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PRODUCT REVIEW

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Belimumab for systemic lupus erythematosus – Focus on lupus nephritis

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ABSTRACT

In recent years, advances in the treatment and management of patients with systemic lupus erythematosus (SLE) have improved their life expectancy and quality of life. However, lupus nephritis (LN) still represents a major life-threatening complication of the disease. Belimumab (BEL), a fully human monoclonal IgG1λ antibody neutralizing soluble B cell activating factor, was approved more than ten years ago as add-on therapy in adults and pediatric patients with a highly active, autoantibody-positive disease despite standard of care (SoC). Recently, the superiority of the addition of BEL to SoC was also demonstrated in LN. In this review, we provide a comprehensive overview of the study landscape, available therapeutic options for SLE (focusing on BEL in renal and non-renal SLE), and new perspectives in the treatment field of this disease. A personalized treatment approach will likely become available with the advent of novel therapeutic agents for SLE and LN.

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Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune disease with a heterogeneous clinical presentation, affecting mainly women of childbearing age and minorities.[1] The condition may manifest in multiple organ systems, such as skin, mucous/serous membranes, and joints. In addition, it may result in life-threatening complications involving vital organs and tissues such as the brain, blood, and the kidney.[1] The production of multiple autoantibodies in chronic inflammation and subsequent immunological events are the leading cause of damage during the disease course.[2] Genetic, environmental, hormonal, epigenetic, and immunoregulatory factors act sequentially or simultaneously on the immune system through several partially elucidated mechanisms leading to a loss of self-tolerance.[1] Almost every immune cell within both the innate and adaptive immune arms is involved in the pathogenesis of the disease.

Immunological pathways involved

A crucial mechanism for triggering the activation of an aberrant immune response is the dysregulation of several cell death pathways, including apoptosis, necrosis, necroptosis, pyroptosis, and neutrophil death through the formation of neutrophil extracellular traps (NETs), and the incomplete clearance of debris which induces the accumulation of remnants into tissues.[3] In addition to other unknown factors, these mechanisms lead to a death-dependent immunogenic and non-tolerogenic immune response.[4] Furthermore, non-phagocytosed dead cells are presented as autoantigens eliciting B and T cell responses in SLE extrafollicular reactions and germinal centers (GCs).[5,6] Consequently, the formation of immune complexes (ICs)-containing autoantibodies that recognize nuclear and cytoplasmic autoantigens released from dead cells induce a potent downstream of pro-inflammatory events, including the synthesis of type I interferons (IFNs).[7]

Immunologic events in the pathogenesis of lupus nephritis

Lupus nephritis (LN), as defined by clinical and laboratory findings, is a common and severe manifestation of the disease occurring in about 40% of SLE patients, most commonly within the first five years after the diagnosis.[8] Clinically asymptomatic urinary sediment abnormalities, nephritic or nephrotic syndromes, and rapidly progressive renal failure represent the broad spectrum of its presentation.[9] Organ damage is the result of glomerular, tubulointerstitial, and vascular lesions.[10] In LN, the main aetiopathogenetic event is the deposition of ICs into the kidney associated with activating the complement system.[11] Autoantibodies can react with glomerular autoantigens, especially those within the glomerular basement membrane (GBM). Thus, the localization of ICs influences the clinical LN phenotype.[12]

Subendothelial ICs cause endothelial dysfunction, complement system activation, and the enrollment of immune cells into crescents, also containing proliferating cells from the parietal layer of the Bowman's capsule ("proliferative" variants). These proliferative variants with subendothelial immune deposits correspond to classes III and IV LN according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification, which is currently in use and is regularly revised.[13,14]

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Moreover, subepithelial ICs, on the other hand, cause podocyte damage with only limited pro-inflammatory cell recruitment because the GBM prevents direct interaction with the intravascular space. As a result, there is less glomerular inflammation, but substantial glomerular filtration unit dysfunction causing significant proteinuria, corresponding to class V LN.[12,13]

In addition, increasing evidence suggests the tubulointerstitial compartment's involvement in the pathogenesis of the more severe LN forms, which are associated with the formation of T and B cell aggregates and ectopic GC-like structures containing follicular dendritic cells.[15] The resulting inflammation, tubular atrophy, and interstitial inflammation/fibrosis influence the long-term prognosis of the disease.[10,12,14]

Belimumab (BEL), a fully human monoclonal IgG1λ antibody neutralizing soluble B cell activating factor (BAFF), is the first biological drug approved for the treatment of active SLE despite standard of care (SoC) since 2011.[16,17] First, BAFF inhibition effectively delayed SLE onset in experimental murine models.[18] Then, four randomized controlled trials—among them the *BLISS-52* and *-76* trials—demonstrated the effectiveness of BEL over SoC therapy in SLE patients.[19–22] Recently, BEL has been approved for the treatment of LN based on a phase III trial (*BLISS-LN*).[23]

This product review on BEL aims to summarize the rationale for its design and mechanism of action and discusses its role within the spectrum of currently available and future SLE and LN therapies.

Key issues

- Considerable clinical heterogeneity exists among patients with SLE
- Lupus nephritis is associated with substantial morbidity and mortality
- Belimumab was the first approved biological therapy for SLE
- Anifrolumab, an interferon receptor antagonist, has recently been approved for non-renal SLE, and numerous other therapies are under investigation
- For LN, standard treatment consists of corticosteroids in combination with either mycophenolate mofetil or cyclophosphamide
- Belimumab has recently been approved in the United States and Europe for LN in addition to standard of care
- Voclosporin has been FDA-approved for LN in addition to standard of care
- Despite negative trials as the sole agent, rituximab is recommended for refractory SLE, and several recent studies have investigated it in combination with BEL

Current treatment options for systemic lupus erythematosus and lupus nephritis

Several therapeutic options are available for the treatment of SLE and LN, which are also supported by current guidelines.[24,25]

The use of the antimalarial drug hydroxychloroquine (HCQ) is considered standard of care (SoC) in all patients with SLE. HCQ is generally well tolerated but does require regular ophthalmological screening. In addition to this, many patients need glucocorticosteroid (CS) therapy to control SLE disease activity, the dose and route of administration depending on SLE severity and end-organ involvement.[24] However, CS contribute to long-term organ damage, and their optimal use is still a matter of debate.[26,27] Even though there is little evidence of superior efficacy for methylprednisolone pulse therapy during the induction phase in LN, doses ranging from 250 to 1000 mg per day for three consecutive days are considered SoC and allow for lower starting doses and more rapid tapering of subsequent oral CS.[25] For long-term management, reducing the daily CS dose to below 7.5 mg or, ideally, discontinuation is optimal. However, if neither is tolerated, the use of additional immunosuppressive agents such as methotrexate (MTX), azathioprine (AZA), or mycophenolate mofetil (MMF) is recommended, all of which can and should be considered early if the initial presentation of SLE is organ-threatening.[24] Intravenous Cyclophosphamide (CYC) can also be used for severe and organ- or life-threatening SLE manifestations, such as LN.[25] Its use is currently disfavored for several reasons, such as the need for intravenous administration and potential toxicities, including hemorrhagic cystitis and female infertility. They can be, in part, avoided by prophylaxis with gonadotropin-releasing hormone agonists[28]and the use of lower cumulative CYC doses.[29] According to the latest European Alliance of Associations for Rheumatology (EULAR) guidelines, biologics should be considered in SLE patients with residual disease activity or frequent disease flares despite SoC.[24] Belimumab is the only biologic mentioned in the latest EULAR recommendations. Nevertheless, rituximab (RTX), an anti-CD20 antibody targeting circulating B cells, may also be considered in refractory disease[25,30]despite negative trial results in SLE.[31,32] Rituximab is discussed as a therapeutic (off-label) option in the EULAR recommendations, but its use is heterogeneous throughout Europe.[33] Recently, RTX has gained interest in combination with BEL. The respective trials will be discussed later in this article. The overall treatment goals for SLE are long-term patient survival and the prevention of organ damage.

