Biologics in Systemic Lupus Erythematosus (SLE)

6

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6.1 Introduction

- SLE is a multisystemic autoimmune disease with an unpredictable course that consists of periods of remission and flares.
- The pathogenesis of SLE is unclear but multiple genetic, epigenetic, hormonal, and environmental factors are involved.

6.2 Unmet Needs in the Management of SLE

- The major reasons for mortality and morbidities of SLE are uncontrolled (refractory) disease activity (e.g., lupus nephritis [LN]) and therapy-related toxicities (especially glucocorticoids).
- Although survival of SLE has improved substantially, further improvement in recent years is hindered by the relatively slow development of novel therapies.
- Many randomized controlled trials (RCTs) of newer biological/targeted therapies failed to show benefits in SLE, which were related to the immunological and clinical heterogeneity of the disease, issues of study design, limitation of existing assessment tools, and potent background immunosuppression.
- More effective but less toxic therapeutic agents and appropriate patient stratification are needed to improve SLE care.

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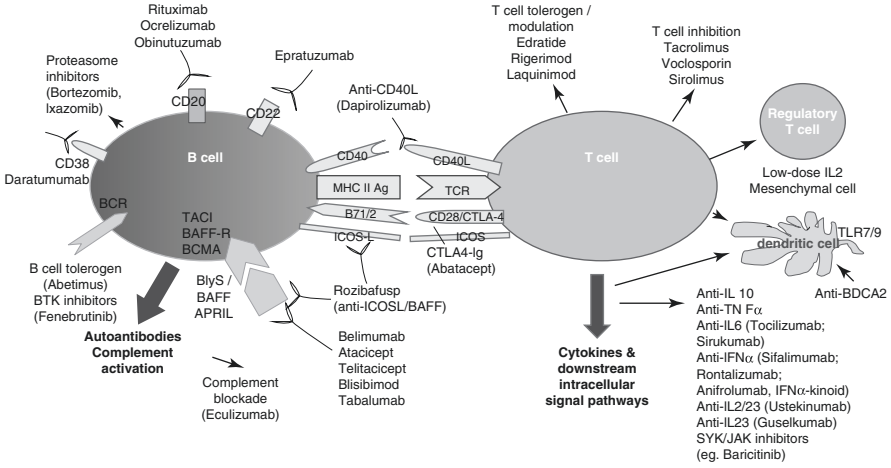

Fig. 6.1 Points of intervention in the immunological pathways of SLE

6.3 Points of Intervention in the Immunological Pathways of SLE (Fig. 6.1)

- Biological/targeted agents interact with cellular receptors, intracellular enzymes and molecules, cytokines, and other proteins to modulate immune activation, autoantibody production, and tissue inflammation (Table 6.1).

6.4 Biological Therapies for SLE

6.4.1 Targeting B Cell Growth and Survival Factors

- B lymphocyte stimulator (BlyS), or B cell-activating factor (BAFF), binds to three surface receptors of B cells (TACI, BCMA, and BAFF-R) and modulates their maturation, survival, proliferation, and immunoglobulin class switching.
- APRIL (a proliferation-inducing ligand), a homolog of BAFF that influences the survival and activation of B cells, binds to TACI and BCMA with a higher affinity compared to BAFF.
- BlyS mRNA and serum levels are increased in SLE patients and correlate with activity scores. Agents have been developed to inhibit BlyS, APRIL, or both (belimumab, tabalumab, blisibimod, and atacicept).

6.4.2 Belimumab

- Two phase 3 RCTs (BLISS-52/76) in seropositive SLE patients with SLEDAI score ≥ 6 and stable treatment were performed [1, 2]. Patients were randomized to intravenous (IV) belimumab or placebo (PBO) in combination with standard of care (SOC) therapies.

