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A critical review of clinical trials in systemic lupus erythematosus

Mary A. Mahieu[1], **Vibeke Strand, MD**[2], **Lee S. Simon**[3], **Peter E. Lipsky**[4], and **Rosalind Ramsey-Goldman**[1]

[1]Department of Medicine, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

[2]Division of Immunology/Rheumatology, Stanford University School of Medicine, Palo Alto, CA, USA

[3]SDG LLC, Cambridge, MA, USA

[4]AMPEL BioSolutions, Charlottesville, VA, USA

Abstract

One challenge in caring for patients with systemic lupus erythematosus (SLE) is a paucity of approved therapeutics for treatment of the diverse disease manifestations. In the last 60 years, only one drug, belimumab, has been approved for SLE treatment. Critical evaluation of investigator initiated and pharma-sponsored randomized controlled trials (RCTs) highlights barriers to successful drug development in SLE, including disease heterogeneity, inadequate trial size or duration, insufficient dose finding before initiation of large trials, handling of background medications, and choice of primary endpoint. Herein we examine lessons learned from landmark SLE RCTs and subsequent advances in trial design, as well as discuss efforts to address limitations in current SLE outcome measures that will improve detection of true therapeutic responses in future RCTs.

Keywords

Systemic lupus erythematosus; outcome measures; clinical trials

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P.E.L.: Consultant to Pfizer, EMD, Serono, GSK, BMS, Medimmune, and UCB.

R.R.G.: Principle investigator or co-site investigator for Genelabs, LaJolla Pharmaceutical Company, Aspreva Pharmaceuticals Corporation, Human Genome Sciences Inc, GSK, and Genentech. Data safety monitoring board member and term chair for BMS. Consultant for GSK and Eli Lilly.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with diverse manifestations, ranging from mild rash or arthritis to severe, organ-threatening involvement of the kidneys or the central nervous system.[1] One challenge in caring for patients with SLE is a paucity of approved medications despite numerous recent efforts to identify efficacious drugs in clinical development programs. Randomized controlled trials (RCTs) evaluating novel biologic and synthetic immune modulators in SLE have been largely unsuccessful at achieving primary endpoints required to gain United States Food and Drug Administration (FDA) approval. Only one new agent, belimumab, has been approved for treatment of SLE in the last 60 years.

Despite these difficulties, methodological and clinically important findings have been detected in sub- and post-hoc analyses from these “failed” RCTs. These analyses have highlighted the limitations in SLE trial design that should be addressed, including heterogeneity of disease, inadequate trial size or duration, insufficient dose finding prior to entering pivotal RCTs, choice of primary endpoints, and non-standardized use of background therapy.

Pharma-sponsored RCTs in SLE are a rather recent development, with the first large trials being initiated in 2000. It quickly became clear that there was no consensus on the best way to conduct these trials, resulting in a rapid evolution in thinking concerning the best practices in SLE RCTs. One important component of this changing landscape was the guidance issued by regulatory agencies, which differed between FDA and European Medicines Agency (EMA). For example, FDA issued a guidance for product development in generalized SLE in 2005 and currently has no issued guidance for SLE nephritis.[2] Reflecting the SLE community’s thinking, the 2005 FDA guidance document embraced the use of composite endpoints, even though they had never been successfully applied in SLE RCTs, did not include patient-reported outcomes, and were not amenable to use in clinical practice, even in academic centers. EMA, on the other hand, issued a detailed and comprehensive draft guideline in 2013, which was subsequently abbreviated in final form in 2015. The expectation that a “complete response” can be achieved in SLE nephritis is a laudable goal articulated by the EMA,[3] but may not be a reasonable or achievable threshold for drug approval. Therapies that provide a statistically significant, measurable benefit (such as partial clinical responsiveness defined a priori) is a threshold clearly applied in other autoimmune diseases and could be reconsidered as a more appropriate outcome by regulators in both the United States and Europe.

Although both regulatory bodies have tried to interact with the trialist community to develop coherent and clinically meaningful outcome measures, presently available ones were devised mostly from observational data sets, not prospective RCTs, and some are very difficult to interpret or even to score. Thus, the complexity of the currently employed responder indices, often involving the use of external adjudication committees to further interpret reported responses from individual principal investigators, significantly complicates trial conduct and cost. The utility, clinical relevance, and practicality of currently employed outcome

measures, as well as their ability to detect clinically meaningful change, have emerged as issues from recent SLE RCTs.[4]

The nature of recent lupus clinical development programs has also contributed to their lack of success. The purpose of RCTs in clinical development is to estimate the overall safety and efficacy of a product. This requires multiple experiments in determining dose/dose regimen, which are often not explored extensively because of both time and economic constraints—decisions by sponsors are typically made in attempts to shorten time to approval. It is common practice to telescope the time spent in phase II, which normally would permit a better understanding of the effect of the therapy at specific doses/dose regimens. Rather than invest in extensive and informative phase II RCTs, often there is rapid progression to phase III or pivotal trials for regulatory approval, and typically phase III RCTs have been conducted in parallel and not sequentially. Thus, the lessons learned from one RCT cannot be implemented in the second trial. Several examples below will describe the negative impact of implementing identical parallel phase III pivotal RCTs when a full understanding of the inclusion/exclusion criteria, dose, dose regimen/duration, effect of background therapy, allowance of rescue therapy, measures of responsiveness, and definitions of treatment failure are not entirely understood.

There are many issues that evolve from the heterogeneity of the patient population. For example, the 2005 FDA guidance document established a pathway for approval of therapies for generalized SLE. This resulted in numerous RCTs in which most patients were recruited with skin or musculoskeletal manifestations. Although these symptoms and signs are of concern to affected patients, such RCTs do not specifically enroll patients with other organ involvement, including renal, central nervous system, and cardiopulmonary. Therefore, little is learned about the impact of a therapy on more serious organ manifestations. Other problems include variable use of background therapies some of which, although not approved for use in SLE, may have significant efficacy. Rescue therapies used for flares of the underlying disease during RCTs can then interfere with measuring the true effect of the study drug. Finally, there is lack of consensus on the role of glucocorticoid use in SLE treatment. The most appropriate way to taper doses and the optimal target dose are not well defined, resulting in a variety of approaches to deal with these potent medications in RCTs. A clear definition of a clinically meaningful decrease in glucocorticoid dose as an outcome measure is also not established, although it often has been recommended to be attainment of a low dose, eg ≤7.5 mg daily.

The Outcome Measures in Rheumatology (OMERACT) international consensus effort, FDA, and EMA have provided guidance for domains to be measured in SLE clinical development that include change in disease activity, change in rate of cumulative organ damage, health-related quality of life (HRQOL), and adverse events.[2] Determining treatment effect is currently limited by the use of inadequate available instruments, such as disease activity measures that were developed in longitudinal observational cohorts for clinical epidemiology research, not RCTs testing therapeutic interventions, and composite responder indices that do not reflect standard clinical practice and lack measurement of patient-reported outcomes (PROs). OMERACT and the Lupus Industrial Council of the Lupus Research Institute (LRI) have now begun to develop comprehensive instruments for use in

RCTs that will be sensitive to change in both global and organ-specific disease activity, inclusive of PROs, and relevant to clinical practice.

Herein we review the successes and failures of SLE RCTs (Tables 1 and 2), and examine in detail a subset of these trials to illustrate challenges and learning points. We also discuss OMERACT and LRI efforts to evaluate data from these trials and develop composite endpoints that capture important therapeutic responses (Table 3).

