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The dawn of a new era of therapies in systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a complicated multisystem autoimmune disease that is associated with significant mortality and morbidity in the younger population. The development of novel therapies of SLE lag behinds other autoimmune inflammatory rheumatic diseases because of its clinical and immunological heterogeneities, the complexity of outcome assessments in multiple systems, and difficulty in optimizing the design of clinical trials. Despite the futility of quite a number of clinical trials, we are seeing the dawn of novel therapeutics in SLE, given the promising results of the newer-generation anti-CD20, anti-CD40L biologics, and calcineurin inhibitors (CNIs), as well as anti-cytokine biologics, Jakinibs, and the mammalian target of rapamycin (mTOR) inhibitors. The initial success of the Jakinibs and combination regimens in SLE illustrates the importance of targeting multiple pathogenetic mechanisms. The results of the ongoing phase III clinical trials in SLE are eagerly awaited.

Keywords

novel • therapeutics • lupus • advance • biologics

Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease that predominantly affects women of the childbearing age. The disease course is characterized by periods of remission and flares, resulting in organ damage caused by disease activity and treatment-related complications. The pathogenesis of SLE remains elusive but multiple genetic, epigenetic, environmental, hormonal, and immunopathological mechanisms are likely involved.[1]

The prognosis of SLE has improved substantially in the past few decades, with a 5-year survival of <50% in the 1960s, rising to >90% in studies published in the 2000s.[2] However, further improvement in SLE survival is limited by the relatively slow development of novel therapies. The major causes of mortality and morbidities of SLE are refractory disease and toxicities from therapies, particularly glucocorticoids. Many randomized controlled trials (RCTs) of newer biological/targeted therapies failed to show benefits in SLE, which were attributed to the clinical and immunological heterogeneity of the disease, flaws in study design, potent background immunosuppression, limitation of existing assessment tools, as well as the lack of validated biomarkers that help stratify patients into subsets that benefit maximally from the therapeutic mechanisms.

Biological Therapies for SLE

B-cells are central to the development of autoantibodies. Biological agents are developed to direct against growth and survival factors, surface molecules, and proteasomes of B-cells. B lymphocyte stimulator (BLyS), or B-cell-activating factor (BAFF), binds to 3 surface receptors of B-cells (transmembrane activator and CAML interactor (TACI), B cell maturation antigen (BCMA), and BAFF receptor (BAFF-R)) and modulates their maturation, survival, proliferation, and immunoglobulin class switching. A proliferation-inducing ligand (APRIL) is a homolog of BAFF that binds to TACI and BCMA with a higher affinity than BAFF.

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Targeting B-cell growth factors

Belimumab

Belimumab is a fully humanized monoclonal antibody that directs against BLyS. Two phase III RCTs (BLISS-52/76) involving seropositive patients with active SLE (systemic lupus erythematosus disease activity index (SLEDAI) score ≥6) were conducted.[3,4] Participants were randomized to receive intravenous (IV) belimumab or placebo (PBO) in addition to standard-of-care (SOC) therapies. The primary efficacy end point was the SLE responder index (SRI)-4 response (improvement in SLEDAI scores ≥4, no British Isles Lupus Assessment Group [BILAG] worsening [≥1 new A or 2 B flares], and no worsening in physicians' global assessment [PGA] by ≥0.3). Both trials showed significantly higher SRI-4 rates in the belimumab (10 mg/kg) group compared with the PBO group (58% *vs.* 44% in BLISS-52; and 43% *vs.* 34% in BLISS-76). Belimumab was superior to PBO in the musculoskeletal and mucocutaneous BILAG domains. Subgroups of patients with SLEDAI ≥10, low complements, positive anti-dsDNA, or the use of prednisolone at baseline showed higher rates of SRI-4 and other secondary end points (severe lupus flares, steroid-sparing, improvement in fatigue, and quality of life) in belimumab-treated patients. Pooled analyses of the phase II/III trials showed that adverse events (AEs) and serious adverse events (SAEs), including serious infections and malignancy, were not increased with belimumab, except for a higher frequency of depression, suicide, and serious infusion reaction.

Extension of the BLISS studies for 8 years in those who remained on belimumab showed a static or reduced annual incidence of AEs and SAEs.[5] Belimumab was discontinued by 9.4% of patients because of AEs. The majority (88%) of patients did not have an increase in the systemic lupus erythematosus international collaborating clinic (SLICC)/SLE damage index from baseline. The results from this study indicate the long-term safety of belimumab in SLE.