As far as LN is concerned, the guidelines differ in some aspects:[25] Again, the SoC consists of HCQ and CS in varying doses. The latter is most frequently administered as initial intravenous pulse therapy for remission induction. In class III and IV LN, MMF (2–3 g per day) or low-dose CYC (500 mg every two weeks for six doses) are recommended to complete the remission induction regimen; high-dose CYC (0.5–1.0 g/m^2 body surface area) is indicated in those patients at high risk of kidney failure (i.e. rapid-progressive glomerulonephritis [RPGN] at biopsy, reduced estimated glomerular filtration rate [eGFR], or severe inflammation). In class V LN with nephrotic range proteinuria, a combination of MMF with tacrolimus (TAC) can be considered as an alternative.[25,34] Finally, the recommendations for maintenance therapy include MMF (especially when used for remission induction) or AZA (particularly when pregnancy is considered in the future), both in combination with low-dose CS if needed.[25]

For refractory disease, RTX is recommended; as an add-on therapeutic approach, BEL is currently discussed and has recently been approved for the treatment of LN based on one large trial.[23,25]

Treatment goals in LN are the preservation or improvement of renal function, and a relevant reduction in proteinuria of at least 25% after three months of treatment, 50% after six months, and a urinary protein-to-creatinine ratio [uPCR] <0.7 g/g after one year (complete renal response, [CRR]).[25,35] In addition, adjunctive therapy with inhibition of the renin-angiotensin-aldosterone-system (RAAS), statins, vitamin D, and calcium is also important.[25]

An overview of the respective mechanisms of action of agents used or potentially used for the treatment of LN in the near future is given in Figure 1.

Recent developments

Several different and new agents have been investigated as treatment options for SLE and LN in the recent past.

Anifrolumab (ANI), a human monoclonal antibody against the receptor for type I interferons, has been tested as a treatment in active SLE in the *TULIP-1*[36] and *-2* trials.[37] The mechanism of action of ANI is through blocking the interferon receptor and downstream pathogenic signaling pathways. The effects seem to be more pronounced in individuals with an increased interferon gene signature, which may be helpful as a biomarker of responsiveness.[38,39] While the primary endpoint of SLE responder index (SRI)-4 after 52 weeks was not reached in *TULIP-1*, several secondary endpoints showed promising results and were re-investigated as primary composite endpoints in *TULIP-2*: Specifically, more patients treated with ANI showed a response after 52 weeks as measured by the BILAG-based composite Lupus assessment (BICLA); in addition, a significant reduction in CS dosage was possible in the ANI group.[37] The FDA has subsequently approved ANI to treat adults with moderate-to-severe SLE in 2021.[40] while European Medicines Agency (EMA) approval was obtained early in 2022. The issue of different endpoints in *TULIP-1* and *TULIP-2* is a matter of ongoing discussion, and the position of ANI in current practice has yet to be established. The reader is referred to other reviews for an in-depth discussion of this matter, which is beyond the scope of this review.[41]

Another new agent is voclosporin (VCS), a novel calcineurin inhibitor (CNI) that has been shown to significantly improve the CRR rates in patients with LN when added to MMF and low-dose CS (*AURORA-1 trial*).[42] It has been approved for adults with active LN by the FDA,[43] whereas EMA approval is pending. The mechanism of action is thought

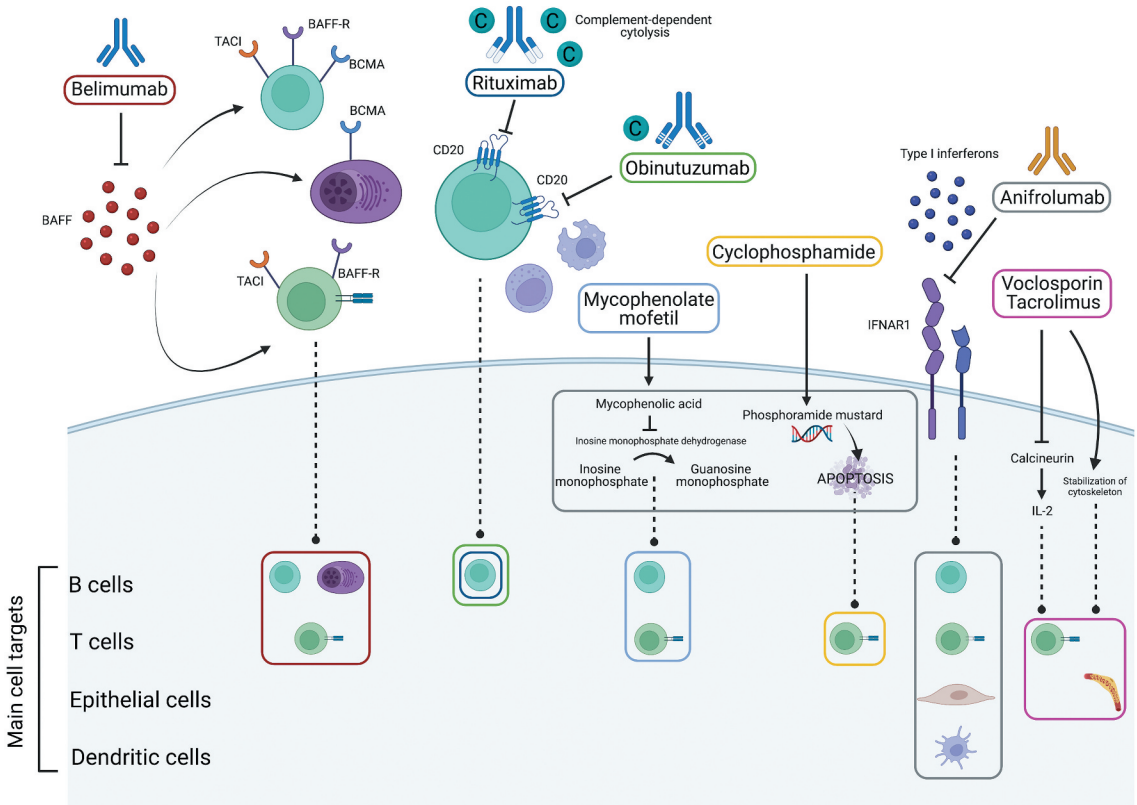

Figure 1. Main mechanisms of action of commonly used and selected promising drugs in Lupus nephritis. The upper part shows the extracellular mechanisms of action of the drugs, and the lower part the intracellular target structures and main cell types involved. Belimumab acts by blocking Bcell activating factor (BAFF) and subsequent inhibition of binding to its receptors (BAFF-R, TACI, BCMA) which are expressed on Band Tcells, thus decreasing antibody production and interfering with Tcell functions. Rituximab is achimeric mouse-human type Iantibody, and obinutuzumab is a humanized type II antibody that act by inhibition of cluster of differentiation (CD) 20 on B cells inducing cell death. They promote complement (C)-dependent cytotoxicity, antibody-dependent cellular toxicity, and antibody-dependent phagocytosis. The first mechanism is prevalent for rituximab, the others for obinutuzumab. Both traditional agents, mycophenolate mofetil and cyclophosphamide, are pro-drugs that are converted intracellularly to their active compounds with subsequent B and T cell apoptosis. Anifrolumab is anovel anti-interferon alpha receptor subunit 1 antibody (IFNAR1), which blocks downstream interferon pathways affecting B, T, epithelial, and dendritic cells. Voclosporin and tacrolimus act similarly as calcineurin inhibitors with subsequent effects on interleukin (IL)-2 inhibiting Tcell proliferation. Another effect is provided by the stabilization of the podocyte cytoskeleton. Created with *biorender.com*.

to be a more potent inhibition of calcineurin and subsequent inhibition of T cell responses compared to cyclosporine A (CsA) or TAC, along with stabilization of the podocyte cytoskeleton, which is dysregulated in LN.[43–45] In addition, VCS has a more stable pharmacologic profile and a better metabolic profile than CsA, making monitoring blood levels unnecessary.[46]

In the past few months, more evidence from phase II clinical trials in LN has been published: First, the *NOBILITY* trial, which investigated obinutuzumab, a type II B cell-depleting agent, in combination with MMF, has shown encouraging results on serological parameters, proteinuria, and CRR.[47] Second, ANI has been tested in LN patients and has beneficial effects on several renal endpoints, including CRR, with an intensified regimen but failed to reach the pre-specified primary endpoint.[48] Phase III clinical trial results for these agents are awaited.

