105</sup>

## Janus-Kinase Inhibitors

Janus-kinase (JAK) and Signal Transducers and Activators of Transcription (STAT) cascade signaling lead to the activation of different proinflammatory cytokines (interleukins, interferons, as well as endocrine factors), enhancing T- and B-cell interaction and antibody production. Thus, inhibiting this pathway could also be a target for SLE patients, and tofacitinib (a JAK/STAT inhibitor) has been used in mice successfully reducing proteinuria and improving renal function.<sup>106</sup> One case report described a patient with RA and SLE with class III LN resistant to azathioprine, hydroxychloroquine, MMF, rituximab and cyclosporin A treatments, who started tofacitinib 5mg bd with persistent complete renal response.<sup>107</sup>

Deucravacitinib is a highly selective tyrosine kinase 2 (TYK2), a JAK family member, studied in SLE patients in the phase II trial PAISLEY, where active LN patients were excluded. However, deucravacitinib treatment led to higher response rates for SRI-4, with an acceptable safety profile.<sup>108</sup> A phase II clinical trial to evaluate the safety and effectiveness of deucravacitinib in LN patients, PAISLEY LN, failed to enroll a sufficient number of patients.

Baricitinib is an oral selective inhibitor of JAK 1 and 2, approved for AR, and was implicated in phase II and III trials for SLE patients (without severe LN). In a phase II trial, baricitinib 4mg significantly improved disease activity compared to placebo.<sup>109</sup> SLE-BRAVE-I and II were phase III trials randomly assigned 760 and 775 patients, respectively, to receive baricitinib 4 mg, baricitinib 2 mg, or placebo once daily for 52 weeks. The SLE-BRAVE I met its primary endpoint (SRI-4 response at week 52) in the 4mg baricitinib group; however, this positive result was not replicated in SLE-BRAVE II.<sup>110,111</sup> None of the secondary endpoints were met in either study, including glucocorticoid tapering. Additional analyses are being performed to understand this discordance.

A 6-month clinical trial with 60 patients to evaluate the efficacy of baricitinib (a JAK1 and 2 inhibitor) to induce remission of active LN versus cyclophosphamide is ongoing (NCT05432531).

## Proteasome Inhibitors

Proteasomes are one of the main protein degradation systems. Its inhibition leads to the accumulation of defective immunoglobulin chains with subsequent apoptosis of plasma cells with a decrease in immunoglobulin production. This mechanism could lead to a better control of SLE severity and damage. Bortezomib approved for multiple myeloma treatment, decreases anti-dsDNA antibody levels, proteinuria and kidney damage, as well as a type-I IFN activity inhibition, leading to a prolonged survival in SLE mice.<sup>112</sup> Case series with class III to V LN patients suggested that bortezomib could be a safe and effective treatment for resistant LN patients, with significantly reduced proteinuria, lower levels of anti-dsDNA levels, and, mostly partial, renal responses.<sup>113–115</sup>

However, bortezomib carried a 30% risk of peripheral neuropathy, as well as thrombocytopenia, and indications for its use need to be better defined. As was noted with bortezomib, next-generation proteasome inhibitors delanzomib and

carfilzomib also have shown a decrease in anti-dsDNA levels, proteinuria, and kidney damage in SLE mice, and could be a good alternative as they are associated with less adverse effect rates.<sup>116,117</sup>

MISSION, a phase Ib/II study of zetomipzomib (KZR-616 – a selective inhibitor of the immunoproteasome) in patients with SLE (with or without LN) was completed recently. However, the results are yet to be published (NCT03393013). A phase II trial comparing the efficacy and safety of two different doses of zetomipzomib with placebo in patients with active LN is ongoing (NCT05781750).