Non-Renal SLE Clinical Trials

Dehydroepiandrosterone (DHEA)

DHEA is a weak androgen with modest immune modulatory effects.[5] Early studies found lower levels of DHEA in SLE patients compared to healthy controls, and low circulating levels correlated with increased SLE disease activity.[6, 7] These observations led to the investigation of DHEA supplementation in the treatment of SLE.

In an open label study, van Vollenhoven and colleagues reported significant improvements in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and physician global assessment (PGA) scores, as well as reduced prednisone doses in 50 female SLE patients taking DHEA 50–200mg/day over 6–12 months.[8] Two subsequent small investigator designed placebo RCTs evaluated DHEA treatment in women with mild-to-moderate (n=28) and severe SLE (n=19).[9, 10] These RCTs demonstrated no significant improvement in SLEDAI score with DHEA treatment compared to placebo, but were limited by small sample size. In the study of women with severe SLE, there was also higher disease activity in the DHEA-treated women compared to placebo despite randomization.

Larger-scale, industry-sponsored RCTs were pursued to establish the effect of prasterone (a DHEA formulation manufactured by Genelabs) on clinical SLE endpoints. A phase II/III RCT enrolled 191 SLE women meeting criteria for glucocorticoid dependence, defined by a failed attempt to taper prednisone in the preceding 12 months or stable prednisone dose for at least 3 months preceding enrollment if no taper had been attempted. In retrospect, these two described groups of patients may have differed in terms of disease activity. Patients were randomized to treatment with prasterone 200mg/day, 100mg/day, or placebo followed by a prednisone taper per protocol over a minimum of 7 months.[11] The primary endpoint was a decrease in prednisone dose to ≤7.5mg/day sustained for at least 2 months. Response rates were not significantly different in patients treated with prasterone 100mg/day or 200mg/day compared to placebo (p=0.110). When patients with active SLE (SLEDAI >2) were considered separately in a pre-specified analysis, the primary endpoint was met for patients taking prasterone 200mg/day compared to placebo (p=0.031). Patients with inactive SLE (SLEDAI ≤2) had a higher likelihood of achieving the primary endpoint even with placebo administration. The protocols of two multi-center, phase III RCTs were subsequently amended to incorporate SLEDAI >2 into the inclusion criteria.[12, 13] Petri and colleagues randomized 381 SLE women to prasterone 200mg/day or placebo and evaluated a composite primary endpoint consisting of improvements in disease activity and fatigue/HRQOL with the absence of new organ damage.[13] The number of responders was not significantly different between treatment arms at 52 weeks when the full sample was considered.

However, in a pre-specified analysis of data from the 293 patients with baseline SLEDAI >2, the primary endpoint was met with 58.5% of the prasterone group responding to treatment compared to 44.5% of the placebo group (p=0.017); as noted, however, this change in inclusion/exclusion criteria occurred after initiation of the trial.

Taken together, these RCTs suggest that DHEA may mildly reduce SLE disease activity and have a steroid-sparing effect among women with mild-to-moderately active SLE. However, the change in protocol during the phase III RCTs was a barrier to understanding the impact of DHEA treatment –therefore FDA approval was not granted and further clinical development ultimately discontinued. These studies underscore the importance of appropriate patient selection and adherence to inclusion/exclusion criteria for SLE RCTs by excluding subjects with a high likelihood of response even without the therapeutic intervention. They also emphasize the need for better outcome measures, as the responder index employed in the phase III RCT was constructed by the sponsor with FDA input, but without being evidence based.

Rituximab

Rituximab is a monoclonal antibody (mAb) directed against CD20 that results in B-cell depletion. A number of uncontrolled studies and case series demonstrated improvements in SLE disease activity and steroid-sparing effects with rituximab treatment,[14] leading to more rigorous evaluation of it for treatment of SLE. It should be emphasized, however, that no pre-clinical work, no dose ranging studies, and no preliminary phase II studies were performed in SLE prior to launch of large and pivotal RCTs.

EXPLORER was a multicenter placebo RCT designed to evaluate the efficacy and safety of rituximab in patients with moderate-to-severe non-renal SLE.[15] The study randomized 257 patients with baseline active SLE (defined as ≥1 new BILAG A scores or ≥2 BILAG B scores) to rituximab or placebo. An oral prednisone burst was initiated at study entry with a protocol-required prolonged taper to a goal of ≤5mg/day by week 52. Background immunosuppressants (azathioprine, methotrexate, or mycophenolate mofetil [MMF]) were continued for the duration of the study. The primary endpoint was the proportion of rituximab versus placebo-treated patients achieving a “complete clinical response”, “partial clinical response”, or no response at week 52. Definitions of complete and partial response were based on BILAG improvement by week 24, duration of response, and absence of a BILAG-defined flare. The primary endpoint was not met, with similar rates of complete and partial responses in rituximab and placebo arms at 52 weeks. Differences in time to first moderate or severe flare and change in HRQOL were also not significant. Laboratory evidence of B-cell depletion was confirmed in 89.5% of rituximab-treated patients, as were significant decreases in anti-double stranded DNA antibodies (anti-dsDNA) and increases in complement C3 and C4 levels compared to placebo.

This trial enrolled SLE patients with high disease activity despite standard of care treatment, and therefore succeeded in identifying a patient population with a possibility of responding to the intervention. However, patients in both treatment arms had significant improvement in disease activity in the first month, suggesting that the initial glucocorticoid exposure induced similar disease control in both treatment arms that persisted over the duration of the study,

even following the prolonged taper. A robust placebo response as the result of improved access to standard of care medications in RCTs has been noted to further complicate detection of early and clinically important improvement from an investigational agent.

Additionally, the definition of treatment failure incorporated into the EXPLORER primary endpoint in the second 6 months of the study was not the same as a severe flare, defined as occurrence of one new BILAG B score, representing new moderate disease activity. Variation in the handling of background therapy, requirement of a prolonged prednisone taper, and too strict a primary endpoint may have contributed to the failure to detect a clinical response to rituximab despite evidence of biologic activity. It is also quite possible that rituximab at doses administered in the RCTs with permitted background medications is not effective, or not to a sufficient degree to be detected in a trial the size of EXPLORER.

Abatacept

Abatacept is a CTLA-4 fusion protein that binds to CD80/86 on the surface of antigen presenting cells and blocks signaling through CD-28 required for T-cell activation. By inhibiting full activation of T-cells, treatment with abatacept may mitigate differentiation of autoreactive B-cells in SLE.[16] Abatacept for treatment of non-renal SLE has been evaluated in one phase IIb RCT.[17] The study enrolled 175 patients with active musculoskeletal, cutaneous, or cardiovascular/respiratory SLE, defined by ≥1 new BILAG A or ≥2 BILAG B scores. Background therapy with non-steroidal anti-inflammatory drugs (NSAIDs), azathioprine, MMF, antimalarials, or methotrexate was continued. Up to 30mg of prednisone was administered as initial flare treatment, then tapered slowly per protocol to a goal of 5mg/day. Patients were randomized 2:1 to receive either abatacept or placebo every 2 weeks for three doses, then every 4 weeks. The primary endpoint was development of new SLE flare, defined as new BILAG A or B score in any organ system, after the initiation of steroid taper through 52 weeks. The primary endpoint was not met, with similar rates of new flare in abatacept (79.7%) and placebo (82.5%) groups (95% CI −15.3, 8.3). However, in post-hoc analyses, significantly fewer abatacept-treated patients had BILAG A flares compared to placebo, most pronounced in patients primarily with polyarthritis. Significant improvements in HRQOL (Medical Outcomes Survey Short Form-36), fatigue (Visual Analog Scale), and sleep quality (Medical Outcomes Survey Sleep Problems Index) at 52 weeks (pre-specified analyses) were reported with abatacept. This phase IIb RCT was designed to study a more homogeneous SLE population by specifying organ system involvement in the inclusion criteria. A PRO assessment, a component of the FDA SLE guidance, was also included. However, similar to EXPLORER, the strict BILAG-based flare definition is sensitive to relatively minor fluctuations in disease activity, making it difficult for primary efficacy endpoint to be achieved.