A phase III RCT with a similar protocol to the BLISS studies was repeated in 49 centers across China, Japan, and South Korea.[6] A total of 677 patients were studied, and at Week 52, a significantly higher SRI-4 response rate was again observed with belimumab *vs.* placebo (53.8% *vs.* 40.1%). Belimumab-treated patients had a 50% lower risk of having a severe lupus flare than those receiving PBO. In those using prednisolone >7.5 mg/day at baseline, a steroid-sparing effect of belimumab was again observed.

Postmarketing experience showed that belimumab is most often used in refractory musculoskeletal and mucocutaneous manifestations, worsening serological activity, and glucocorticoid dependence.[7–10] Clinical improvement and a steroid-sparing effect were reported in 49%–78% of patients.[10]

Subcutaneous (SC) belimumab has also been studied in SLE. A phase III RCT (BLISS-SC) recruited 836 patients with SLE with SLEDAI ≥8 to receive either weekly SC belimumab (200 mg) or PBO in addition to SOC.[11] At Week 52, SC belimumab was associated with a significantly higher SRI-4 response compared with PBO (61% *vs.* 48%). IV belimumab has been approved by many countries for the treatment of adult and pediatric (age ≥5 years) patients with active, seropositive SLE despite SOC. The SC preparation has also been licensed in adult patients for the same indications.

Belimumab is not indicated in patients with severe lupus nephritis (LN) (proteinuria ≥6 g/day or serum creatinine >2.5 mg/dL) or neuropsychiatric (NP) SLE because these patients were excluded from the pivotal RCTs. A recent phase III RCT (BLISS-LN) showed promise of belimumab in LN.[12] A total of 446 patients with biopsy-proven LN were randomized to receive either IV belimumab (10 mg/kg) or PBO in addition to SOC for induction therapy (74% mycophenolate mofetil (MMF); 26% cyclophosphamide (CYC)/azathioprine (AZA)). At Week 104, the primary outcome renal response (urine protein-to-creatinine ratio (uP/Cr) ≤0.7; estimated glomerular filtration rate (eGFR) ≤20% below pre-flare value or ≥60 mL/min/1.73 m^2; and no treatment failure) rate was significantly higher in the belimumab group compared with the than PBO group (43.0% *vs.* 32.3%; $P = 0.03$). As the efficacy is modest, the cost-effectiveness of the first-line use of belimumab in LN requires further evaluation.

Other BLyS inhibitors

Tabalumab is a humanized monoclonal antibody against both soluble and membrane bound BAFF. Two phase III RCTs of SC tabalumab in moderate-to-severe active SLE without serious renal and NP manifestations were conducted.[13,14] The primary efficacy outcome, SRI-5 response, was met in one study but not in the other. Although SAEs and treatment-emergent adverse events (TEAEs) were not increased with tabalumab, further development of the drug was aborted.

Blisibimod is a fusion protein consisting of 4 BAFF binding domains fused to the Fc portion of a human antibody. A phase III RCT (CHABLIS-SC1) of seropositive patients with SLE with severe lupus (SLEDAI ≥10) did not show benefit of SC blisibimod over PBO when combined with the SOC[15] in terms of SRI-6 response (primary outcome) at Week 52 (47% *vs.* 42%). Exploratory end points, including SRI-4 and SRI-8 responses, were also negative.

Atacicept is a fully human recombinant fusion protein that blocks the activity of both soluble and membrane-bound BAFF and APRIL.[16] A phase II/III RCT of atacicept involving patients with active LN who received high-dose steroid and MMF was terminated for the occurrence of serious

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infections.[17] Another phase II/III RCT involving patients with active SLE (≥1 BILAG A and/or B) did not demonstrate the benefit of SC atacicept (75-mg arm) over PBO in achieving the primary outcome (proportion of patients having a new BILAG A/B flare).[18] The atacicept 150 mg arm was terminated because of two fatal pulmonary infections. Patient subset with elevated serum BLyS and APRIL levels showed a greater reduction in SLE flares. More recently, a 24-week phase IIb RCT (ADDRESS II) in seropositive patients with active SLE (SLEDAI-2K ≥6), despite SOC, was repeated.[19] No increase in TEAEs, including serious infections, was demonstrated with the two atacicept arms. Although the primary SRI-4 end point was not met, patient subgroups with higher baseline disease activity or active serology, or both, showed a significantly greater SRI-4 and SRI-6 rates in the atacicept groups. In view of the conflicting results of these RCTs, further studies are needed for developing this agent in SLE further.