## Interleukin-Targeting Therapies

IL-23 is an important contributor to the expansion and maintenance of Th17 cells, enhancing the CD4+ production of IL-17, which induces the production of several inflammatory cytokines. IL-17 has been found to be a good biomarker for SLE activity and a predictor of LN remission.<sup>118</sup>

Two case reports suggest that secukinumab (an antibody targeting IL-17) may bring some improvement for LN patients.<sup>119,120</sup> One described a 29-year-old woman with SLE previously treated with prednisolone, thalidomide, azathioprine, methotrexate, and rituximab, who developed a class IV lupus nephritis that relapsed despite the addition of immunoglobulin and belimumab to the previous therapy. Leflunomide was started with no renal response. After that, secukinumab was started (300mg id subcutaneously) with a complete renal response 8 months after the treatment.<sup>120</sup> The other case described a 62-year-old woman with psoriasis vulgaris and SLE with LN previously treated with steroids and cyclosporin A, who presented with a nephrotic syndrome along with exacerbation of psoriasis and alopecia. The kidney biopsy showed a Class IV and V LN. She was first started on high-dose steroids and MMF, then changed to cyclophosphamide without any renal response. Peripheral blood mononuclear cells were analyzed using flow cytometry, suggesting a substantial proliferation of Th17 cells. Secukinumab was started (300mg weekly) with a marked reduction in SLE activity and reduced levels of creatinine, proteinuria and serological markers.<sup>119</sup>

A two-year phase III trial is ongoing to evaluate the efficacy and safety of subcutaneous secukinumab 300 mg compared to placebo, in combination with standard of care therapy, in patients with active class III or IV LN (NCT04181762).

Ustekinumab is a monoclonal antibody that inhibits both IL-12 and IL-23, interfering with Th17 activity. This anti-IL12/23 drug met its endpoints in a phase II trial of non-LN but failed to do so in a phase II trial. Further studies have been abandoned.<sup>121,122</sup>

Guselkumab is a monoclonal antibody that binds to IL-23. A phase II randomized trial to assess the efficacy and safety of this drug in LN patients has already finished. Results are yet to be published (NCT04376827).

IL-1 is a proinflammatory cytokine associated with mesangioproliferative nephritis in mice. Treatment with an IL-1 antagonist (such as anakinra) has demonstrated a reduction in proteinuria and lower renal damage in LN mice.<sup>123</sup> Measurement of an anti-IL-1 antagonist could help to predict future renal involvement in LN patients.<sup>124</sup> Some case reports suggest that anakinra may be an effective and safe treatment for SLE patients; however, no randomized trials have been done so far.<sup>125,126</sup>

IL-2 is a main regulator of Treg cells, and its deficiency can lead to B- and T-cell hyperactivity. Aldesleukin (a recombinant human IL-2) was used in a single center in Germany in 10 SLE patients with active and refractory disease. Its use was associated with an increase in Treg-cells, as well as an increase in levels of complement. All of the patients showed a reduction in disease activity, with 8 patients achieving a complete response after 9 weeks of treatment.<sup>127</sup> More studies are needed in order to address its efficacy in SLE patients. A prospective, single-center study is comparing the efficacy and safety of human umbilical cord mesenchymal stem cells and low-dose IL-2 in the treatment of LN (NCT05631717).

Another interleukin strongly implicated in LN pathogenesis is IL-6, and like IL-17, is also considered to be a biomarker of SLE activity and a good predictor of LN remission.<sup>118</sup> IL-6 inhibition delays LN onset in mice and reduces proteinuria and serum creatinine levels helping to preserve glomerular function and structure.<sup>128</sup> A phase II study randomized 25 class III or IV LN patients with persistent disease, despite standard-of-care therapy, to receive either sirukumab (an anti-IL6 monoclonal antibody) or placebo. However, treatment with sirukumab did not result in an overall change in proteinuria from baseline to week 24, despite binding to IL-6 with high affinity and specificity. There was also

no significant improvement in disease activity scores, and patients treated with sirukumab experienced significantly more adverse effects, mostly infection-related ones, during this trial.<sup>129</sup> No further trials have been undertaken with this drug.