Table 6.1 Biologic/targeted agents in SLE trials

Drugs	Nature	Targets and actions	Pivotal studies	Background therapies	Dosage regimens in studies
Belimumab	mAb (H)	Soluble BAFF and prevents its interaction with the BAFF receptors	BLISS-52, BLISS-76, BLISS-SC, BLISS-LN (p3)	SOC	10 mg/kg (IV) every 2 weeks for 3 doses, then every 4 weeks; 200 mg (SC) weekly
Tabalumab	mAb (H)	Soluble and membrane-bound BAFF	ILLUMINATE1/2 (p3)	SOC	120 mg (SC) every 2 weeks
Blisibimod	Fusion protein	Soluble BAFF	CHABLIS-SC1 (p3)	SOC	200 mg (SC) once weekly
Atacicept	Fusion protein	Soluble and membrane-bound BAFF and APRIL	2RCTs (P2/3), ADDRESS II (p3)	SOC	75 mg/150 mg (SC) weekly
Rituximab	mAB (C)	CD20 on B cells, leading to depletion of B cells, from pre-B to memory B stage, with sparing of pro-B cells and plasma cells	EXPLORER, LUNAR (p3)	SOC, HD Pred + MMF	1 g 2-weekly for 2 doses × 2 courses (month 0 and 6)
Ocrelizumab	mAb (H)	CD20 on B cells	BEGIN, BELONG (p3)	HD Pred + MMF or euro-lupus CYC/AZA	IV (400 mg or 1000 mg) every 2 weeks for 2 doses; repeat after 4 months
Obinutuzumab	mAb (H)	CD20 on B cells (more ADCC, less CDC)	NOBILITY (p2)	HD pred + MMF/MPA	IV (1000 mg) infusion on days 1,15, 168, 182
Epratuzumab	mAb (H)	CD22 on B cells, modulate BCR signaling, cellular activation and survival	EMBODY 1/2 (p3)	SOC	IV 600 mg every week or 1200 mg every other week for 4 cycles
Abatacept	Fusion protein	Binds CD80/86 with a higher affinity than CD28, thus inhibits the co-stimulatory signal for T cell activation	RCT (p3), ACCESS (p2)	HD Pred + MMF, HD Pred + euro-lupus CYC/AZA	10 mg/kg or 500-1000 mg depending on body weight

(continued)

Table 6.1 (continued)

Drugs	Nature	Targets and actions	Pivotal studies	Background therapies	Dosage regimens in studies
Dapirolizumab	Fab fragment (H)	CD40L	RCT (p2b)	SOC	IV (6/23/45 mg/kg) every 4 weeks
Sirukumab	mAb (H)	IL-6	RCT (p2)	SOC	IV (10 mg/kg) every 4 weeks
Rontalizumab	mAb (H)	Neutralizes 12 subtypes of IFNα but does not bind to IFNβ or IFNω.	RCT (p2)	Existing therapies stopped except HCQ and Pred	750 mg IV every 4 weeks till week 20, followed by 300 mg SC every 2 weeks till week 22
Sifalimumab	mAb (H)	Binds and neutralizes most subtypes of IFNα	RCT (p2b)	SOC	IV (200/600/1200 mg) on days 1, 15 and 29, then every 28 days
Anifrolumab	mAb (H)	Type I IFN receptor—blocks signaling of type I IFNs, including IFNα, IFNβ, IFNε, IFNκ and IFNω	RCT (p2), 2RCTs (p3)	SOC	IV (150/300 mg) (p2); IV (300 mg) (p3) every 4 weeks
Interferon-α-kinoid	IFNα vaccine	Induces neutralizing antibodies against 13 IFNα subtypes	RCT (p2b)	SOC	Five injections of vaccine at days 0,7,28 and months 3 and 6
Ustekinumab	mAb (H)	IL-12 and IL-23 (p40 subunit)	RCT (p2)	SOC	IV 260-520 mg at week 0, followed by SC 90 mg every 8 weeks
Baricitinib	Jakinib	JAK1/2	RCT (p2)	SOC	2 or 4 mg/day
Fenebrutinib	BTKi	BTK	RCT (p2)	SOC	150 mg or 400 mg/day

mAb monoclonal antibody, *H* fully humanized, *C* chimeric, *BAFF* B cell activation factor, *SOC* standard of care, *p2* phase 2, *p3* phase 3, *RCT* randomized controlled trial, *IV* intravenous, *SC* subcutaneous, *HD* high-dose, *Pred* prednisolone, *MMF* mycophenolate mofetil, *MPA* mycophenolic acid, *CYC* cyclophosphamide, *AZA* azathioprine, *HCQ* hydroxychloroquine, *IL* interleukin, *JAK* Janus kinase, *ADCC* antibody dependent cytotoxicity, *CDC* complement dependent cytotoxicity, *BCR* B cell receptor, *IFN* interferon, *BTKi* Bruton tyrosine kinase inhibitor