Atacicept

The fusion protein atacicept contains the ligand-binding portion of the TACI receptor (transmembrance activator and calcium-modulator and cyclophilin ligand [CAML] interactor) and modulates B-cell activation by blocking B-cell activating factor (BAFF; also known as B-lymphocyte stimulator [BLyS]) and a proliferation-inducing ligand (APRIL). Efficacy of atacicept for the treatment of SLE was evaluated in two phase II/III placebo

RCTs. The APRIL-LN trial was designed to compare renal response to atacicept versus placebo plus standard of care (newly initiated MMF and glucocorticoids) in patients with SLE nephritis.[18] The trial was discontinued after enrolling only 6 patients because of hypogammaglobulinemia and serious infections, likely related to the newly initiated MMF interacting with the study drug. Meanwhile, APRIL-SLE randomized 455 patients with moderate-to-severe general SLE to atacicept 150mg weekly, 75mg weekly, or placebo; the 150mg arm was ultimately discontinued early for safety concerns.[19] Each patient also received an oral glucocorticoid burst with taper per protocol. The primary endpoint was the proportion of patients who developed an SLE flare, defined as at least one BILAG A or B score, at 52 weeks. There was no difference in flare rates between patients taking atacicept 75mg compared to placebo (background standard of care therapy alone) (58% and 54%, respectively, p=0.543). Time to first flare was also similar between treatment groups. Post-hoc analyses of the suspended atacicept 150mg arm, however, suggested lower flare rates than placebo. Further studies evaluating the efficacy and safety of atacicept for the treatment of general SLE are ongoing (ADDRESS II trial and extension study, clinicaltrials.gov ID NCT01972568 and NCT02070978)

It is notable that the aforementioned RCTs all failed to meet primary efficacy endpoints despite different trial designs and outcome measures. The DHEA and rituximab RCTs enrolled patients with or without active SLE and assessed improved disease activity, whereas the abatacept and atacicept RCTs monitored flare occurrence in patients with stable disease. It remains unclear which approach, if not both, are appropriate for evaluating efficacy of novel therapeutics. Further, these RCTs underscore the need for validated and comprehensive disease assessment tools that are sensitive to induced changes in disease activity. Additionally, the use of prolonged glucocorticoid treatment regimens demonstrates their clear benefit in treatment of SLE patients, even after tapering, that may have obscured any therapeutic benefit of study drug. Finally, variation in the background immunosuppressive medications, as well as a lack of standardization in their use, may have obscured the results.

Belimumab

Belimumab is a mAb that inhibits B-cell survival and persistence of autoreactive B-cells by binding the soluble form of BAFF/BLyS. The phase II RCT randomized 449 patients with non-renal SLE to one of three doses of belimumab (1, 4, or 10mg/kg) or placebo.[20] A history of positive autoantibodies (anti-nuclear antibody [ANA], anti-dsDNA, anti-Smith, anti-RNP, anti-SSA, anti-SSB, or anticardiolipin) was an inclusion criterion, but serologic positivity was not required at time of enrollment. Changes in glucocorticoid and immunosuppressant doses were allowed at investigators' discretion. The co-primary endpoints were 1) change in Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) -SLEDAI score at week 24 and 2) time to first SLE flare (SELENA-SLEDAI Flare Index [SFI]) over 52 weeks. Though the primary endpoints were not met, an exploratory post-hoc subgroup analysis suggested that serologically active patients (71% of the study cohort) had significant improvement in SELENA-SLEDAI score, physician global assessment (PGA), and HRQOL with belimumab compared to placebo. Additionally, the

unrestricted use of background medications may have inflated response in the placebo treatment arm.

The phase II belimumab RCT also highlighted the limitations of applying available disease activity indices as solitary endpoints in clinical trials. As previously mentioned, SLEDAI and BILAG were developed for use in observational cohort studies, and each index has recognized strengths and weaknesses.[21, 22] The SLEDAI and its modifications (2000 update [SLEDAI-2K][23] and SELENA-SLEDAI[24]) measure changes in global disease activity, but are not sensitive to worsening or improvement in individual organ systems. BILAG, which is based on physicians' intention to treat, discriminates SLE disease activity at the organ level but at the expense of greater complexity. Additionally, the FDA draft guidance includes provisions that observed improvements in a disease activity score should correspond with clinical benefit and occur without worsening of other disease manifestations.[2] The novel SLE Responder Index (SRI) was therefore developed, based on the phase II belimumab data, as a composite endpoint for use in clinical trials and to define clinically meaningful improvement.[25] The SRI incorporates SELENA-SLEDAI score to measure improvement, BILAG score over baseline to evaluate for worsening in organ system manifestations, and PGA to ensure no overall decline in health. SRI-4 response is defined as 1) a ≥4 point decrease in SELENA-SLEDAI score (a cutoff chosen based on the established minimal clinically important difference[26]), 2) no new BILAG A or ≤1 new BILAG B scores, and 3) no deterioration in PGA by ≥0.3 points. In a post-hoc analysis of seropositive patients in the belimumab phase II RCT, SRI-4 response at 52 weeks was significantly higher in the pooled belimumab group compared to the placebo group (46% vs 29%, respectively, p=0.006).[25] SRI-4 response was thus chosen as the primary efficacy endpoint for subsequent belimumab RCTs.

BLISS-52 and BLISS-76 were both multicenter phase III RCTs, run in parallel, evaluating efficacy of belimumab 1mg/kg or 10mg/kg every 4 weeks compared to placebo in patients with non-renal SLE.[27, 28] Taking advantage of lessons learned from the phase II RCT, only seropositive patients (ANA and/or anti-dsDNA positive during screening) were enrolled, and stricter control of background glucocorticoids and immunosuppressants was required. The belimumab 10mg/kg group met the primary efficacy endpoint, SRI-4 response rate at 52 weeks, in both RCTs. SRI-4 response rates with belimumab 10mg/kg and placebo were 58% and 44%, respectively in BLISS-52 (total n=867, p=0.006) and 43.2% and 33.5%, respectively, in BLISS-76 (total n=819; p=0.017). It is notable, however, that the efficacy of belimumab was lost at 76 weeks in BLISS-76. Key secondary endpoints were also met. In BLISS-52, the belimumab 10mg/kg group had fewer severe flares, measured with SFI and BILAG, while fewer severe flares over 76 weeks were seen with belimumab 1mg/kg in BLISS-76. Clinically meaningful improvements in HRQOL and fatigue were also evident in a pooled analysis of both RCTs.[29]

Based on this evidence, belimumab was approved by FDA and EMA in 2011 for the treatment of seropositive patients with active SLE despite standard of care treatment. Unfortunately, these RCTs included relatively few African American patients, and those that were included did not appear to benefit when clinical response was assessed. A post-approval study was required to recruit larger numbers of such patients to define the expected

response, which is ongoing (clinicaltrials.gov ID NCT01632241). Additionally, other regulatory agencies in the United Kingdom have not approved belimumab because of concerns of modest efficacy in the setting of high cost. A post-hoc analysis has since suggested benefit to patients with SLE nephritis, and RCTs evaluating efficacy in patients with active SLE nephritis are ongoing (clinicaltrials.gov ID NCT01639339, NCT02260934). A subcutaneous belimumab formulation also demonstrated efficacy in the BLISS-SC trial despite a large placebo response.[30]