Many more targets, some long-established while others are newly developed, are currently under research and investigation for the treatment of non-renal SLE, as summarized recently.[49] Among them are JAK-inhibitors such as tofacitinib or baricitinib; antibodies targeting B cells and plasma cells (e.g., ofatumumab, obexelimab, daratumumab), T cells, plasmacytoid dendritic cells, as well as co-stimulation mechanisms (e.g., belatacept, lulizumab). However, we will not review details on these drugs in this article as clinical trial data are awaited in the near future.

Design

B cell activating factor and rationale for the development of belimumab

Anti-double-stranded DNA (anti-dsDNA) and other antinuclear autoantibodies (ANA), produced by autoreactive plasma cells, are the hallmark laboratory finding of SLE.[50] Soluble B cell activating factor (BAFF), a member of the tumor necrosis factor superfamily, was first described in 1999 by several independent groups.[51–54] BAFF has a pivotal role in promoting B cell tolerance checkpoint defects, most likely occurring at the transitional stage between new bone marrow emigrants and extramedullary mature naïve B cells. Hence, an expansion of transitional B cells may be detected in the peripheral blood of SLE patients, along with increased levels of circulating BAFF.[55] Some studies have demonstrated a direct association between BAFF serum concentrations, disease activity, and the occurrence of LN.[56–58]

The possible pathogenetic role of BAFF in SLE stems from the observation of a lupus-like illness characterized by B cell hyperplasia, anti-dsDNA, and intrarenal ICs, in two independently derived strains of BAFF transgenic mice.[59] Together with its primary function as a survival factor for transitional and mature B cells, BAFF increases B cell responses via complex interactions with the B cell receptor (BCR) and Toll-like receptor (TLR) pathways, promoting extrafollicular B cell activation that has a role in the production of class-switched autoantibodies in SLE.[60]

Furthermore, autoreactive B cells show a downregulation of BCR during "learned ignorance" ruled out by autoantigen-BCR interactions.[61] Consequently, in an environment of increased serum BAFF levels, the survival and maturation of these lower affinity self-reactive clones are enhanced, escaping from deletion and anergic processes, as their survival is strictly dependent on BAFF/BAFF-R signaling.[62] Thus, BAFF levels play a role in maintaining long-lived humoral immunity, influencing plasma cell survival, and impacting IgM and IgG production.[63] Indeed, patients on BEL for longer than seven years possessed fewer autoreactive IgM-expressing B and plasma cells compared to non-BEL users, suggesting that activated autoreactive B cells undergo negative selection.[64]

The presence of BAFF-R on T cells and BAFF-dependent T cell activation pathways have been demonstrated, even if its functional effect has to be elucidated.[65] In general, in SLE pathogenesis, T cells, particularly interleukin (IL)-17-producing T helper cells (Th) and T follicular helper (Tfh) cells, play an essential role in helping B cells produce antibodies. Furthermore, they participate in tissue damage by synthesizing multiple soluble local and systemic mediators.[66] In addition to the breakdown of the self-tolerance mechanisms described above, intrinsic hyperactivity and hyperresponsiveness of lymphocytes, thus related to B and T cell receptor defects, are found in SLE.[67] This process could be sufficient to initiate spontaneous, autoimmune GC responses, resulting in a loss of T cell tolerance and epitope spreading, perpetuating systemic autoimmunity.[60]

Interestingly, BAFF, which is secreted by hematopoietic cells, has also been shown to be produced locally in the kidney. In one study, BAFF was found in renal tubular epithelial cells and correlated with proliferative forms of LN and disease activity.[68] The increased local BAFF levels may thus contribute to a local pro-inflammatory environment in the kidneys of lupus-prone mice and human biopsies and correlate with histopathological activity scores.[68] Another group showed elevated BAFF expression in proliferative LN (class III/IV).[69] In class IV, BAFF expression was also demonstrated in the glomeruli.[69]

Based on the mechanisms described above, BEL was developed by the company Human Genome Sciences (HGS) with considerable efforts and brought into phase I clinical trials by GlaxoSmithKline,[70] which later acquired HGS and is now the official vendor of BEL. Additional details on the preclinical and development of BEL were comprehensively reviewed by Stohl and Hilbert.[16]

The product of interest

The fully human monoclonal IgG1λ antibody BEL is available in two formulations: an intravenous route administered every four weeks (the first three doses are given two weeks apart) at a dose of 10 mg/kg of body weight, and as a subcutaneous injection, designed for self-administration, at a dose of 200 mg per week for SLE. A considerable amount of evidence observing its effect has emerged over the past years. A timeline with all relevant clinical trials and studies is shown in Figure 2.