Targeting B-cell surface molecules

Rituximab

Rituximab is a chimeric monoclonal antibody directing against the CD20 molecule on B-cell surface. B-cells, from pre-B to memory B stage, are depleted by this compound, but not the pro-B-cells and terminally differentiated plasma cells that do not express CD20. Repopulation of B-cells usually occurs at 6–9 months after the administration of rituximab.[20] The EXPLORER study randomized patients with moderate-to-severe extra-renal lupus (≥1 BILAG A or ≥2 BILAG B domains), despite SOC,[21] to receive 2 courses of either rituximab or PBO at a 6-month interval. After 52 weeks, clinical responses (major/partial), disease activity, lupus flares, and time to flare did not differ significantly between the two groups, although AEs and SAEs were not increased with rituximab. The LUNAR study recruited patients with active LN (class III/IV) using a similar protocol.[22] Patients were randomized to receive rituximab or PBO in combination with steroid and MMF. No statistically significant differences in the primary and secondary end points were observed between the two groups at Week 52, but leukopenia, hypotension, infusion-related reactions, herpes zoster (HZ) infection, and opportunistic infections were numerically more frequent in the rituximab group.

Despite these negative trials, rituximab is widely used off-label for refractory SLE. Registries reported clinical response to rituximab in 67%–86% of patients with SLE with various refractory manifestations that included renal, articular, mucocutaneous, and hematological disease.[23–29] Efficacy did not seem to differ between rituximab monotherapy and in combination with other immunosuppressive agents.[23] SLE flares occurred in 41% of responders and usually responded to rituximab re-treatment in most cases.[23]

Newer-generation anti-CD20 biologics

Ocrelizumab is fully human anti-CD20 monoclonal antibody with lower immunogenicity than rituximab. A phase III double-blind RCT in non-renal SLE (BEGIN) was prematurely terminated.[13] Another RCT (BELONG) in patients with active LN (class III/IV) who were randomized to receive 2 doses of ocrelizumab or PBO in addition to high-dose steroid and MMF or Euro-Lupus CYC/AZA for induction was also terminated because of an excess rate of serious infections in ocrelizumab-treated patients.[14] However, in those who completed treatment for ≥32 weeks, the renal response rate of the combined ocrelizumab groups was numerically higher than the PBO group.

Obinutuzumab is a second generation anti-CD20 monoclonal antibody that exhibits greater B-cell cytotoxicity than rituximab. The preliminary results of a phase II RCT involving patients with LN (class III/IV) showed its superiority to PBO when combined with steroid and MMF/mycophenolic acid (MPA).[30]

Anti-CD22 biologics

Epratuzumab is a humanized monoclonal antibody that specifically targets CD22 on mature B-cells, which is involved in the modulation of B cell receptor (BCR) signaling, cellular activation, and survival.[31] Clinical trials showed that epratuzumab causes a modest reduction in peripheral B-cells without significant effects on T cells, autoantibody titers, or immunoglobulin levels. Two phase III RCTs (EMBODY 1/2) randomized seropositive patients with SLE with moderate-to-severe activity (SLEDAI-2K ≥6, BILAG ≥1 A or ≥2 Bs in mucocutaneous, musculoskeletal, or cardiorespiratory domains), despite SOC, to receive infusions of epratuzumab (2 doses) or PBO.[32] However, the primary end point, BILAG-based combined lupus assessment (BICLA) response rate at Week 48, was not significantly better with epratuzumab despite a similar frequency of AEs and TEAEs.

Combination/sequential anti-B-cell biological therapies

Depletion of B-cells is variable after treatment with rituximab and the time to repopulation of B-cells explains the differential clinical response in different patients. The rise of serum BLyS level after the treatment with rituximab may be responsible for diminished response and disease flare. A phase IIa proof-of-concept study (SynBioSe) of combined rituximab and belimumab in refractory SLE has reported safety of the regimen, with the aim of blocking the increase in BLyS after B-cell depletion by anti-CD20 therapy.[33] Three RCTs are in progress: BLISS-BELIEVE (combined SC belimumab and rituximab *vs.* SC belimumab ± SOC), CALIBRATE (IV CYC-rituximab with *vs.* without belimumab in LN), and BEAT-LUPUS (SOC + rituximab, followed by belimumab *vs.* PBO 4–8 weeks later).