## Anti-IFN $\alpha$

Type I interferon plays an important role in SLE pathology and is correlated with disease activity, especially in LN patients.<sup>130</sup> Anifrolumab is a human monoclonal antibody that binds to type I interferon receptor subunit 1, was approved by the FDA in 2021 for SLE patients with moderate-to-severe manifestations (but without severe active renal or neuropsychiatric involvement) following MUSE, TULIP-1 and 2 trials.<sup>131</sup> Evidence that it is effective in LN patients is lacking. TULIP-LN is a 52-week phase II trial, aiming to randomize 147 class III and IV LN patients to receive anifrolumab 300mg monthly, anifrolumab 900mg three times and then 300mg monthly, or placebo along with standard therapy. The primary endpoint, a change in baseline 24-hour urine protein–creatinine ratio at week 52 combined anifrolumab versus placebo groups, was not met. However, a more intensive treatment with anifrolumab was associated with more complete renal responses (45.5% with anifrolumab vs 31.1% placebo) and also with sustained corticoid reductions. The incidence of herpes zoster and influenza infections was higher among patients on anifrolumab treatment (16.7% vs 8.2% placebo).<sup>132</sup> Overall, anifrolumab in higher doses could be a good alternative to LN patients, but more studies are needed to support this hypothesis. IRIS, a 116-week phase III randomized controlled trial, is recruiting LN patients to evaluate the efficacy and safety of anifrolumab plus standard of care (mycophenolate mofetil and corticosteroids) in active class III or IV LN patients (NCT05138133).

Sifalimumab is another IFN $\alpha$  inhibitor. A phase II trial that randomized 431 patients given different doses of sifalimumab versus placebo demonstrated clinical efficacy of sifalimumab in the treatment of moderate-to-severe SLE patients with an inadequate response to standard-of-care treatments.<sup>133</sup> However, active LN patients were not included in this study, and its efficacy in this group of patients needs to be better addressed.

## Complement Inhibition

Complement is a component of the innate immune system with significant implications for modulating adaptive immune response, T-cell activation and B-cell regulation. Its inhibition has already been demonstrated to be implicated in lupus pathogenesis.

Eculizumab is a recombinant humanized monoclonal antibody that binds to C5 complement, blocking the activation pathway. Its use in mice has demonstrated a significant reduction in proteinuria and renal dysfunction.<sup>134</sup> However, eculizumab has not been studied for LN. However, phase II clinical trials to study other complement inhibitors such as ravulizumab (an anti-C5 monoclonal antibody – NCT04564339), narsoplimab [an anti- mannose-binding protein-associated serine protease 2 (MASP-2) antibody targeting the lectin pathway of the complement system – NCT02682407], APL-2 (an anti-C5 monoclonal antibody – NCT03453619), iptacoban (a factor B inhibitor of the complement pathway – NCT05268289), ALXN2050 (a factor D inhibitor of the complement pathway – NCT05097989) in LN patients are ongoing.

## Other Immunosuppressants

Following the inflammatory cascade, renal-tissue macrophages are activated, contributing to tissue damage. Laquinimod (5-chloro-N-ethyl-4-hydroxy-1-methyl-2-oxo-N-phenyl-1,2-dihydroquinoline-3-carboxamide) is an immunomodulatory drug that increases the proportion of anti-inflammatory type II monocytes/macrophages, decreasing proinflammatory ones, reducing antigen presentation, thus leading to a decrease in INF- $\gamma$ , IL-12, IL-17, IL-23 and TNF $\alpha$ . Studies with LN mouse models suggested that Laquinimod could contribute to improved survival, proteinuria and glomerular changes.<sup>135</sup> In a phase II trial 46 patients were randomized to receive laquinimod 0,5mg/day, laquinimod 1mg/day, or placebo, together with standard-of-care therapy, for 24 weeks. Patients receiving laquinimod had a greater eGFR and proteinuria change vs placebo. However, this trial was not powered to establish definitely any difference between these groups.<sup>136</sup> No further studies have been done in LN.