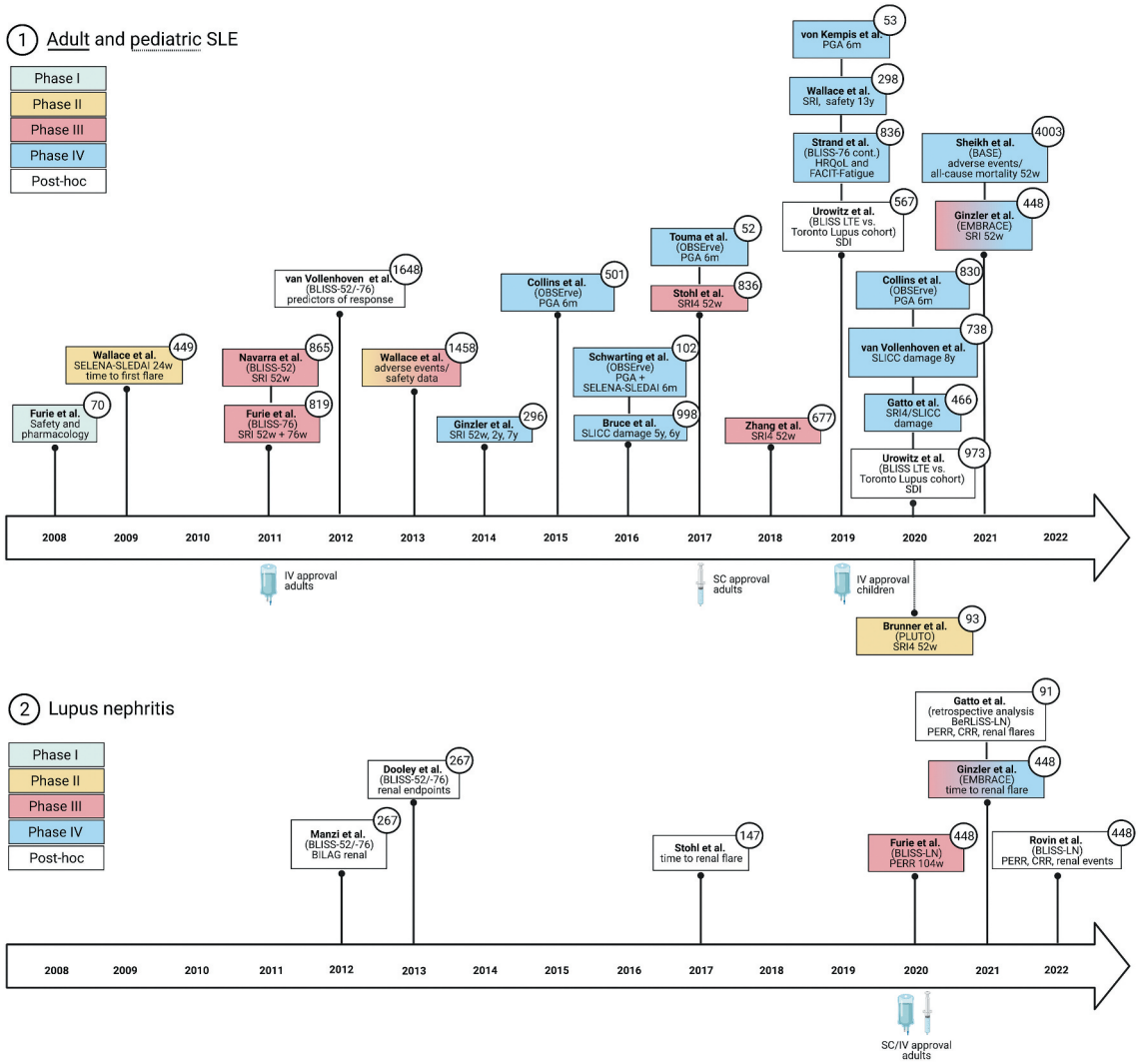

Figure 2. Timeline of milestone belimumab Phase I-IV trials, including *post hoc* analyses. The respective study phases are color-coded. The boxes show the first author and the name of the trial, if available. In addition, the main primary and secondary outcome measures are reported.
General outcome measures: BILAG, British Isles Lupus Assessment Group; PGA, Physician Global Assessment; SDI, Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus: National Assessment Version of the Systemic Lupus Erythematosus Disease Activity Index; SLICC, SLE International Collaborating Clinics; SRI, Systemic Lupus erythematous Responder Index. Renal outcome measures: CRR, complete renal response; PERR, primary efficacy renal response. w, weeks; y, years. Numbers in circles denote the number of patients. Created with *biorender.com*.

Evidence in non-renal SLE

Clinical trials assessing the efficacy and safety of BEL have been published for more than ten years, consisting of a portfolio of phase II, III, and IV clinical trial data. Early phase I and II trials showed that BEL, in addition to SoC (CS and antimalarial drugs with or without an immunosuppressant), was biologically active and well-tolerated in several different dosing regimens.[70,71] Two major phase III trials were published in 2011: *BLISS*-52 and −76.[21,22] The study design compared three treatment groups: SoC + BEL 1 mg/kg; SoC + BEL 10 mg/kg; and SoC + placebo (PBO). 865 and 819 patients were enrolled, respectively, and then analyzed regarding the same endpoint, once after 52 and after 76 weeks. Both analyses used the SLE Responder Index (SRI) as the primary endpoint, showing that numerically more patients receiving BEL + SoC reached at least a 4-point reduction in their SELENA-SLEDAI scores after 52 and 76 weeks, respectively. With the additional six months of follow-up provided by *BLISS-76*, the authors concluded that BEL also significantly reduced flares and was generally well-tolerated in the longterm. The rates of adverse events were similar when comparing the BEL and PBO groups.[21,22] An increasing amount of "real world" evidence showing a clinically relevant benefit with BEL treatment is becoming available from international and long-term observation cohorts (*OBSErve* studies).[72–76]

While the *BLISS* trials showed that many SLE patients benefited from BEL when added to standard treatment, they had excluded important end-organ manifestations of SLE, most notably patients with active LN. Several *post hoc* analyses of the *BLISS* trials have been published regarding possible renal endpoints under BEL.[19,77] Manzi *et al.* showed that BEL mainly improved SLE activity in the musculoskeletal and mucocutaneous domains.[19] However, those patients without renal involvement at baseline showed a minor worsening in specific organ domains (as measured by the British Isles Lupus Assessment

Group [BILAG] Score) under BEL than SoC alone. In addition, those patients with significant proteinuria at enrollment showed a more remarkable improvement with BEL than with PBO.[19]

Dooley *et al.* established several renal endpoints for their *post hoc* analysis of the *BLISS* trial database, including renal flare rate, renal remission rate, as well as nephritic urine sediment; they were able to show that those 267 patients with some renal involvement at baseline showed a more noticeable improvement with BEL than with SoC alone.[77] The same observations were reported for those receiving MMF and those with serologically active disease.

Another study with at least one secondary endpoint concerning the renal domain was published by Stohl *et al.*, although patients with active LN were also excluded.[20] Weekly subcutaneous BEL significantly improved SRI4 responses at week 52, and renal improvement favored BEL as well, although the time to the first renal flare among those patients with significant baseline proteinuria was shorter with BEL than with PBO.[20]

Around the same time, several case reports and case series reported that patients who received BEL as an add-on treatment for SLE also showed significant renal benefits, most commonly reported by a reduction of proteinuria and markers of serological disease activity.[78–80] All relevant clinical trials and studies of BEL in SLE are summarized in Table 1.

Evidence in lupus nephritis

With LN being an important and often mortality-determining organ manifestation of SLE, these *post hoc* results of secondary endpoints and case series were welcomed. However, a randomized, controlled trial for LN itself was still eagerly awaited. *BLISS-LN* was then published in 2020: the primary endpoint for 448 patients was the primary efficacy renal response (PERR) at week 104, which was defined as uPCR <0.7 g/g, eGFR no worse than 20% below pre-study values, and no need for rescue therapy.[23] Furthermore, significantly more patients achieved PERR with BEL than PBO in *BLISS-LN*. Those patients treated with BEL showed a lower risk of a renal-related event (defined as doubling of serum creatinine or end-stage renal disease [ESRD]) and death.[23]

More recently, Ginzler *et al.* have studied the efficacy and safety of BEL in patients of black African ancestry and included a secondary renal endpoint as well (*EMBRACE*).[93] Unfortunately, the *EMBRACE* study did not reach its primary endpoint of SRI improvement at week 52; however, there was a numerically lower risk of renal flare and a longer timespan until the first renal flare in the BEL group. In addition, patients with high disease activity or renal involvement at baseline benefited from BEL compared to PBO + SoC.[93] This result is particularly telling as LN is more common in SLE patients of African ancestry and progresses to ESRD more frequently, which is strongly influenced by the presence of risk alleles of the apolipoprotein 1 (APOL1) gene.[95,96] Studies and trials of BEL reporting renal endpoints are shown in Table 2.