Tabalumab

Another B-cell targeted therapy, tabalumab is an anti-BAFF/BLyS monoclonal antibody that antagonizes both soluble and membrane-bound BAFF/BLyS. Efficacy and safety of tabalumab were evaluated in the ILLUMINATE-1 and ILLUMINATE-2 studies, two 52-week, phase III placebo RCTs of patients with moderate-to-severe SLE.[31, 32] In ILLUMINATE-1, 1164 patients were randomized to receive tabalumab 120mg every 2 weeks, 120mg every 4 weeks, or placebo.[31] Background therapy with antimalarials and immunosuppressants was allowed, but participants with any change in dose, including decrease in dose if the patient improved, were considered treatment non-responders. Unrestricted use of glucocorticoids was allowed until week 24 when it was required that the glucocorticoid dose be equal to or lower than enrollment and only dose decreases were allowed for the remainder of the study period. The primary efficacy endpoint was SRI-5 response at 52 weeks, a modified version of the SRI requiring a 5-point SLEDAI improvement to be considered a responder. The primary endpoint was not met, although there was a trend towards greater response with tabalumab 120mg every 4 weeks compared to placebo (35.2% and 29.3%, respectively, p=0.052). Additionally, when patients who decreased antimalarial or immunosuppressant dose were not considered to be non-responders (a pre-specified sensitivity analysis), there were significantly more SRI-5 responders in the tabalumab 120mg every 4 weeks group compared to the placebo group (37.0% and 29.8%, respectively, p=0.021). Key secondary endpoints, such as time to SLE flare and ability to taper glucocorticoids, were also not met despite pharmacodynamic evidence of tabalumab biological activity (significant decreases in anti-dsDNA, total B-cells, and immunoglobulins). Of interest, pharmacokinetics between the two selected dose regimens were overlapping.

The ILLUMINATE-2 study,[32] which was nearly identical to ILLUMINATE-1, randomized 1124 patients to the same tabalumab or placebo treatment arms, handled background medications similarly, and used the same primary endpoint (achievement of SRI-5 at 52 weeks) as ILLUMINATE-1. However, patients who lowered antimalarial or immunosuppressant dose were not considered per-protocol non-responders in ILLUMINATE-2. The primary endpoint was met in the tabalumab 120mg every 2 weeks group, with 38.4% responders compared to only 27.7% in the placebo group (p=0.002); there was a trend towards higher response in the tabalumab 120mg every 4 weeks group (34.8% vs 27.7%, respectively, p=0.051). Similar to ILLUMINATE-1, tabalumab-treated patients had significant improvement in laboratory parameters compared to placebo, but no key secondary endpoints were met.

Despite evidence of efficacy in ILLUMINATE-2 and a trend towards efficacy in ILLUMINATE-1, tabalumab development was suspended given the small effect size and inability to meet other important clinical endpoints. Of note, when the belimumab SRI-4 endpoint was applied to the data, the primary endpoint was met in both ILLUMINATE-1 (for both tabalumab doses) and ILLUMINATE-2 (for the every 2 week dose). The ILLUMINATE studies succeeded in attaining a large sample size and long study duration. However, achievement of the primary endpoint is strongly influenced by the definition of response to study drug—both in the choice to use the modified SRI-5 and to designate patients with any change in antimalarial or immunosuppressant as a non-responder. Furthermore, little phase II work preceded the slightly staggered implementation of these two large phase III pivotal RCTs, which demonstrated similar pharmacokinetic and pharmacodynamic effects with both dose regimens.

Epratuzumab

Epratuzumab, another mAb, modulates B-cell activity by binding to CD22 on the surface of mature B-cells. The phase IIb placebo RCTs, ALLEVIATE 1 and 2, were designed to assess the efficacy of epratuzumab with a BILAG-based primary endpoint in patients with moderate-to-severe SLE.[33] The trials were ultimately suspended early because of limited supply of study drug, but analysis of available data showed a trend towards clinical efficacy. The primary endpoint, which was assessed in a pooled analysis (n=90) and at 12 instead of the planned 24 weeks, was met by more patients treated with epratuzumab than placebo. Epratuzumab treatment also led to improvements in HRQOL and mean glucocorticoid dose.[34]

A second epratuzumab phase IIb dose-ranging RCT, EMBLEM, was the first to use the BILAG-Based Composite Lupus Assessment (BICLA) as the primary efficacy endpoint.[35] BICLA, another composite responder index, requires improvement in baseline disease activity, no disease worsening (global or organ-specific), and no treatment failure to be considered a responder.[36] Specific criteria for BICLA response include 1) all BILAG A scores at study entry improved to B/C/D and all BILAG B scores improved to C/D, 2) no new BILAG A or ≤2 BILAG B scores, no worsening of SLEDAI score from baseline to endpoint, and no worsening in PGA (<10% worsening), and 3) no addition of non-protocol SLE treatment, such as new or increased immunosuppressants or antimalarials.

In EMBLEM, 227 patients with moderate-to-severe SLE were randomized to one of five epratuzumab doses or placebo.[35] Background glucocorticoids were tapered per investigator discretion after week 4, while immunosuppressant and antimalarial doses were held constant. BICLA response at 12 weeks, the primary endpoint, was greater with all doses of epratuzumab than placebo, but the effect was not statistically significant. Improved HRQOL and decreased glucocorticoid use were also seen with epratuzumab treatment in EMBLEM and the open-label extension study.[34] However, the subsequent multicenter phase III RCTs, EMBODY 1 (n= 786) and EMBODY 2 (n= 791), employed every 3 month dosing cycles, which had never been tested, and showed no significant benefit.[37] Patients with moderate-to-severe SLE were randomized to receive epratuzumab 600mg every week, 1200mg every other week, or placebo; study drug was administered for a 4-week period in 12-week cycles.

The primary efficacy endpoint, BICLA response at 48 weeks, was not met. Moreover, no significant differences were seen in secondary endpoints such as total SLEDAI-2K score, PGA, or mean glucocorticoid dose. The EMBODY studies included a robust study design and large sample size, and the negative results of these phase III RCTs indicate that epratuzumab was truly not effective for the treatment of SLE. It is also possible that, as observed in other RCTs, early rescue of non-responders with increased doses of glucocorticoids confounded the data.

PF-04236921

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that is elevated in SLE patients. The efficacy of PF-04236921, a mAb that binds soluble IL-6, was evaluated in a phase II RCT of 183 patients with active SLE.[38] Patients were randomized to receive either subcutaneous PF-04236921 10mg, 50mg, or 200mg or placebo every 8 weeks; the 200mg dose arm was discontinued early because of 3 deaths. The primary efficacy endpoint was SRI-4 response at 24 weeks, with BICLA as a secondary endpoint. The primary endpoint was not met, but there was a trend towards higher SRI-4 response rate in the 10mg group compared to placebo (59.9% vs 40.1%, respectively, p=0.076). Among secondary endpoints, BICLA response was significantly higher in the 10mg group compared to placebo (p=0.026). In a pooled analysis, patients receiving PF-04236921 also had significantly fewer severe SLE flares (defined by SFI) than placebo (p=0.004) (10mg: 0; 50mg: 2; placebo: 10). The discrepancy in responder rates – a significant response to PF-04236921 when assessed with BICLA but not SRI-4 – further underscores that clinical trial success could hinge on choice of primary endpoint, even when composite indices are used.