- The primary efficacy endpoint was the SRI (SLE responder index)-4 response (improvement in SLEDAI scores ≥4, no worsening of British Isles Lupus Assessment Group [BILAG] [new A or two B flares] and physicians' global assessment [PGA] [increase ≥0.3]). Both trials showed significantly higher SRI-4 rates in belimumab (10 mg/kg) than PBO groups (58% vs 44% in BLISS-52; and 43% vs 34% in BLISS-76). Belimumab was more effective than PBO in the musculoskeletal and mucocutaneous domains of BILAG.

- Patient subsets with SLEDAI ≥10, anti-dsDNA positivity, depressed complements, or steroid use at baseline had higher rates of SRI-4 and other secondary endpoints (severe SLE flares, steroid-sparing effect, improvement in quality of life and fatigue) to belimumab.
- In phase 2/3 trials, the frequencies of adverse events (AEs) and serious AEs (SAEs), including serious infections and cancer, were not higher with belimumab, except for depression and suicide (numerically more common).
- Serious infusion reaction, which might be delayed, was more frequent in belimumab than PBO (0.9% vs 0.4%).
- Extension of the BLISS studies for 8 years in those who were continuously treated with belimumab showed a static yearly incidence of AEs and SAEs [3]. Majority (88%) of patients did not have an increase in SLICC/ACR SLE damage index compared to baseline, indicating low organ damage accrual and a stable safety profile of belimumab.
- Post-marketing experience: Belimumab is most frequently used in refractory musculoskeletal and mucocutaneous manifestations. Clinical improvement and a steroid-sparing effect were achieved in 49–78% of patients.
- Belimumab is not indicated in patients with severe renal or neuropsychiatric (NP) SLE.
- In a RCT (BLISS-SC), SLE patients with SLEDAI ≥8 were randomized to receive weekly subcutaneous (SC) belimumab or PBO in combination with SOC for 52 weeks [4]. Similar to IV belimumab, the SC preparation was associated with a significantly higher SRI-4 response than PBO (61% vs 48%).
- IV belimumab is approved for treatment of adult and pediatric (age ≥5 years) patients with active, autoantibody-positive SLE despite standard therapies. The SC preparation has also been approved in adult patients with the same indications.
- A phase 3 RCT (BLISS-LN) showed that IV belimumab increased the renal response rates at 104 weeks when added to SOC treatment (mycophenolate mofetil [MMF] and glucocorticoids in 74% patients) in patients with LN without increasing the incidence of AEs [5].

6.4.3 Tabalumab

- Two phase 3 RCTs of SC tabalumab in moderate/severe active SLE without serious renal or NP manifestations were published [6, 7].
- The primary efficacy endpoint (SRI-5 response) was met in one study but not in the other, although SAEs and treatment-emergent AEs (TEAEs) were not more common with tabalumab treatment. Further clinical trial of the drug was halted.

6.4.4 Blisibimod

- A phase 3 RCT (CHABLIS-SC1) randomized autoantibody-positive SLE patients with active disease (SLEDAI ≥10) to receive either SC blisibimod or PBO in combination with SOC [8].
- The SRI-6 response (primary outcome) was not significantly different between blisibimod and PBO at week 52 (47% vs 42%).

6.4.5 Atacicept

- A phase 2/3 RCT of atacicept in patients with active LN who were treated with background high-dose steroid and MMF was halted for the development of serious infections [9].
- Another phase 2/3 RCT randomized patients with active SLE (≥1 BILAG A and/or B) to receive two doses of SC atacicept or PBO with a steroid taper [10]. The primary outcome, percentage of patients having a new BILAG A/B flare, was not achieved in the atacicept (75 mg) arm.
- The atacicept 150 mg arm was terminated because of fatal pulmonary infections in two patients. TEAEs (including serious infections) were not different across the three groups.
- Patients with increased serum BlyS and APRIL levels achieved a greater reduction in lupus flares.
- Despite the increased risk of infections with atacicept, a 24-week phase 2b RCT (ADDRESS II) in seropositive SLE patients with active disease (SLEDAI-2K ≥6) despite SOC was repeated [11]. No increase in TEAEs (including serious infections) was demonstrated in users of atacicept (75 mg/150 mg).
- Although the primary SRI-4 endpoint was not met, subgroups of patients with more active disease at baseline (SLEDAI-2K ≥10) or active lupus serology, or both, achieved a significantly higher SRI-4 and SRI-6 rates in the atacicept arms.
- Further studies are necessary in view of the conflicting evidence in efficacy and toxicity.