Another immunomodulating agent – iguratimod, whose mechanisms of action are not fully understood, seems to have an inhibitory effect on inflammatory cytokines and immunoglobulin production. In preclinical studies with lupus-prone mice, this



drug prevented LN and decreased the amount of proteinuria as well as decreased immunocomplex deposition.<sup>137</sup> A Chinese study cohort with 14 refractory or relapsing LN patients (with no SLE extra-renal involvement) substituted iguratimod for previous immunosuppressant agents, with no changes in steroid dosing. Of the thirteen eligible patients, 38.5% achieved complete response and 53.8% achieved partial response at week 24, with the maintenance of eGFR in all patients. However, 25% of the patients experienced a relapse during the 144-week follow-up.<sup>138</sup> A Chinese multicenter randomized 52-week parallel positive drug-controlled trial is ongoing in order to demonstrate whether iguratimod can be used as an alternative induction or maintenance therapy for class III to V LN patients (NCT02936375).<sup>139</sup>

Mizoribin is an immunosuppressant similar to MMF that inhibits inosine monophosphate dehydrogenase, by inhibiting both humoral and cellular immune responses. It has been approved for LN only in Japan (where the experience with this drug is largely confined), invariably co-prescribed with steroids in LN maintenance therapy, and seems to be well tolerated.<sup>140</sup> However, some reports had shown inconsistent results regarding its effects on proteinuria and on the timing to flare versus steroids.<sup>141–144</sup> The optimal dose of this drug is yet to be found.<sup>145</sup> Some other reports suggest that mizoribin could have increased efficacy when associated with other immunosuppressants, such as tacrolimus, as an induction therapy.<sup>146,147</sup> A post-marketing surveillance study that included 559 patients on mizoribin plus steroids (with or without tacrolimus) showed renal remission in 63.3% of patients, with 26.5% achieving complete renal remission at week 24, and a good safety profile.<sup>148</sup> More studies are needed in order to establish mizoribin efficacy versus placebo or other drugs in LN patients.

Sirolimus is an mTOR inhibitor (also called rapamycin). A recent meta-analysis included 49 patients with SLE treated with sirolimus and demonstrated that 41.2% of LN patients achieved renal remission; however, no significant changes in proteinuria were found.<sup>149</sup> A study to investigate the efficacy of sirolimus for mild proteinuric flares in patients with Class III/IV (with or without class V) LN is currently ongoing (NCT04892212).

## Cell-Based Therapies

Hematopoietic stem cell transplantation (HSCT), by eliminating self-reactive memory T and B cells, has been reported as a potential target for refractory SLE patients, already reported in some small trials, with a good and long-term clinical and serological response, without evidence of relapse or progression in 5 years achieving 50% in two cohort studies with 85 and 50 SLE patients. However, no randomized trials have been done so far. In addition, the invasive nature of this procedure, its toxicity and the high infectious risk associated with it should be weighed up for each patient.<sup>150–152</sup> Mesenchymal stem cells (MSCs) can also exert immunomodulatory effects, downregulating active immune responses. The clinical efficacy of MSC in treating patients with refractory autoimmune disorders, including SLE, is encouraging. An open-label clinical trial with 81 active LN patients refractory to standard-of-care treatment was submitted to allogeneic bone marrow MSC transplantation. A total of 60.5% of patients experienced complete or partial remission during the 12 months, and a significant difference was observed in the average renal BILAG score, proteinuria and creatinine values.<sup>153</sup> However, MSC treatment has been associated with relapsing rates of 12.5% and 16.7% at 6 and 12 months, respectively, which could reflect the need to repeat MSC infusions after 6 months to a more prolonged efficacy.<sup>154</sup>

A Chinese randomized trial with 18 LN patients showed that MSC had no additional effect over standard immunosuppression, and the trial was abandoned.<sup>155</sup>

Chimeric antigen receptor T (CAR-T) cells targeting the surface antigen CD19, depleting B-cells, have emerged recently from cancer immunotherapy development, as a potential target for SLE patients, especially LN.<sup>156</sup> A small series of 5 resistant LN patients were treated with anti-CD19 CAR-T cells. Clinical remission was observed in all of the 5 patients, with marked reductions in proteinuria and creatinine levels. Serological markers normalized, including anti-dsDNA antibody levels, and, despite B-cell reconstitution, no SLE relapse was seen during the follow-up (5 to 17 months) and no immunosuppressive medication was required since the initiation of CAR T cell treatment.<sup>157</sup> A clinical trial with 9 refractory LN patients to assess safety and effectiveness of CD19/BCMA CAR-T cells is currently ongoing (NCT05085418).