Anifrolumab

Anifrolumab, a type I interferon (IFN) receptor antagonist, inhibits type I interferon signaling that has been implicated in the pathogenesis of SLE. In a phase II placebo RCT, 305 patients with moderate-to-severe active SLE were randomized to either anifrolumab 300mg, 1000mg, or placebo every 4 weeks for 48 weeks.[39] Patients were stratified by a number of variables, including high versus low IFN gene signature defined by the company. The primary efficacy endpoint, SRI-4 response at 24 weeks, was met by more anifrolumab 300mg treated patients than placebo (34.3% vs 17.6%, respectively, p=0.014), but not by patients receiving 1000mg. Importantly, significant clinical benefit was only observed in subjects with an increased interferon gene expression signature. Additionally, two key secondary endpoints were met by the anifrolumab-treated high interferon group: 1) composite endpoint of SRI-4 response at 52 weeks with sustained reduction in prednisone dosage between 40 and 52 weeks, and 2) reduction of prednisone to ≤7.5mg/day at week 52 among patients who were taking ≥10mg at enrollment (300mg dose only). Decrease in IFN-regulated gene expression was documented with both doses of anifrolumab, confirming biologic activity. In sum, the primary and key secondary endpoints were all met in this phase II trial, and an extension study and two phase III RCTs to further evaluate the efficacy and safety of anifrolumab for the treatment of SLE are underway (clinicaltrials.gov ID NCT02446899 and NCT02446912). Despite noting benefit only in the interferon high group, these trials will enroll both interferon high and interferon low subjects.

Renal SLE Clinical Trials

Mycophenolate mofetil (MMF)

Interest in large-scale evaluation of the role of MMF in the treatment of SLE nephritis stemmed from small trials and meta-analyses indicating that MMF was as or more effective than standard of care IV cyclophosphamide with fewer adverse effects.[40, 41] The ALMS trial was an international, open-label randomized trial designed to determine whether MMF was non-inferior to IV cyclophosphamide for induction treatment of SLE nephritis.[42] Three hundred and seventy patients with active, biopsy-proven International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III, IV, or V SLE nephritis were randomized to treatment with either MMF or cyclophosphamide. MMF was titrated to a target of 1.5g twice daily by week 3, and 0.5–1.0g/m^2 IV cyclophosphamide was administered once a month. Patients in both treatment arms were administered oral prednisone 60mg/day with a per protocol taper; IV glucocorticoids were not allowed within 2 weeks of randomization or throughout the study. The primary endpoint was the proportion of patients with renal response at 24 weeks, defined as 1) decrease in urine protein/creatinine ratio (UPC) to <3 in patients with baseline UPC ≥3 or by ≥50% and 2) stabilization (±25%) or improvement in serum creatinine. The primary endpoint was met by a similar proportion of patients in the MMF (56.2%) and cyclophosphamide (53.0%) treatment arms (p=0.58). Thus, the study established that MMF was not different than cyclophosphamide for induction treatment of SLE nephritis. An important difference in response to treatment among racial groups was also noted. Patients who self-identified as black or mixed race had a greater response to MMF than cyclophosphamide (60.4% vs 38.5%, respectively, p=0.033). A post-hoc analysis also showed a greater MMF treatment response in Hispanic patients (60.9% response with MMF vs 38.8% with cyclophosphamide, p=0.011).[43] Renal response at 24 weeks was similar among white and Asian patients in both treatment arms. There was no significant difference in secondary endpoints, such as change in SELENA-SLEDAI score or serologic activity, with either treatment. Patients who met renal response criteria at 24 weeks were subsequently re-randomized to either MMF or azathioprine as maintenance therapy.[44] Using time to treatment failure as a primary endpoint, this second phase of ALMS established that MMF was superior to azathioprine in maintaining renal response and preventing relapse.

ALMS suggested that MMF is similar to the effects of IV cyclophosphamide for induction treatment of SLE nephritis, but it was not possible for FDA to conclude that MMF was non-inferior to cyclophosphamide. Although cyclophosphamide is widely used for the treatment of SLE nephritis, the drug is not approved for this indication and no clinical trials have been conducted to document the effect size. As an unapproved comparator, the non-inferiority margin for MMF could not be determined, and the trial could not serve as grounds for approval. Nonetheless, MMF is increasingly used for the treatment of SLE nephritis.

Rituximab

LUNAR was a phase III double-blind, placebo-controlled, RCT that evaluated the efficacy and safety of rituximab in 144 patients with active proliferative SLE nephritis.[45] Inclusion criteria were ANA positive patients, ISN/RPS class III or IV nephritis on renal biopsy within

the last 12 months, and proteinuria (UPC >1.0); active urinary sediment was required if renal biopsy was >3 months before enrollment. Nearly half of participants were enrolled with their first SLE nephritis flare. All patients were treated with background standard of care treatment that included IV methylprednisolone at study enrollment then prolonged protocol mandated taper of prednisone, as well as MMF titration to 3g/day, as tolerated. No other immunosuppressant agents were allowed. The primary endpoint was complete renal response, partial renal response, or no response at 52 weeks. Complete renal response was defined as 1) normal serum creatinine if abnormal at baseline or ≤115% of baseline if normal at baseline, 2) inactive urinary sediment (<5 RBCs/hpf and no RBC casts), and 3) UPC <0.5. Partial renal response was defined as 1) serum creatinine ≤115% of baseline, 2) RBCs/hpf ≤50% above baseline and no RBC casts, and 3) at least 50% decrease in UPC to <1 (if baseline UPC was ≤3) or to <3 (if baseline UPC was >3). Patients were considered non-responders if they did not meet criteria for complete or partial response or required rescue therapy with an additional immunosuppressant. Previously noted concerns were the heterogeneity of the patient population in terms of renal disease activity, as well as use of effective background therapy including MMF and glucocorticoids.

The primary endpoint of the study was not met. Rates of renal response in rituximab and placebo-treated arms, respectively, were 26.5% and 30.6% for complete response, 30.6% and 15.3% for partial response, and 43.1% and 54.2% for no response (p=0.55). Although there were more partial renal responders and fewer non-responders in the rituximab arm, the study was small, and not powered to assess these endpoints. A number of pre-specified secondary clinical endpoints, such as time to complete renal response and change in HRQOL, were also not significant at 52 weeks. Important exploratory analyses suggested that rituximab-treated patients had improvement in proteinuria and higher rates of complete or partial renal response compared to placebo at week 78 but not at week 52.

There are several flaws to the LUNAR study design that may have resulted in an apparent lack of efficacy with rituximab treatment. First, whereas rituximab was reported to be effective in treatment of refractory SLE nephritis in uncontrolled studies, half of LUNAR participants were treated during their first renal flare – it is possible that rituximab is more effective for refractory nephritis. Additionally, significant improvements in proteinuria were not observed until 78 weeks, indicating that the trial duration may have been too short to see an effect. The relatively small sample size precluded a statistical assessment of differences in partial renal response rates between treatment arms. Finally, despite these shortcomings in the LUNAR trial design, it is also possible that rituximab is simply not effective for the treatment of SLE nephritis. RITUXILUP, a phase III RCT evaluating rituximab plus MMF without oral glucocorticoids for the treatment of lupus nephritis, is ongoing (clinicaltrials.gov ID NCT01773616; EudraCT ID 2012-004893-25).