6.4.6 Targeting B Cell Surface Molecules

6.4.6.1 Rituximab

- Two pivotal RCTs of rituximab in SLE were performed.
- The EXPLORER study randomized patients with moderate/severe extra-renal SLE (≥1 BILAG A or ≥2 BILAG B domains) despite SOC [12] to receive either rituximab or PBO (two courses 6 months apart).
- Clinical responses (major and partial), disease activity scores, flares, and time to flare did not show statistically significant differences between the two groups, although rituximab was not associated with increased rates of AEs and SAEs.
- The LUNAR study included patients with active LN (class III/IV) using a similar protocol [13]. Patients were randomized to receive rituximab or PBO in addition to steroid and MMF.
- At week 52, the primary and secondary endpoints did not show statistically significant differences between the two groups.
- Hypotension, leukopenia, infusion-related reactions, herpes zoster (HZ), and opportunistic infections were more numerically more frequent in patients treated with rituximab.

- Post-marketing experience: 13% SLE patients developed infusion reaction to rituximab (serious in 12% and delayed in 29%). Serious infections: 6.6/100 patient-years.
- Despite benefits not shown in RCTs, rituximab is often used off-label to treat refractory SLE. Clinical response to rituximab was reported in 67–86% of SLE patients with various refractory manifestations such as articular, mucocutaneous, renal, and hematological disease.
- Rituximab (375 mg/m^2 weekly × 4 doses or 1 g 2-weekly × 2 doses) was often administered in combination with steroid and/or cyclophosphamide (CYC), MMF, azathioprine (AZA), and methotrexate (68–76% cases).

6.4.6.2 Ocrelizumab

- A phase 3 double-blind RCT of ocrelizumab in non-renal SLE (BEGIN) was terminated prematurely [14].
- Another RCT (BELONG) [15] recruited patients with active LN (class III/IV) to receive ocrelizumab for two doses or PBO in combination with high-dose steroid and either MMF or Euro-Lupus CYC/AZA.
- This study was also terminated prematurely for an excess rate of serious infections in the ocrelizumab group.
- In patients who completed ≥32 weeks' treatment, the renal response rate of the combined ocrelizumab groups was numerically higher than PBO.

6.4.6.3 Obinutuzumab

- Obinutuzumab is a newer generation anti-CD20 monoclonal antibody that induces greater B cell cytotoxicity than rituximab.
- Results of a phase 2 RCT in patients with class III/IV LN showed superiority of this biologic to PBO when combined with steroid and MMF or mycophenolic acid (MPA) [16].

6.4.6.4 Epratuzumab

- Two phase 3 RCTs (EMBODY 1/2) recruited seropositive SLE patients with moderate/severe activity (SLEDAI-2K ≥6, BILAG ≥1A or ≥2Bs in mucocutaneous, musculoskeletal, or cardiorespiratory domains) despite SOC to receive epratuzumab (two doses) or PBO infusion [17].
- The primary endpoint, BILAG-based combined lupus assessment (BICLA) response rate at week 48, was not significantly different between the epratuzumab and PBO groups.
- AEs and TEAEs were, however, similar across all treatment arms.

6.4.6.5 Daratumumab

- Daratumumab is an anti-CD38 monoclonal antibody that depletes plasma cells.
- A recent report described two SLE patients with refractory disease responding clinically to daratumumab in addition to SOC, with documented depletion of the long-lived plasma cells [18].
- The safety and efficacy of daratumumab in SLE has to be confirmed by further studies.