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Targeting co-stimulatory molecules

Abatacept (CTLA4-Ig) is a fusion protein comprising the extracellular domain of CTLA4 and an Fc domain that binds CD80/CD86 with a higher affinity than CD28 and thus inhibits this co-stimulatory pathway for T-cell activation.[34] A phase II/III RCT involving patients with active LN (class III/IV) compared the efficacy of IV abatacept infusion (2 dosing regimens) with PBO in addition to steroid and MMF.[35] The primary end point, time to complete renal response, was not significantly different between the abatacept and PBO groups at Week 52. HZ, gastroenteritis, and SAEs were numerically higher in abatacept users. Another phase II RCT in patients with active LN (ACCESS) also did not show a benefit in the complete renal response rate of IV abatacept over PBO at Week 24 when combined with high-dose steroid and the Euro-Lupus CYC regimen.[36] The frequencies of partial renal response and other secondary end points were also similar between the two groups and so were the AEs and SAEs.

Dapirolizumab pegol is a newer-generation anti-CD40L molecule that consists of a Fab fragment conjugated to polyethylene glycol and lacks the Fc portion. The preliminary results of a phase II trial of dapirolizumab in moderate-to-severe non-renal SLE showed safety and greater improvement in multiple end points when compared with PBO at Week 24.[37] A phase III study is in progress.

Targeting cytokines

Interleukin-6 (IL-6) was elevated in patients with SLE and correlated with the disease activity. Despite a phase I study showed promise of IL-6 receptor blockade (tocilizumab) in SLE with mild/moderate activity,[38] a phase II RCT of sirukumab, a monoclonal antibody against IL-6, in refractory LN[39] did not demonstrate the anticipated efficacy or safety.

Type I interferons (IFNs) are produced by plasmacytoid dendritic cells upon induction by immune complexes in patients with SLE. IFN-α activates T-cells and promotes autoantibody production by B-cells. Levels of IFN-α, IFN-driven chemokines, and the expression of IFN-regulated genes (IFN signature) were elevated in SLE and correlated with the disease activity. Monoclonal antibodies directing against IFN-α (rontalizumab and sifalimumab) or the IFN-α receptor (anifrolumab) have been tested in SLE.

A phase II study of rontalizumab in patients with moderate-to-severe non-renal SLE (≥1 BILAG A or ≥2 BILAG B domains)[40] did not meet the primary efficacy end points at Week 24, although viral or other infectious AEs were not more common with rontalizumab. A phase II RCT of sifalimumab in patients with active SLE (SLEDAI of ≥6, ≥1 BILAG A or ≥2 BILAG B, and PGA ≥1) showed a significantly higher SRI-4 response rate at Week 52 in the sifalimumab 1,200 mg group compared with the PBO group when used with SOC.[41] Improvement was also demonstrated in skin lesions cutaneous lupus erythematosus disease area and severity index (CLASI) and joint counts. Sifalimumab was well-tolerated, except for a higher frequency of HZ infection. Despite these results, further development of this biologic was not pursued.

A phase IIb RCT of anifrolumab was conducted in patients with active non-renal SLE that did not respond adequately to SOC.[42] Participants were randomized to receive IV anifrolumab or PBO monthly for 48 weeks. At Day 169, the primary end point of SRI-4 and a sustained steroid-sparing effect was met in the anifrolumab 300 mg group compared with the PBO (34% *vs.* 18%; $P = 0.01$). Rates of secondary end points (SRI-4, reduction in steroid dosage, improvement in skin activity score, and joint counts) were also significantly higher in the anifrolumab group, particularly in those with high IFN signature at baseline. AEs were not more frequent in anifrolumab users, except for influenza and HZ infection.

The recently published phase III RCT (TULIP-2) confirmed that monthly IV anifrolumab (300 mg) was superior to PBO in achieving a BICLA response at Week 52 (47.8% *vs.* 31.5%; $P = 0.001$) in patients with active SLE (SLEDAI-2K ≥6 and clinical SLEDAI-2K ≥4) receiving SOC therapies (NEJM 2019).[43] Secondary end points (steroid dosage reduction and severity of skin disease) also showed benefit with anifrolumab. However, HZ infection was more common in anifrolumab-treated patients (7.2% *vs.* 1.1%). The regulatory approval for the use of anifrolumab in SLE is pending.

Neutralizing antibodies against subtypes of IFN-α are induced by active immunization of interferon-α-kinoid (IFN-K). A phase IIb RCT involving patients with SLE with moderate-to-severe disease activity (SLEDAI-2K ≥6 and one BILAG A ± two BILAG B scores) and positive IFN signature reported the safety of IFN-K, which reduced the IFN gene signature significantly.[44] Although the co-primary efficacy end point was not met, secondary end points such as achievement of lupus low disease activity state (LLDAS) and a steroid-sparing effect were in favor of IFN-K.