Abatacept

To date, two RCTs have evaluated the efficacy of abatacept as add-on therapy for the treatment of proliferative SLE nephritis. Furie and colleagues reported the results of a 52-week phase II/III placebo RCT in 298 patients with active, biopsy-proven ISN/RPS class III or IV SLE nephritis treated with abatacept or placebo in addition to background MMF and

glucocorticoids.[46] Abatacept treatment included two arms with patients receiving either 30mg/kg loading doses then 10mg/kg monthly (30/10 group), or 10mg/kg loading doses then 10mg/kg monthly (10/10 group). MMF was titrated to a target dose determined based on race/ethnicity, and administration of glucocorticoids (clearly proven to be a successful treatment but limited by associated chronic adverse events) was allowed at investigator discretion. The primary endpoint was time to confirmed complete renal response, defined as 1) estimated glomerular filtration rate (eGFR) ≥90% of screening level if normal at baseline or eGFR ≥90% 6 month pre-flare value if abnormal at screening, 2) UPC <0.26, and 3) inactive urinary sediment (RBCs and WBCs per hpf within normal limits and no RBC or WBC casts). Criteria had to be met 4 weeks later to be considered a confirmed complete response. The primary endpoint was not met, with similar time to confirmed complete renal response across all treatment arms. Further, few patients achieved the primary endpoint at any time during the study: 22.2% of abatacept 30/10 group, 27.3% of abatacept 10/10 group, and 20.0% of placebo group. It is also notable that mean UPC was lower in placebo than abatacept arms despite randomization. The definition of confirmed complete renal response has been criticized as being too strict. A post-hoc analysis suggested that the primary endpoint may have been met if the LUNAR definition of complete renal response had been applied.[47] Additionally, the unrestricted use of background glucocorticoids could have mitigated differences in partial renal response between abatacept and placebo treatment. A second phase III trial of abatacept with MMF and glucocorticoids for the treatment proliferative SLE nephritis is ongoing (clinicaltrials.gov ID: NCT01714817).

ACCESS, a 52-week, double-blind, placebo-controlled, RCT evaluated the efficacy of abatacept for SLE nephritis treatment in the setting of induction with background cyclophosphamide and glucocorticoids and maintenance with azathioprine.[48] All 134 patients were initially treated with IV cyclophosphamide per the Euro-Lupus Nephritis trial protocol[49] and prednisone 60mg/day. The use of pulse-dose IV glucocorticoids was per investigator discretion. Sixty-six patients randomized to the abatacept arm began treatment with monthly abatacept (weight-based dosing) concurrent with IV cyclophosphamide and glucocorticoid therapy. A predefined prolonged prednisone taper was started after 2 weeks. Azathioprine was initiated following six doses of IV cyclophosphamide. The primary endpoint was the proportion of patients achieving a complete renal response at 24 weeks. Complete renal response was defined as 1) UPC of <0.5, 2) serum creatinine level ≤1.2 mg/dl or ≤125% of baseline, and 3) adherence to the prednisone taper to 10mg/day by 12 weeks. The primary endpoint was not met, and the proportion of patients achieving complete renal response was 33% and 31% in abatacept and placebo-treated patients, respectively. A number of pre-specified secondary endpoints were also not met at week 24, including difference in BILAG score, number of renal and non-renal SLE flares, and PROs. All endpoints were also evaluated at 52 weeks as exploratory analyses, and no significant differences were detected between treatment arms. The definition of complete renal response in the ACCESS trial was less strict and more attainable than in the study by Furie and colleagues. The recommended glucocorticoid taper, albeit quite prolonged, was also a strength of the study protocol by minimizing a placebo response from standard of care medications. However, the trial suffered from relatively small sample size and also a short duration to primary endpoint assessment.

Tacrolimus

The calcineurin inhibitor tacrolimus, frequently employed following solid organ transplant to prevent rejection, has been evaluated for a role in treatment of SLE nephritis. Several uncontrolled studies and small RCTs of SLE patients showed successful treatment of membranous or refractory nephritis with tacrolimus.[50–52]

A large-scale, open randomized trial was designed to compare the efficacy of tacrolimus to MMF for treatment of active SLE nephritis.[53] The study enrolled 150 Chinese SLE patients with biopsy-proven ISN/RPS class III, IV, or V nephritis within 4 weeks of study entry. Patients were randomized to receive MMF 2–3g/day for 6 months or tacrolimus 0.06–0.1mg/kg/day for 6 months, titrated depending on dose response at 3 months and patient tolerance. All patients were treated with a weight-based dose of prednisone for 6 weeks then forced taper per protocol to <10mg/day. The primary outcome was proportion of patients achieving complete renal response at 6 months. Complete renal response was defined as 1) stabilization (within 25%) or improvement in serum creatinine with UPC <1, 2) inactive urinary sediment, and 3) persistent improvement in C3 and anti-dsDNA levels. For patients with a complete or good partial response to either tacrolimus or MMF at 6 months, therapy was changed to azathioprine maintenance, while non-responders were treated with salvage cyclophosphamide and glucocorticoids. Participants were monitored for a follow-up period of 5 years. There was no difference in the proportion of patients meeting the primary endpoint at 6 months, with complete renal response in 62% and 59% of the tacrolimus and MMF groups, respectively (p=0.71). Tacrolimus efficacy was similar to MMF even when the stricter American College of Rheumatology definition of complete renal response (creatinine clearance ≥90ml/min, UPC <0.2, and inactive urinary sediment) was applied, although few patients in each arm achieved this endpoint (14% and 11% in tacrolimus and MMF groups, respectively, p=0.59). The need for salvage cyclophosphamide treatment was also similar between groups. In long-term follow-up, there was a non-significant suggestion of a higher incidence of nephritis flares in patients receiving tacrolimus compared to MMF induction therapy (p=0.13 for trend). Strengths of this trial design included long duration of follow-up and tight control of background medications, including a forced glucocorticoid taper.

OMERACT/LRI Project overview

As has been demonstrated in the previous discussion, outcome measures for SLE are complex, not uniform, poorly responsive to trial interventions, and are not relevant to the practicing clinician. The presently used instruments were not developed originally for use as outcomes in RCTs, and composite responder indices are also only intermittently successful. One way to develop more effective and appropriate outcome measures is to analyze the available clinical trial data base, deconstruct the data captured in the current measures, and reconstruct them in a manner that more effectively separates responders from non-responders.

The approach will involve an analysis of data from the available RCTs, beginning with the BLISS trial data sets that led to the approval of belimumab. The data collected in these RCTs will be dissected to determine whether novel combinations can be employed as new outcome measures to be assessed in future clinical trials. The statistical analysis will be

informed by an iterative process with a committee of experienced clinicians, trialists, and statisticians.

Several voluntary organizations including the LRI and the Alliance for Lupus Research, collaborating with the LRI-Lupus Industry Council and the international consensus effort, OMERACT, have developed a working committee along with statistical support to collect the data bases from SLE RCTs. The working committee will deconstruct and analyze the available data to develop better composite outcome measures that will demonstrate responsiveness in clinical trials. Following processes outlined by OMERACT over the years to define such outcomes measures, table 3 demonstrates the steps to evaluate the data sets.

Conclusion

Many therapeutics have failed to reach efficacy endpoints in SLE clinical trials, but lessons learned from these unsuccessful trials have led to advances in trial design. Building on weaknesses identified in the phase II belimumab RCTs, for example, the BLISS studies enrolled only seropositive SLE patients and employed the novel composite SRI efficacy endpoint. However, even composite responder indices have limited success as primary efficacy endpoints. Ongoing efforts to develop composite endpoints for SLE clinical trials may lead to advances in capturing clinically meaningful therapeutic responses.