De-Novo lupus nephritis with belimumab

As mentioned above, Stohl *et al.* were among the first to note a shorter time to first renal flare with BEL, although the overall progression of renal involvement was ameliorated with the new treatment.[20] Indeed, several case reports and small studies are concerned with new-onset LN or a new LN flare during BEL treatment (Table 3). Those with the largest cohorts are Hui-Yuen *et al.* (3 new cases of LN among 195 subjects)[101] and Parodis *et al.* (3 de-novo LN out of 66 patients without prior LN; and 2 LN flares among 29 patients with known LN).[102]

Most recently, Ginzler *et al.* discussed that among those patients without renal involvement at baseline, very few developed worsening renal function during BEL treatment (15 of 244 patients) in the *EMBRACE* trial, and those numbers were similar for the PBO group (9 of 115).[93] Importantly, these do not necessarily represent new-onset LN, as no renal biopsies were performed during the trial. In contrast to the above concerns about new-onset LN or flares during BEL treatment, a *post hoc* analysis of the *BLISS-LN* study cohort recently demonstrated fewer LN flares and a slower decline in eGFR during *BLISS-LN*, concluding that BEL might help preserve kidney function in LN.[100]

Combination and sequential therapies including belimumab

As BEL became established as an add-on treatment for SLE and considering its mechanism of action in the B-cell domain of (auto)immunity, the potential benefits of a combination treatment with RTX were discussed. Rituximab is well-established in treating a plethora of hematological and rheumatological disease entities.

However, the role of RTX in SLE without renal involvement is ambivalent, as the largest trial investigating its effect in SLE (*EXPLORER*) found no statistically significant benefit neither in primary nor secondary endpoints.[32] After the *LUNAR* study found no statistically significant difference in complete or partial response rates in LN patients but noted a better reduction in anti-dsDNA levels,[31] RTX has regained some favor after the publication of *RITUXILUP*. This prospective cohort study combined RTX with MMF and achieved favorable outcomes and a notable CS-sparing capacity in LN patients.[108]

Combining RTX as a B-cell depleting agent with BEL as a substance that hinders B-cell activation seemed a good fit. Indeed, multiple case reports highlighted the use of RTX treatment followed by BEL, which led to a reduction in proteinuria and enabled CS reduction.[109,110] Several authors also reported a significant improvement with BEL after their patients had become refractory to RTX.[111,112] However, a small study focusing explicitly on SLE patients with secondary non-depletion and non-response (2NDNR) to RTX found no benefit from switching to BEL but instead favored a shift to different anti-CD20 agents, such as ocrelizumab, ofatumumab, or obinutuzumab.[107]

Seeing as a combination of B-cell targeting therapeutics was becoming a valid option, several small proof-of-concept studies were able to show a reduction of NET formation[113] as well as anti-dsDNA antibody titers and anti-C1q levels after RTX +

Table 1. Study landscape of belimumab in systemic lupus erythematosus.

First author	Year	Trial phase (name if available)	N of patients	Primary endpoint	Renal endpoint	Concomitant medication	Key messages
Furie R[70]	2008	I	70	AEs, pharmacokinetics, B cell counts, serology, SELENA-SLEDAI	none	SoC	BEL was well tolerated; treatment reduced peripheral B cell counts
Wallace DJ[71]	2009	II	449	SELENA-SLEDAI at 24w; time to first SLE flare	none	SoC	BEL was well tolerated; effect on SLE activity was not significant, except in serologically active pts.
Navarra SV[22]	2011	III *BLISS-52*	865	SRI at 52w	only in *post hoc* analysis; see Manzi and Dooley in Table 2 (*active LN excluded*)	SoC	more pts. with SELENA-SLEDAI reduction (at least 4 pts.) with BEL+SoC than with PBO+SoC; similar rates of AEs
Furie R[21]	2011	III *BLISS-76*	819	SRI at 52w and 76w	only in *post hoc* analysis; see Manzi and Dooley in Table 2 (*active LN excluded*)	SoC	BEL+SoC significantly improved SRI response rates, reduced flares, and was well tolerated; similar rates of AEs compared to PBO
van Vollenhoven R[81]	2012	BLISS-52/-76 (*post hoc*)	1648	SRI at 52w (subgroup analyses)	none	SoC	suggestion of greater therapeutic benefit of BEL in pts. with high disease activity at baseline
Wallace DJ[82]	2013	II/III (*post hoc*)	1458	adverse events/safety data	none	SoC	BEL+SoC was generally well tolerated
Ginzler EM[83]	2014	IV	296	SRI at 52w, 2y and 7y	none	SoC	SLE disease control and BEL safety were maintained for up to 7y
Collins CE[72]	2015	IV *OBSErve*	501	PGA at 6 m, and every 6 m for 24 m	none	SoC	improved disease activity and reduced CS use at 6 m with continued benefit until at least 24 m
Bruce IN[84]	2016	IV	998	SLICC damage index at 5/6y	none	SoC	low incidence of organ damage accrual with long-term BEL
Schwarting A[74]	2016	IV *OBSErve*	102	PGA and SELENA-SLEDAI at 6 m	none (*active LN excluded*)	SoC	reduced SLE activity and CS use after 6 m
Touma Z[76]	2017	IV *OBSErve*	52	PGA at 6 m, CS use	none	SoC	improved disease activity and reduced CS use at 6 m; study highlights the lack of formal disease activity assessments in a number of pts.
Stohl W[20]	2017	III	836	SRI4 at 52w	yes, see Table 2	SoC	weekly SC BEL significantly improved SRI4 response and decreased flares in pts. with moderate-to-severe SLE; details on secondary renal endpoints see Table 2; more pts. in the BEL group had improved FACIT-Fatigue score at 52w
Zhang F[85]	2018	III	677	SRI4 at 52w	none (*active LN excluded*)	SoC	significant improvement in disease activity and no new safety concerns (Asian cohort)
Strand V[86]	2019	IV (*BLISS-76 cont.*)	268	HRQoL (SF-36) and FACIT-Fatigue score	none	SoC	improved SLE control correlates with improved fatigue and HRQoL with BEL
Wallace DJ[87]	2019	IV (*II cont.*)	298	AEs; SRI every 16w, CS use every 4w	none	SoC	BEL was well tolerated and effective for up to 13y; no new safety concerns
Urowitz M[88]	2019	BLISS LTE (*post hoc*)	567	propensity-matched SDI score after 5y	none (*proteinuria as one propensity-matched variable*)	SoC	lower rates of organ damage over 5y with BEL+SoC than with SoC alone
von Kempis J[75]	2019	IV OBSErve	53	overall clinical response (PGA-like scale) at 6 m	none	SoC	clinical and serological improvement, reduced CS use after 6 m
Gatto M[89]	2020	IV (*post hoc*)	466	SRI4 and SLICC damage index	none	SoC	early BEL treatment in pts. with little SLE organ damage at baseline is favorable
Brunner HI[90]	2020	II	93	SRI4 at 52w	SELENA-SLEDAI and BILAG renal involvement	SoC	safety and efficacy of IV BEL in pediatric SLE pts. consistent with adult trials
van Vollenhoven RF[91]	2020	III-IV (III ext.)	738	AEs (monthly); SLICC/ACR damage index every 48w	none	SoC	stable safety profile of BEL over 8y; minimal organ damage progression

(*Continued*)

Table 1. (Continued).

First author	Year	Trial phase (name if available)	N of patients	Primary endpoint	Renal endpoint	Concomitant medication	Key messages
Urowitz M[92]	2020	BLISS LTE *(post hoc)*	973	propensity-matched SDI score after 5y	none	SoC	pts. receiving BEL were 60% less likely to accrue organ damage during follow-up as measured by SDI score
Collins CE[73]	2020	IV *(OBSErve post hoc)*	830	PGA at 6 m	none	SoC	BEL is well-tolerated and improves SLE manifestations in a 'real world' setting; reduction of CS use to <7.5 mg in >50% of pts.
Ginzler EM[93]	2021	III-IV *EMBRACE*	448 of black African ancestry	SRI at 52w	yes, see Table 2	SoC	primary endpoint was not achieved; numerically lower risk of renal flare with BEL, details see Table 2
Sheikh SZ[94]	2021	IV *BASE*	4003	all-cause mortality and AEs up to 52w	none	SoC	higher incidence of fatal infections, suicidal ideation, and self-harm in the BEL group; similar mortality, serious infections, and malignancies in BEL and PBO groups

Outcome measures: AE, adverse events; BILAG, British Isles Lupus Assessment Group; FACIT, Functional Assessment of Chronic Illness Therapy; HRQoL, Health-related quality of life; PGA, Physician Global Assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus: National Assessment Version of the Systemic Lupus Erythematosus Disease Activity Index; SF-36, short form 36; SLICC, SLE International Collaborating Clinics; SRI, SLE Responder Index.
Treatments: BEL, belimumab; CS, corticosteroids; PBO, placebo; SoC, standard of care: CS plus antimalarials (± immunosuppression) according to the 2019 EULAR recommendations.
Other: ACR, American College of Rheumatology; IV, intravenous; LN, Lupus nephritis; pts., patients; SC, subcutaneous; SLE, Systemic lupus erythematosus. m, months; w, weeks; y, years.