IL-12 and IL-17/23 axis are involved in the pathogenesis of SLE.[45] Ustekinumab is a monoclonal antibody that targets IL-12/23. In a phase II RCT, seropositive patients with active SLE (SLEDAI-2K ≥6 and 1 BILAG A ± 2 BILAG B) were randomized to receive ustekinumab or PBO in addition to SOC.[46] The primary outcome, SRI-4 response rate at Week 24, was significantly higher in the ustekinumab group (62% *vs.* 33%; $P = 0.006$). Improvement in ≥50% of the skin score (CLASI), but not in reduction of joint counts, was significantly more frequent with ustekinumab (53% *vs.*

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35%; *P* = 0.03). The frequency of AEs or infections was not increased with treatment. A confirmatory phase III study is underway.

Targeting intracellular pathways

Targeting the downstream intracellular signaling pathways from the type I/II cytokine receptors mediated by the Janice kinase-signal transducer and activator of transcription protein (JAK-STAT) proteins allows simultaneous suppression of multiple cytokines. The Jakinibs are being tested in SLE. In a phase II RCT, patients with SLE and active joint/skin disease were assigned to receive baricitinib (4 mg/day) or PBO in addition to SOC.[47] At Week 24, remission of skin disease or arthritis occurred in a significantly higher proportion of patients treated with baricitinib compared with PBO (67% *vs.* 53%, *P* = 0.04), and so was the rate of SRI-4 response (64% *vs.* 48%; *P* = 0.02). Tender joint count, but not the extent or severity of skin lesions, significantly improved with baricitinib. Although serious infections were numerically more frequent with baricitinib, the positive results called for 2 further phase III RCTs in non-renal SLE.

Bruton's tyrosine kinase (BTK) is a mediator of B-cell receptor and Fc receptor signaling of innate immune cells such as monocytes. A phase IIb study of fenebrutinib, an oral BTK inhibitor, did not meet the primary and secondary end points.[48] Despite this, another BTK inhibitor, evobrutinib, that has been shown to suppress B-cell and innate immune responses, is being evaluated in SLE.

Targeting T-cells and small molecules

The calcineurin inhibitors (CNIs) have been increasingly used in SLE.[49] Newer-generation CNIs such as voclosporin exhibits a stronger binding capacity to cyclophilin A, hence, more potent CNI, faster elimination, and less variability in plasma concentration.[50] A phase II RCT (AURA-LV) involving 265 patients with LN showed that low-dose voclosporin (23.7 mg BID) was superior to placebo (PBO) when added to MMF and glucocorticoid as induction therapy at Week 24 in terms of complete renal remission (CRR) rate (32.6% *vs.* 19.3%).[51] The significant increase in CRR rate persisted in the voclosporin arm through Week 48. However, there were more SAEs and deaths in the voclosporin group. The promising data lead to a larger phase III global study.

Sirolimus (rapamycin) is an inhibitor of the mammalian target of rapamycin (mTOR), which is involved in the regulation of the Th1/17 pathway and regulatory T-cell development. An open-label, phase I/II, single-arm, 52-week study reported the safety and efficacy of sirolimus in 40 patients with SLE,[52] with gradual improvement in the disease activity and achievement of the SRI-4 response in 2/3 of the patients. However, withdrawal rate was high (28%) because of noncompliance or intolerance.

Other biologic/targeted agents and small molecules being studied in SLE included lulizumab pegol (anti-CD28), guselkumab (anti-IL23), eculizumab (terminal complement inhibitor), anti-IFN-γ, proteasome inhibitors (bortezomib and ixazomib), RNase, edratide, rigerimod, and laquinimod.

The Dawn of a New Era of Therapies of SLE

Despite the futility of many recent clinical trials in SLE, we see the dawn of a new era of novel therapeutics in SLE. Combination strategies with the aim of targeting multiple molecules or cytokines to achieve a synergistic effect and minimize toxicities of individual drugs appear to be a promising approach. The initial success of the JAK inhibitors illustrates the complexity of the pathogenesis of SLE and the merits of intervening multiple effector molecules simultaneously. Reducing the PBO response by optimizing background immunosuppression, adoption of organ-specific improvement criteria, and patient stratification by clinical characteristics or biomarkers may better differentiate the effect of the treatment from PBO. Composite end points and quantification of improvement in different organs may emerge as more suitable outcome measures in SLE clinical trials. Finally, the long-term safety and cost-effectiveness of novel therapies in serious or refractory SLE manifestations have to be explored from the health economic point of view.

Conflict of Interest

None declared.

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