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Table 1

Summary of clinical trials in non-renal systemic lupus erythematosus (SLE)

Drug	Target	Mechanism	Study and Design	Key Findings
DHEA	Unknown	Sex hormone precursor	Chang *et al.*[12] • RCT • Females with mild-to-moderate SLE • 1° endpoint: SLAM score at 24 weeks	• 1° endpoint not met • Patient global assessment scores improved and fewer SLE flares in DHEA group compared to placebo
			Petri *et al.*[11] • Phase II/III RCT • Females with GC-dependent SLE • 1° endpoint: Sustained decrease in prednisone (≤7.5mg/day) for 2 consecutive months	• 1° endpoint not met • Patients with active SLE (SLEDAI >2) had significant decrease in GC dose with 200mg/day of DHEA compared to placebo
			Petri *et al.*[13] • Phase III RCT • Females with active SLE[&] • 1° endpoint: Clinical response[§] at 52 weeks	• 1° endpoint not met • More responders among patients with SLEDAI >2 treated with DHEA than placebo • Development program suspended, but DHEA studies guided choice of study population for subsequent trials
Rituximab	CD20	Deplete CD20+ B-cells	Merrill *et al.*[15] (EXPLORER) • Phase II/III RCT • Moderate-to-severe SLE • 1° endpoints: a) Major[*] or b) partial[^] clinical response at 52 weeks	• 1° endpoints not met • Pre-specified subgroup analysis found better response in blacks and Hispanic group treated with rituximab vs placebo • Strict definitions for major and partial clinical response • Amount of background therapy mitigated differences between treatment arms

Drug	Target	Mechanism	Study and Design	Key Findings
Abatacept	CD80/86	Inhibit T-cell co-stimulation	Merrill *et al.*[17] • Phase IIb RCT in mild-to-moderate SLE • 1° endpoint: ≥1 BILAG A or B flare during 52 weeks	• 1° endpoint not met; similar flare rates with abatacept and placebo • Improvements in PROs (health-related quality of life, fatigue, and sleep) with abatacept
Atacicept	BAFF/BLyS and APRIL	Neutralize BAFF/BLyS (TNFSF13B) and APRIL (TNFSF13A)	Isenberg *et al.*[19] (APRIL-SLE) • Phase II RCT • Moderate-to-severe SLE • 1° endpoint: ≥1 BILAG A or B flare during 52 weeks	• 1° endpoint not met • Atacicept 75mg and placebo had similar flare rate • Atacicept 150mg arm halted for adverse events, but signal of fewer flares relative to placebo
Belimumab	BAFF/BLyS	Neutralize BAFF/BLyS (TNFSF13B)	Wallace *et al.*[20] • Phase II RCT • Active SLE • 1° endpoints: a) Change in SELENA-SLEDAI score from baseline to 24 weeks and b) time to first flare (SFI) in 52 weeks	• 1° endpoints not met; guided choice of patient selection and endpoints for phase III RCTs • Serologically active patients (ANA or anti-dsDNA antibody positive) had significant improvement in SELENA-SLEDAI and 2° endpoints at week 52 • Led to development of SRI composite endpoint • Unlimited changes in immunosuppressants and GC confounded results
			Navarra *et al.*[27] and Furie *et al.*[28] (BLISS-52 and BLISS-76) • Phase III RCTs • Moderate-to-severe seropositive SLE • 1° endpoint: SRI-4 response at 52 weeks	• 1° endpoint met; greater SRI-4 response with belimumab vs placebo in both studies • First use of SRI composite endpoint • Stricter control of GC and immunosuppressants near end of study

Drug	Target	Mechanism	Study and Design	Key Findings
				• Pre-specified analyses showed improvements in HRQOL, fatigue[29] • Pooled post-hoc analysis suggested benefit in renal disease[54]
Tabalumab	BAFF/BLyS	Neutralize BAFF/BLyS (TNFSF13B)	Isenberg *et al.*[31] and Merrill *et al.*[32] (ILLUMINATE 1 and 2) • Phase III RCTs • Moderate-to-severe SLE • 1° endpoint: SRI-5 response at 52 weeks	• ILLUMINATE 1 did not meet 1° endpoint • ILLUMINATE 2 met 1° endpoint; greater SRI-5 response with tabalumab vs placebo • Neither study met key secondary endpoints (fatigue, time to flare, GC dose) • Patients with any change in immunosuppression dose, including decrease, were considered non-responders • Development suspended
Epratuzumab	CD22	Alter B-cell responsiveness	Wallace *et al.*[33] (ALLEVIATE 1 and 2; SL0006 open label extension) • Phase II RCTs • Moderate-to-severe SLE • 1° endpoint (modified): BILAG response[#] with no treatment failure at week 12	• Enrollment suspended early for low supply of study drug; 1° endpoint evaluated at 12 weeks instead of intended 24 weeks • Greater achievement of 1° endpoint with epratuzumab than placebo • Improvements in HRQOL and reduced GC doses at 48 weeks[34]
			Wallace *et al.*[35] (EMBLEM) • Phase IIb dose-ranging study • Moderate-to-severe SLE • 1° endpoint: BICLA response at 12 weeks	• First use of BICLA composite endpoint • Not powered for significance, but suggested efficacy and safety of 2400mg combined monthly dose • More homogeneous patient population than prior RCTs

Drug	Target	Mechanism	Study and Design	Key Findings
			Clowse *et al.*[37] (EMBODY 1 and 2) • Phase III RCT • Moderate-to-severe SLE • 1° endpoint: BICLA response at 48 weeks	• 1° endpoint not met; no difference in BICLA response rate and secondary efficacy measures between epratuzumab and placebo
PF-04236921	IL-6	Neutralize IL-6	Wallace *et al.*[38] • Phase II RCT • Moderate-to-severe SLE • 1° endpoint: SRI-4 at 24 weeks	• 1° endpoint met for 10mg dose; also showed improvements in BICLA and HRQOL (secondary pre-specified endpoints) • Reduction of flares (SFI) with 50mg dose • 200mg treatment arm discontinued for serious adverse events
Edratide	Unknown	Unknown	Urowitz *et al.*[55] • Phase II RCT • Mild-to-moderate SLE • 1° endpoint: Reduction in SLEDAI-2K and Adjusted Mean SLEDAI (AMS) through 26 weeks	• 1° endpoint not met, but significant improvements in BILAG were seen (secondary pre-specified endpoint) • Background GC use may have confounded results
Sifalimumab	IFN- α	Neutralize some species of IFN-α	Khamashta *et al.*[56] • Phase IIb RCT • Moderate-to-severe SLE • 1° endpoint: SRI-4 response at 52 weeks • Statistical significance set at $p<0.098$	• 1° endpoint met; greater achievement of SRI-4 and improvements in skin disease, joint count, and fatigue with sifalimumab compared to placebo

Drug	Target	Mechanism	Study and Design	Key Findings
Anifrolumab	Type 1 IFN receptor	Neutralize type 1 IFN activity	Furie *et al.*[39] • Phase II RCT • Moderate-to-severe SLE • 1° endpoint: SRI-4 response at 24 weeks and sustained reduction in GC dose	• 1° endpoint met; more SRI-4 responders and reduced GC doses with anifrolumab than placebo • Effect size greater in patients with high IFN at baseline

DHEA = dehydroepiandrosterone; RCT = randomized controlled trial; SLAM = Systemic Lupus Activity Monitor; GC = glucocorticoid; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; BAFF = B-cell activating factor; BLyS = B-lymphocyte stimulator; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–SLEDAI; SFI = SLE Flare Index; ANA = anti-nuclear antibody; dsDNA = double-stranded DNA; SRI = SLE Responder Index; HRQOL = health-related quality of life; BILAG = British Isles Lupus Assessment Group; BICLA = BILAG-based Combined Lupus Assessment; APRIL = a proliferation inducing ligand; PRO = patient-reported outcome; IFN = interferon.