## Discussion

In this article, we have summarized the new drugs that have been and are being developed for LN patients. LN treatment is still based on conventional immunosuppressants, and there has been little evidence of improved outcomes in the past thirty years.

The development of new biological drugs is an expensive and laborious process. SLE is a very heterogeneous disease, with a wide interindividual variation in molecule expression, which could explain why some LN patients respond well to one drug, while others do not. A precision approach is badly needed.

Belimumab is the only FDA-approved drug for LN patients. However, complete renal response was only observed in 30% of LN patients included in the BLYSS-LN trial, and this response was more clear-cut in patients with a urine protein/creatinine ratio  $<3\text{g/g}$ . It is only approved for patients with an incomplete response or persistent disease after the standard therapy, and with positive serology for anti-dsDNA antibodies, which excludes almost a third of all SLE patients.<sup>16,36,37</sup>

Rituximab has only been approved by NHS England but is also recommended as an alternative treatment for non-responding or refractory LN by ACR and EULAR outlines.<sup>28,29</sup> Despite its failure to achieve its primary endpoint in the LUNAR trial, rituximab has been associated with several clinical and serological improvements. Since it is a widely available and reasonably safe drug, it has been widely used off-label, with good clinical outcomes.<sup>13,47</sup> Rituximab failure has been associated with increased levels of BAFF.<sup>44</sup> Thus, combined therapies with a B-cell depleting therapy, rituximab plus a BAFF inhibitor, have been undertaken, notably the CALIBRATE and BLISS-BELIEVE trials. However, the potential benefits of combining both drugs have given some conflicting results. CALIBRATE was a reassuring study on LN patients and not powered to look at benefit.<sup>79,81</sup> BEAT-Lupus and SynBioSe trials suggested that belimumab added to rituximab in induction therapy, with belimumab added to standard-of-care therapy for maintenance, could reduce the risk of a severe disease flare, but also could improve renal outcomes inducing remission.<sup>80,83</sup> However, the BLISS-BELIEVE trial (of non-renal SLE patients) in which every patient received belimumab and half also received rituximab showed no benefit for those treated with combination of monoclonals.<sup>81</sup> It may be the sequence of giving biologics is important, with rituximab to be given first, followed by belimumab, being more likely to succeed.

Encouragingly, new drugs are showing some promising results in phase II and III trials regarding LN [Table 1]. Obinutuzumab, blisibimod, abatacept, anifrolumab and baricitinib added to standard-of-care therapy for LN have been shown to improve outcome for LN patients.

In the NOBILITY phase II trial, obinutuzumab showed significantly higher complete renal responses at week 76 and week 104 together with a potent depletion of CD19+ B-cells. If phase III trials confirm these results, obinutuzumab – a fully humanized antibody, with a lower risk of allergic reactions – could potentially replace rituximab in the treatment of refractory LN.<sup>56</sup>

Blisibimod, a BAFF-inhibitor, has also demonstrated in CHABLIS-SC1 trial, a reduction of urinary protein/creatinine ratio between the 24 to the 52 weeks, suggesting that this drug could have benefits in LN patients.<sup>76</sup>

Abatacept trials showed little difference in clinical endpoints (although criteria for response were more strict than other LN trials), but improvements in proteinuria and earlier sustained complete response have been associated with this treatment, leaving some hope for future trials with abatacept in LN patients.<sup>88,90,91,93</sup>

Anifrolumab, already approved for SLE patients, has been associated with more complete renal responses compared to a placebo.<sup>132</sup> Phase III trials are ongoing, and LN patients might benefit from this drug.