6.4.7 Targeting Co-Stimulatory Molecules

6.4.7.1 Abatacept

- A phase 2/3 RCT recruited patients with active class III/IV LN to be randomized to IV abatacept (two dosing regimens) or PBO infusion in combination with steroid and MMF [19].
- The primary endpoint, time to complete renal response, was not significantly different in the abatacept group as compared to PBO at week 52.
- However, HZ infection, gastroenteritis, and SAEs were non-significantly more frequent in abatacept users.
- Another phase 2 RCT randomized patients with class III/IV LN (ACCESS) to receive IV abatacept or PBO in combination with high-dose steroid and the Euro-Lupus CYC regimen [20].
- The rate of complete renal response was not significantly higher in the abatacept group at week 24.
- The rates of partial response, AEs and SAEs, and other secondary endpoints were also similar between the two groups.

6.4.7.2 Dapirolizumab

- Despite an earlier study of anti-CD40L monoclonal antibody (ruplizumab) raised the concern of thromboembolism in SLE, a newer anti-CD40L molecule that consists of a Fab fragment conjugated to polyethylene glycol and lacks the Fc portion (dapirolizumab pegol) was tested in moderate/severe nonrenal SLE in a phase 2 trial [21].
- Preliminary results demonstrated safety and greater improvement in multiple endpoints as compared to PBO at week 24. However, a dose response relationship was not observed.

6.4.8 Combination/Sequential Biological Therapies

- Rituximab treatment leads to variable B cell depletion and time to repopulation (particularly memory B cells and plasmablasts), which might contribute to the differential clinical response and lupus flares.
- Rise of BlyS level after rituximab treatment, which may contribute to reduced response and more flare, may be reduced by concomitant belimumab therapy.
- A phase 2a proof-of-concept study (SynBioSe) of combined rituximab and belimumab in refractory SLE has reported safety of the regimen [22]. Three RCTs with similar objectives are ongoing: BLISS-BELIEVE (combined SC belimumab and rituximab vs 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).

6.4.9 Targeting Cytokines

6.4.9.1 IL-6

- Elevation of IL-6 was demonstrated in SLE and correlated with disease activity.
- Despite a phase I study showed promise of IL-6 receptor blockade (tocilizumab) in SLE patients with mild/moderate activity [23], a phase 2 proof-of-concept RCT of an anti-IL6 monoclonal antibody (sirukumab) in refractory LN [24] did not demonstrate the anticipated efficacy or safety.

6.4.9.2 Type I Interferons (IFNs)

- In SLE, type I IFNs are produced by plasmacytoid dendritic cells when induced by immune complexes.
- IFNα promotes T cell activation and autoantibody production by B cells.
- Levels of IFN-α, IFN-driven chemokines and expression of IFN-regulated genes increased in SLE patients and correlated with activity score.
- Two monoclonal antibodies (rontalizumab and sifalimumab) that direct against IFNα and one monoclonal antibody against the IFNα receptor (anifrolumab) have been developed.

6.4.9.3 Rontalizumab

- A phase 2 study was conducted in SLE patients with moderate/severe nonrenal disease (≥1 BILAG A or ≥2 BILAG B domains) [25].
- Participants were randomized to receive rontalizumab or PBO. At week 24, the BILAG and SRI response rates were not different between the rontalizumab and PBO groups.
- Although a significant increase in viral or other infectious AEs was not observed with rontalizumab, further development of this biologic was halted.

6.4.9.4 Sifalimumab

- A phase 2 RCT [26] randomized seropositive SLE patients with active disease (SLEDAI of ≥6, ≥1 BILAG A or ≥2 BILAG B, and PGA ≥1) to receive IV sifalimumab or PBO in addition to SOC.
- At week 52, the SRI-4 response rate was significantly higher in the 1200 mg group compared to PBO (60% vs 45%; $p = 0.03$).
- Sin scores (CLASI) and joint counts also improved.
- Patients with baseline high IFN signature responded better to sifalimumab.
- Sifalimumab was generally well-tolerated but HZ reactivation was more common.
- Further trial of this biologic was not pursued.

6.4.9.5 Anifrolumab

- A phase 2b RCT included nonrenal SLE patients with active disease despite SOC [27].
- Participants were randomized to IV anifrolumab or PBO monthly for 48 weeks.