Table 2. Trials and studies of belimumab reporting renal endpoints.

First author	Year	Study type [*trial name if applicable*]	Number of patients	Primary renal endpoint	Secondary renal endpoints	Concomitant medication	Key findings
Manzi S[19]	2012	III/*post hoc* analysis of *BLISS-52* and *-76*	267 (/1684)	-	SELENA-SLEDAI and BILAG renal involvement (*active LN excluded*)	SoC	BEL improved SLE activity in musculoskeletal and mucocutaneous domains; less worsening in renal domain (with no organ involvement at baseline); in pts. with proteinuria >1 g/d, improvement from baseline was greater with BEL than with PBO
Fließer E[78]	2013	case report	1	proteinuria	-	MMF	patient with LN class III and good clinical response but progressive proteinuria after MMF; proteinuria improved significantly after additional BEL
Dooley MA[77]	2013	III/*post hoc* analysis of *BLISS-52* and *-76*	267 (/1684)	-	SELENA-SLEDAI and BILAG renal involvement, renal flare rate, renal remission rate, proteinuria, hematuria, creatinine (*active LN excluded*)	SoC	most renal endpoints favored BEL; among 267 pts. with renal involvement at baseline, those receiving MMF and serologically active disease showed greater improvement with BEL
De Scheerder[97]	2015	case report	1	proteinuria	-	SoC	SLE treatment initiated with CS, MMF, and HCQ; diagnosis of LN class V, TAC with no improvement of proteinuria; add-on BEL with marked reduction of proteinuria and CS-sparing effect
Stohl W[20]	2017	RCT phase III	147 (/836)	-	time to first renal flare in pts. with proteinuria >0.5 g/d ($n = 147$) (*active LN excluded*)	SoC	shorter time to first renal flare with BEL; renal improvement overall favored BEL, but small sample size
Margiotta D[80]	2018	case series	2	CRR	-	CS + low-dose MMF	both pts. achieved lasting remission and CRR
Fontana F[98]	2018	case report	1	proteinuria, C3/C4, anti-dsDNA	-	CS, CYC, TAC (all discontinued)	induction treatment of LN with CS and CYC resulted in severe cryptococcal meningitis and was discontinued; TAC poorly tolerated; off-label BEL for LN resulted in reduced proteinuria, normalized C3/4, and anti-dsDNA titer; no further complications
Furie R[23]	2020	RCT phase III *BLISS-LN*	448	PERR at 104w	-	SoC	significantly more pts. achieved PERR or CRR with BEL; lower risk of renal-related event (ESRD, doubling of creatinine) or death
Plüß M[79]	2020	case series	6	proteinuria over time in preexistent LN	-	CS + MMF	6 pts. with BEL for SLE and LN at baseline; all had a reduction of proteinuria to various degrees; no new LN flares
Binda V[99]	2020	case series	17	proteinuria over time in preexistent LN	-	SoC	proteinuria normalized in 3 and improved in 13 pts.; one LN flare during BEL therapy
Gatto M[89]	2021	retrospective cohort study *BeRLiSS-LN*	91	PERR at 6, 12, 24 m	CRR at 6, 12, 24 m number of renal flares	SoC	91 pts. in the BeRLiSS-cohort with SLEDAI-2K renal items or eGFR <60 ml/min at the time of BEL initiation; 70.3% achieved PERR at 6 months; of those, 86.7% maintained the response at 24 m
Ginzler EM[93]	2021	RCT phase III-IV *EMBRACE*	448 of black African ancestry	-	time to first renal flare; renal SS-S2K domain improvement or worsening at 52w; percentage reduction in proteinuria in pts. with proteinuria >0.5 g/d	SoC	numerically lower risk of renal flare as well as longer time to renal flare with BEL compared with PBO; more pts. with renal involvement at baseline experienced improvement with BEL; worsening of renal function in those without renal involvement at baseline was similar in BEL and PBO group
Rovin BH[100]	2021	III/*post hoc* analysis of *BLISS-LN*	448	PERR at 104w	-	SoC	pts. treated with BEL+SoC had a slower decline in eGFR compared to the SoC group; fewer LN flares with BEL; BEL might help to preserve kidney function

Outcome measures: BILAG, British Isles Lupus Assessment Group; CRR, complete renal response; eGFR, estimated glomerular filtration rate; PERR, primary efficacy renal response; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Treatments: BEL, belimumab; CS, corticosteroids; CYC, cyclophosphamide; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; PBO, placebo; SoC, standard of care: GC plus antimalarials (± immunosuppression) according to the 2019 EULAR recommendations; TAC, tacrolimus.

Other: dsDNA, double-stranded deoxyribonucleic acid; LN, Lupus nephritis; pts., patients; RCT, randomized controlled trial; SLE, Systemic lupus erythematosus. m, months; w, weeks; y, years.

Table 3. *De Novo* lupus nephritis or lupus nephritis flares reported with belimumab.

First author and reference	Year	Study type [*trial name if applicable*]	Number of patients	Concomitant medication	Key findings
Sjöwall C[103]	2014	case report	1	CS, MMF	pts. with no history of LN developed active urine sediment 10 m after initiation of BEL; biopsy showed LN class III; BEL was discontinued and CYC initiated, renal remission achieved after 3.5 m, biopsy-proven remission after 7 m
Hui-Yuen JS[101]	2015	prospective observational study	3/195	SoC	3 new cases of LN during the first year of BEL therapy for SLE
Staveri C[104]	2017	case report	2	GC, HCQ, AZA (case 1) GC, AZA (case 2)	patient 1 with no history of LN developed pathologic urinalysis 3 m after BEL initiation, biopsy-proven LN class III; urinalysis reverted to normal after BEL discontinued patient 2 with no history of LN developed pathologic urinalysis and nephrotic syndrome 2 m after BEL initiation, biopsy-proven LN class V; proteinuria halved after BEL was discontinued (and MMF started)
Anjo C[105]	2019	retrospective analysis	1/23	SoC	1 case of *de novo* LN in a cohort of 23 SLE pts. treated with BEL
Binda V[99]	2020	case series	1/17	SoC	1 case of LN flare in a cohort of 17 LN pts. treated with BEL
Riancho-Zarrabeitia L[106]	2020	retrospective analysis	1/11	HCQ (all) MMF, AZA, CYC, LEF (several)	1 case of *de novo* LN in a cohort of 11 SLE pts. treated with BEL for musculoskeletal and/or cutaneous manifestations
Hassan S[107]	2020	prospective observational study	2/14	SoC	study with secondary non-responders to RTX in SLE, details see Table 4 1 patient relapsed with LN class III during BEL treatment, another developed *de novo* LN class V; both were then treated with CYC
Parodis I[102]	2020	prospective observational study	6/66 de novo 2/29 flare	SoC	6 out of 66 SLE pts. with no prior history of LN developed biopsy-proven LN during BEL treatment (after a median of 7.4 m); 2 out of 66 control pts. with SLE but no BEL developed *de novo* LN under SoC 2 out of 29 pts. with previous history of LN experienced a nephritic flare under BEL (after 1 and 7 m)
Ginzler M[93]	2021	III-IV *EMBRACE*	448 of black African ancestry	SoC	among those with no renal involvement at baseline, the percentage of worsening renal function during the trial was low and similar in both the BEL (15/244) and PBO (9/115) groups

Treatments: AZA, azathioprine; BEL, belimumab; CS, corticosteroids; CYC, cyclophosphamide; HCQ, hydroxychloroquine; LEF, leflunomide; MMF, mycophenolate mofetil; PBO, placebo; RTX; rituximab; SoC, standard of care: GC plus antimalarials (± immunosuppression) according to the 2019 EULAR recommendations.
Other: LN, Lupus nephritis; pts., patients; SLE, Systemic lupus erythematosus; m, months.