Baricitinib, a JAK 1 and 2 inhibitor, demonstrated promising results in phase II trials on SLE patients.<sup>109</sup> However, phase III trials, SLE-BRAVE I and II, were discordant on the results since the primary endpoint reached in SLE-BRAVE I with baricitinib 4mg was not replicated in SLE-BRAVE II.<sup>110,111</sup> Additional studies are needed to better clarify these results. A trial to evaluate the efficacy of baricitinib on LN is ongoing.

More recently, CAR-T-cells have emerged with some impressive results in 5 LN patients in terms of proteinuria and creatinine levels, as well as in serological markers, with no relapses seen during their follow-up and with no other immunosuppressive medication required.<sup>157</sup> Results on rather more LN patients are awaited to determine whether this costly and potentially hazardous approach may have a role for hard-to-treat LN patients.

**Table I** Phase II and III Trials for Lupus Nephritis

Target	Name	Trial	Phase	Result
<b>B-CELLS</b>				
<b>CD20</b>	Obinutuzumab	REGENCY	III	In progress
	Ocrelizumab	BELONG	III	Interrupted
	Rituximab	LUNAR	III	Negative
<b>BAFF</b>	Belimumab	BLYSS-LN	III	Approved
	Blisibimod	CHABLIS 7.5	III	In progress
	Tabalumab	ILLUMINATE-2	II	Negative
<b>BAFF+APRIL</b>	Atacicept	APRIL-LN	II/III	Negative
	Telitacicept	NCT05609812 NCT05680480	III II	Recruiting In progress
<b>TWEAK</b>	BIBB023	ATLAS	II	Negative
<b>CD20 + BAFF</b>	Belimumab + Rituximab	CALIBRATE	II	Reassuring
		BEAT Lupus	II	Positive
		SynBioSe-1	II	Negative
		SynBioSe-2	III	In progress
<b>CD38</b>	Daratumumab	NCT04868838	II	Recruiting
<b>T-CELLS</b>				
<b>CD40L</b>	Dapirolizumab	NCT04294667	II	Negative
<b>CD80/CD86</b>	Abatacept	ACCESS	II	Negative
	Iscalumab	NCT03610516	II	In progress
	BI 655064	NCT02770170	II	Negative
	VIB4920	NCT05201469	II	In progress
<b>INTRACELLULAR SIGNALING</b>				
<b>JAK-TYK2</b>	Deucravacitinib	PAISLEY LN	II	Interrupted
<b>PROTEASOME INHIBITOR</b>				
	Zetomipzomib	NCT05781750	II	In progress
<b>CYTOKINES</b>				
<b>IL-12/23</b>	Secukinumab	NCT04181762	III	In progress
<b>IL-23</b>	Guselkumab	NCT04376827	II	Results awaited
<b>IL-17</b>	Sirukumab	CNTO 136	II	Negative
<b>Type I INF receptor</b>	Anifrolumab	IRIS	III	In progress
<b>COMPLEMENT PATHWAY</b>				
<b>C5</b>	Ravulizumab	NCT04564339	II	In progress
<b>MASP-2</b>	Narsoplimab	NCT02682407	II	In progress
<b>Factor B</b>	Iptacoban	NCT05268289	II	In progress
<b>Factor D</b>	ALXN2050	NCT05097989	II	In progress

**Abbreviations:** APRIL, A proliferation-inducing ligand; BAFF, B-cell activating factor; CD40L, CD40 ligand; IFN, interferon; IL, interleukin; JAK-TYK2, Janus tyrosine kinase 2; MASP-2, mannose-binding protein-associated serine protease 2; TWEAK, tumor necrosis factor-like inducer of apoptosis.

## Conclusions

The development of new drugs to improve outcome in patients with LN has been a challenging process compared to other rheumatological diseases. This could be explained by the big heterogeneity between SLE patients in terms of clinical features, serological and molecular markers, as well as histological features. However, there is an urgent need to improve clinical trial design, with an appropriate population, and adjusted-outcome measures, in order to prove proper benefits of these new drugs and change the outcome of LN patients.

## Disclosure

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