- The SRI-4 response (primary endpoint) and a persistent steroid-sparing effect were met in the anifrolumab group (300 mg) compared to PBO at day 169 (34% vs 18%; $p = 0.01$).
- Achievement of secondary endpoints (SRI-4, reduction in steroid dosage, improvement in skin and joint activity) were also significantly more common in those treated with anifrolumab.
- Improvement in multiple endpoints was more pronounced in patients with high IFN signature.
- AEs were not more common in anifrolumab users except for influenza and HZ infections.
- A phase 3 RCT (TULIP-2) in patients with active SLE (SLEDAI-2K ≥6 and clinical SLEDAI-2K ≥4) receiving SOC therapies showed superiority of IV anifrolumab (300 mg) to PBO in achieving a BICLA response at week 52 (47.8% vs 31.5%; $p = 0.001$) [28].
- Secondary endpoints (glucocorticoid dose reduction, severity of skin disease) were also in favor of anifrolumab.
- However, HZ infection was more frequent in anifrolumab-treated patients (7.2% vs 1.1%).

6.4.9.6 Interferon-α-Kinoid (IFN-K)

- Active immunization of IFN-K generates neutralizing antibodies against 13 subtypes of IFNα.
- A recent phase 2b RCT in ANA positive SLE patients with moderate/severe disease activity (SLEDAI-2 K ≥6 and 1 BILAG A ± 2 BILAG B scores) and positive IFN signature showed that IFN-K was well-tolerated and did not lead to more TEAEs than PBO [29].
- Achievement of a low disease activity state and a steroid-sparing effect was in favor of IFN-K.

6.4.9.7 IL-12/23

- Ustekinumab is a monoclonal antibody targeting IL12/23.
- In a phase 2 RCT, seropositive SLE patients with active disease (SLEDAI-2K ≥6 and 1 BILAG A ± 2 BILAG B) were randomized to receive ustekinumab or PBO in combination with SOC [30].
- The SRI-4 response was significantly higher in the ustekinumab group at week 24 (62% vs 33%; $p = 0.006$).
- Improvement of active joint count was not better but improvement in ≥50% of the skin score (CLASI) was significantly more common with ustekinumab (53% vs 35%; $p = 0.03$).
- The frequency of AEs or infections was similar between ustekinumab and PBO.
- A phase 3 RCT of ustekinumab in SLE (LOTUS) was prematurely terminated for the lack of efficacy on interim analysis.

6.4.10 Targeting Intracellular Pathways

6.4.10.1 JAK Inhibition and Other Small Molecules

- Targeting the downstream intracellular signaling pathways from the type I/II cytokine receptors mediated by the JAK-STAT proteins allows simultaneous suppression of multiple cytokines. A number of Jakinibs have been developed.
- In a phase 2 RCT, SLE patients with active joint/skin disease were randomly assigned to receive baricitinib or PBO in combination with SOC [31].
- At week 24, resolution of skin disease or arthritis was significantly more frequent in the baricitinib 4 mg group (67% vs 53%, $p = 0.04$), and so was the SRI-4 response (64% vs 48%; $p = 0.02$).
- The number of tender joints, but not the severity of skin lesions, was reduced significantly in the baricitinib group.
- Serious infections were nonsignificantly more frequent in the baricitinib 4 mg group (6%) than PBO (1%). Deep vein thrombosis developed in one patient (1%) treated with baricitinib 4 mg.
- Although the effect size of baricitinib in reducing tender joints was small, two further phase 3 RCTs in nonrenal SLE are in progress.
- 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 2 RCT of fenebrutinib, a BTK inhibitor, in SLE did not meet the primary endpoint of SRI-4 at week 48 [32]. Another BTK inhibitor, evobrutinib, is being evaluated in SLE (phase 2 RCT).

6.4.10.2 Other Biological Agents and New Molecules

- Lulizumab pegol (anti-CD28), eculizumab (terminal complement inhibitor), anti-IFNγ, voclosporin (a newer generation calcineurin inhibitor), proteasome inhibitors (bortezomib, ixazomib), RNase, edratide, rigerimod, and laquinimod.

6.5 Conclusions

- Despite the futility of many recent trials of biologics in SLE, quest for novel therapies for this disease continues.
- Minimizing the PBO response by reducing background immunosuppression and adoption of organ-specific disease activity indices may better differentiate the treatment effect from PBO.
- Novel endpoints such as low disease activity state and percentage improvement of validated composite indices should be further explored.
- The long-term safety and cost-effectiveness of novel therapeutics in serious or refractory SLE manifestations have to be investigated.

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