BEL,[114] the last study comparing results with a group that received RTX monotherapy. Similarly, and most recently, the *BEAT-Lupus* trial[115] demonstrated that add-on BEL after RTX resulted in lower anti-dsDNA levels and fewer SLE flares than RTX (plus SoC) alone.

Regarding the use of sequential B-cell targeting therapy in LN more specifically, the *SYNBIoSe*-study[113]had a secondary renal endpoint and showed that out of 13 patients with LN, five achieved a CRR. Another phase II study investigated treatment with a re-induction regimen of CYC + RTX and added BEL as maintenance therapy in refractory LN patients, which was deemed safe but did not improve outcomes except in those patients with more severe renal involvement, particularly those with nephrotic-range proteinuria.[116]

So far, the sequence of RTX first/BEL second has been used more frequently. However, several authors asked whether anti-BAFF treatment with BEL first and then finalizing B-cell depletion with RTX might be beneficial. Preliminary results of this combination showed no significant difference in SELENA-SLEDAI scores at week 52 and 104 compared with BEL alone; however, there were more serious adverse events such as severe infections.[117] Another study investigating sequential SLE treatment with BEL, then RTX, and then maintenance therapy again with BEL is currently recruiting (*SYNBIoSe-2*, NCT03747159). In light of novel type II B cell depleting agents in development or early phase clinical trials, we will have a clearer understanding of the use of combination therapies in the context of recently approved drugs soon. The trials investigating RTX/BEL combinations are summarized in detail in Table 4.

Safety

As a new drug among a plethora of more established treatment options, the safety of BEL has been monitored from the early phase II and III trials onwards. Wallace *et al.* reported that serious adverse events (AEs) were not statistically different between the three different dose groups of BEL and the PBO group in the phase II trial.[71] Still, urticaria was reported more frequently in the BEL group. There was one case of respiratory failure and one suicide in the BEL group, both of which were deemed unrelated to the study medication by the investigators. The *BLISS-52* and *-76* trials found statistically similar rates of AEs in the treatment and the PBO groups, too;[21,22] the *post hoc* analysis of the pooled safety data confirmed that BEL was generally well tolerated.[82] Again, hypersensitivity with urticaria was rare but more frequent in the BEL group than in the PBO group. A similar safety profile as in the adult population was reported in pediatric SLE patients receiving BEL.[90] Dedicated studies of populations with Asian[85]or Black African[93]ancestry also showed a similar safety profile compared with previous trials.

In addition, long-term safety data are available. For example, Ginzler *et al.*,[83] van Vollenhoven *et al.*,[91] and Wallace *et al.*[87]reported no new AEs or other safety concerns after 7, 8, and 13 years of BEL use.

One concern that has been raised repeatedly by different authors is an increased rate of psychiatric AEs with BEL use: these mainly include insomnia, anxiety, and depression-related AEs.[82] Wallace *et al.* report that there was a doubling of the risk

Table 4. Studies on sequential B cell-depleting therapies in systemic lupus erythematosus.

First author and reference	Year	Study type [*trial name if applicable*]	Number of patients	Primary endpoint	Renal endpoint	Concomitant medication	Sequence and dosing of therapy	Key findings
Kraaij T[109]	2014	case report	2	-	-	SoC (incl. previous MMF and CYC induction)	RTX (dose not reported) > BEL[#]	both pts. achieved renal remission and were able to discontinue CS
Gonzalez-Echavarri C[111]	2016	case report	1	-	-	CS, HCQ, MMF, TAC	4 x RTX (refractory) > BEL (10 mg/kg)	patient with RTX-refractory LN achieved and maintained remission with BEL +SoC+TAC; TAC was discontinued after 2y
Simonetta F[112]	2017	case report	1	-	-	CS, MMF	BEL (10 mg/kg) > RTX (2x1000 mg) > BEL (10 mg/kg)	BEL added to CS/MMF led to reduced proteinuria; another flare treated with RTX showed serological but no renal response; added BEL again with sustained renal response
Gualtierotti R[110]	2018	case series	3	-	-	SoC	RTX (2x1000 mg) > BEL (10 mg/kg)	all 3 pts. (2 with LN) achieved remission and were able to taper or end CS therapy
Kraaij T[113]	2018	proof-of-concept IIA *SYNBloSe*	16	autoantibody titers and NET formation at 24w	CRR	CS, MMF (each with a quick taper) HCQ allowed	RTX (2x1000 mg) > BEL (10 mg/kg)	reduction of ANA and NET formation, concomitant immunosuppressive medication was tapered; 5/13 pts. with LN achieved CRR
Petricca L[118]	2020	case report	1	-	-	SoC (incl. previous RTX)	RTX (2x1000 mg) > BEL (10 mg/kg)	patient achieved remission of both LN and bullous pemphigoid
van Dam LS[114]	2020	retrospective laboratory analysis	31	autoantibody titers	none	SoC	RTX (2x1000 mg) > BEL	16 pts. received RTX, 15 RTX+BEL; RTX+BEL significantly reduced all-avidity anti-dsDNA as well as anti-C1q; both regimens improved C3 levels and NET formation
Hassan S[107]	2020	prospective observational	14	SRI4 at 6 m	BILAG renal involvement at 6 m	SoC	RTX 2NDNR > BEL (10 mg/kg) or > alternative anti-CD20 (Ocrelizumab or Ofatumumab or Obinutuzumab)	small post-RTX population with 2NDNR; all pts. with CD20-to-CD20 switch benefitted, whereas SLEDAI-2K did not improve in the group that received BEL after RTX/2NDNR
Atisha-Fregoso Y[116]	2020	RCT phase II *CALIBRATE*	43	safety/AEs at 48w	renal response at 24w, 48w, 96w	CS HCQ allowed	CYC+RTX (2x1000 mg) > BEL (10 mg/kg)	addition of BEL to the regimen was safe but did not statistically improve renal response; authors suggest BEL can prove beneficial in more severe LN (good effect in nephrotic pts.)
Kraaij T[119]	2021	*SYNBloSe* follow-up	15 (12 LN)	time to and on LLDAS	CRR at 104w	CS, MMF (each with a quick taper) HCQ allowed	RTX (2x1000 mg) > BEL (10 mg/kg)	reduction of ANA was long-lasting; clinical response persisted; 60% of LN pts. achieved CRR
Shipa M[115]	2021	RCT phase II *BEAT-Lupus*	52	anti-dsDNA at 52w	none	SoC	RTX (2x1000 mg) > BEL	anti-dsDNA antibody levels were lower in the group that received BEL after RTX instead of PBO; BEL reduced the risk of severe flare; no increase in AEs in the BEL group
Aranow C[117]	2021	RCT phase III *BLISS-BELIEVE*	292	SELENA-SLEDAI at 52w	none	SoC (without immunosuppression in the PBO arm)	BEL (200 mg/w SC) > RTX (2x1000 mg)	*ACR abstract 10/2021*: no statistically significant difference in disease control and remission (at 52w *and* 104w) between the BEL/RTX and BEL/PBO groups; more serious AE in the BEL/RTX group, mostly severe infections
Teng YKO		RCT phase II *SYNBloSe-2*	70	treatment failure rate at 104w	none	SoC	BEL (10 mg/kg) > RTX (2x1000 mg) > BEL (10 mg/kg) as maintenance	*recruiting* NCT02284984

Outcome measures: AE, adverse events; BILAG, British Isles Lupus Assessment Group; CRR, complete renal response; LLDAS, Low Lupus disease activity state; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus: National Assessment Version of the Systemic Lupus Erythematosus Disease Activity Index; SRI, SLE Responder Index.

Treatment: BEL, belimumab; CS, corticosteroids; CYC, cyclophosphamide; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; PBO, placebo; RTX; rituximab; SoC, standard of care: CS plus antimalarials (± immunosuppression) according to the 2019 EULAR recommendations; TAC, tacrolimus.

Other: 2NDNR, secondary non-depletion and non-response; ACR, American College of Rheumatology; ANA, anti-nuclear antibody; dsDNA, double-stranded deoxyribonucleic acid; LN, Lupus nephritis; NET, neutrophil extracellular traps; pts., patients; SLE, Systemic lupus erythematosus; m, months; w, weeks; y, years.

of developing a psychiatric disorder in all treatment groups if there was a previous history of psychiatric illness; however, severe depression was reported more frequently in the BEL than in the PBO groups, and two suicides occurred in the BEL cohort of the studies that were analyzed *post hoc*.[82] The most recent phase IV RCT, the *BASE* trial,[94] showed similar mortality and serious as well as opportunistic infections with BEL *vs.* PBO; however, also in the *BASE* trial, there was not only a higher rate of fatal infections with BEL but also of depression, suicidal ideation, and self-harm.[94] Although the absolute numbers were low, these results were discussed in detail. There is currently no known etiological link between BEL and an increased risk of suicide; however, a role of BAFF in neural cell survival has been stipulated.[120] The authors conclude that patients and clinicians should be aware of a higher incidence of depression and self-harming behavior in SLE patients than in the general population, whether or not they are treated with BEL, due to the high disease burden.

A large meta-analysis of 11 RCTs found no increased risk of psychiatric events with BEL treatment but does recommend caution when starting BEL in a patient with a previous medical history of depression or suicidal ideation.[121]

Role of belimumab for the treatment of SLE and LN in the current treatment landscape

With the recent approvals of several agents for non-renal SLE and LN, physicians treating SLE patients are faced with the question of when to use these agents, in which patients, and for which organ manifestations. Belimumab has been in clinical use for over ten years now, and experience as well as published data have shown that it is a valuable add-on agent, especially in patients with high clinical disease activity (SLEDAI-2K > 10), serologic activity (high anti-dsDNA antibodies, low complement), and need for continued CS treatment.[81] Typically, one would use BEL in patients with active disease or failure to achieve remission despite therapy with CS at tolerable doses (<5 mg/d), antimalarials, and another immunosuppressive agent, such as AZA, MTX (non-renal SLE), or MMF (LN). In patients experiencing intolerable side effects from conventional immunosuppressives, BEL also has excellent efficacy in combination with antimalarials and low-dose CS in the authors' experience. This latter situation could also be a setting where the recently approved ANI may have a role. *Post hoc* data from the *TULIP* trials show that ANI has relevant effects on musculoskeletal and skin disease in SLE.[122]

In LN, one must distinguish BEL-treated from BEL-naïve patients: The former should continue their usual doses if a decision is made to continue BEL. However, as per the label, the latter should receive BEL at standard IV doses (10 mg/kg of body weight). For the SC route of administration, 400 mg per week (twice the standard dose) for four weeks is recommended for remission induction, and 200 mg per week (the standard dose) afterward.

In the *BLISS-LN* trial, around 60% of patients had LN classes III or IV, roughly 25% class III/IV in combination with V, and a minority only class V LN.[23] As of yet, it is not clear which patients with LN will likely benefit most. However, *post hoc* data suggest that pure class V LN patients do not benefit as much as class III/IV with or without class V.[100] In class V without III or IV LN, combination therapies of MMF + TAC are a reasonable choice for patients not responding to CS + MMF alone.[34] MMF + TAC has been studied mostly in Asian populations and trial results may thus not be generalizable to other populations.[34] In prominent class V LN, VCS is likely to have a strong role as a new agent.[123]

The authors' approach is to start remission induction therapy in LN with methylprednisone for three days (dose between 250–1000 mg per day) and tapering in combination with MMF (1 g/d for the first week, then 2 g/d from the second week onwards, dose slowly increased as tolerated up to 3 g/d). The response is monitored every month for the first three months, then every three months for the first year. If at least a partial renal response has not been achieved after three months, BEL is added to MMF rather than switching to CYC due to toxicity concerns and ease of use of BEL and MMF in an outpatient setting. It is, however, acknowledged that this approach may differ from other physicians' practice.

In the future, combining agents may be an option. Currently, most evidence exists for BEL/RTX combinations, but this constitutes an off-label use and should be reserved for refractory cases until more trials become available.

Commercial and public-health issues

Currently, BEL is the only approved biological drug for treating both SLE and LN. Nevertheless, SLE experts have been using RTX in refractory cases for years and are convinced of its usefulness despite the lack of evidence in clinical trials. In many places, however, insurance companies deny the reimbursement for RTX treatment in SLE or LN because BEL is approved. Therefore, RTX is likely to become a third-line agent in LN. Furthermore, the fact that BEL is approved both by the FDA and EMA resolves prescribing issues and thus ensures availability for patients who require BEL. However, it remains unclear if patients with diverse ethnic backgrounds and LN benefit equally well from the add-on treatment with BEL.

Soon, it is expected that patient selection will become more of an issue with more available and licensed therapies, such as ANI (for non-renal SLE) and VCS (for LN). Based on the available published data, ANI is likely to be used primarily in patients with dominant musculoskeletal or skin disease. Voclosporin, as a calcineurin inhibitor, will initially likely be administered to patients with nephrotic or sub-nephrotic range proteinuria due to the existing experience with TAC or CsA.

A subcutaneous formulation of BEL is available, which is a significant advantage for many SLE patients, who are typically young and have to accommodate their treatments with their daily lives. Nevertheless, some patients appreciate the advantage of being seen by healthcare professionals every four weeks with the IV administration.

The yearly costs for BEL are significant at about 10,000–15,000 € per year. These must be balanced against indirect costs (e.g., loss of productivity, unemployment, disability) for insurers and society in general.

Conclusions

The field of rheumatology, specifically SLE, has seen major advances in the last few years. Of note, two new drugs (ANI and VCS) have been approved recently for SLE and LN, respectively. In addition, BEL has an established role in SLE and a promising new role in LN. The coming years will be exciting for scientists, patients, and physicians to develop and test new and potent immunotherapeutics. Still, it will also be challenging to find the right place in future therapeutic algorithms and recommendations. It is expected that additional combination therapies will be tested and may allow for a considerable reduction of overall CS doses and their well-known side effects. However, drug development is expensive, and new drugs will be costly for several years. Future trials and clinical experience will tell if the benefit of these therapies justifies their costs. Nevertheless, SLE affects many people worldwide and has not seen any significant advancement regarding approved therapies between the 1950s and 2011. Therefore, the development of new candidate drugs is reason enough to look confidently into the future of the therapeutic landscape in SLE and LN.

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