[&]Defined as SLAM score ≥7; amended to include SLEDAI >2 during enrollment

[§]Composite endpoint of improvement or stabilization of two disease activity measures (SLAM and SLEDAI) and two HRQoL measures (patient global assessment and fatigue severity scale) without evidence of clinical deterioration (organ damage)

[*]Defined as BILAG C or better score in all organs at week 24 without a severe flare (≥1 new BILAG A or ≥2 new BILAG B scores) from day 1 to week 24 and maintaining this response without moderate or severe flare (≥1 BILAG A or B score) to week 52

[^]Defined as 1) BILAG C scores or better at week 24 and maintaining response without a new BILAG A or B scores for 16 weeks; 2) no more than 1 organ with BILAG B score at week 24 a new BILAG A or B score to week 52; 3) 2 BILAG B scores at week 24 without developing BILAG A or B scores in new domains until week 52 if baseline BILAG score was 1 A score plus ≥2 B scores, ≥2 A scores, or ≥4 B scores.

[#]Defined as BILAG A scores decreased to B or lower OR both BILAG B scores decreased to C or lower and no new BILAG A or <2 BILAG B scores in other organ systems

Table 2

Summary of clinical trials in renal systemic lupus erythematosus (SLE)

Drug	Target	Mechanism	Study and Design	Key Findings
Abetimus sodium	Anti-DNA	Bind anti-DNA antibodies	Alarcon-Segovia *et al.*[57]; Cardiel *et al.*[58] • Phase II/III RCT; phase III RCT • Previously treated SLE nephritis • 1° endpoint: Time to renal flare over 76 week treatment period [%] ASPEN trial • Phase III RCT • Higher doses of abetimus than above studies • 1° endpoint: Time to renal flare [%]	• 1° en simil flare renal vs pl reduc dsDN both • Post- analy longe flare patie affini • Stabl HRQ recei durin for re wors arm • Redu antib abeti place analy • Study devel disco interi to sh
Mycophenolate Mofetil (MMF)	Purine biosynethesis	Inhibits T- and B-cell proliferation	Appel *et al.*[42] (ALMS) • MMF vs IV CYC for induction therapy • 1° endpoint: Renal response[#] at 24 weeks	• MMF CYC induc • Bette MMF Hispa • Basel and e prote renal week analy
Rituximab	CD20	Depletes CD20+ B-cells	Rovin *et al.*[45] (LUNAR) • Phase III RCT • Background MMF and GC • 1° endpoint: Complete or partial renal	• 1° en • Unde • Dura short prote statis until

Drug	Target	Mechanism	Study and Design	Key Findings
			response * at 52 weeks	
Abatacept	CD80/86	Inhibits T-cell co-stimulation	Furie *et al.*[46] • Phase II/III RCT • Background MMF and GC • 1° endpoint: Time to complete renal response ¶	• 1° en • Strict respo very • Posit abata hoc a LUN comp appli • Unre likely respo
			ACCESS Trial Group[48] • Phase III RCT • Background CYC and GC induction, AZA maintenance • 1° endpoint: Complete renal response γ at 24 weeks	• 1° en • Limi interv of pri • No si differ secon 24- o up
Tacrolimus	FK-BP12	Inhibits calcineurin-mediated signaling	Mok *et al.*[53] • Tacrolimus vs MMF for induction therapy • 1° endpoint: Renal response § at 24 weeks	• Tacro to MI nephr thera • Used defin renal
Ocrelizumab	CD20	Depletes CD20+ B-cells	Mysler *et al.*[63] (BELONG) • Phase III RCT • Background GC and CYC or MMF	• Disco adver infec ocrel arms) • More use r place patie CYC
Atacicept	BAFF/BLyS and APRIL	Neutralize BAFF/BLyS (TNFSF13B) and APRIL (TNFSF13A)	Ginzler *et al.*[18] (APRIL-LN) • Phase II/III RCT	• Halte patie adver infec

Drug	Target	Mechanism	Study and Design	Key Findings
			• Background MMF and GC	hypo a)

RCT = randomized control trial; dsDNA = double-stranded DNA; HRQOL = health-related quality of life; CYC = cyclophosphamide; GC = glucocorticoid; IV = intravenous; BAFF = B-cell activating factor; BLyS = B-lymphocyte stimulator; APRIL = a proliferation inducing ligand; AZA = azathioprine

[%] Defined by any of the following: reproducible increase in 24-hour urine protein based on baseline value (to >1g/day if baseline was <0.2g/day, to >2g/day if baseline was between 0.2–1g/day, and twice baseline value if baseline >1g/day); reproducible increase in serum creatinine by >20% or 0.3mg/dl, whichever was greater, accompanied by proteinuria (>1g/day), hematuria (≥4 RBCs/hpf), and/or RBC casts; or new, reproducible hematuria (≥11–20 RBCs/hpf) or a reproducible in hematuria by 2 grades compared with baseline accompanied by a 0.8g/day increase in proteinuria or new RBC casts.

[#] Defined as decrease in urine protein/creatinine ratio (UPC) to <3 in patients with baseline UPC ≥3 or by ≥50% AND stabilization or improvement in serum creatinine

[§] Defined as stabilization (within 25%) or improvement in serum creatinine with UPC <1, inactive urinary sediment, and persistent improvement in C3 and anti-dsDNA antibody levels

[*] Complete renal response defined as normal serum creatinine if abnormal at baseline or ≤115% of baseline if normal at baseline; inactive urinary sediment (<5 RBCs/hpf and no RBC casts); UPC <0.5. Partial renal response defined as serum creatinine ≤115% of baseline; RBCs/hpf ≤50% above baseline and no RBC casts; at least 50% decrease in UPC to <1 (if baseline UPC was ≤3) or to <3 (if baseline UPC was >3).

[¶] Defined as estimated glomerular filtration rate (eGFR) ≥90% of screening level if normal at baseline or eGFR ≥90% 6 month pre-flare value if abnormal at screening; UPC <0.26; and inactive urinary sediment (RBCs and WBCs per hpf within normal limits and no RBC or WBC casts). Criteria had to be met again 4 weeks later to be considered a complete response.

[γ] Defined as UPC of <0.5 on 24-hour urine collection; serum creatinine level ≤1.2 mg/dl or ≤125% of baseline; and adherence to the prednisone taper to 10mg/day by 12 weeks.

Table 3

Steps to developing outcome measures in SLE clinical trials

- Review of the data from SLE RCTs to determine whether a unique combination of outcome measures distinguishes responders to active therapy plus standard of care from those receiving placebo plus standard of care.
  - Detailed statistical review of data from RCTs reporting both significant benefit and those that failed to achieve their primary outcome.
  - Establish whether changes in background therapy confound response by analyzing changes over time within individuals.
  - Determine if organ-specific versus global measures are more appropriate depending the study design.
  - Ascertain if individual components of response correlate with outcomes.
- Proposed new response measures will be reviewed, discussed and agreed upon by the participants as applied to one data set will be tested in subsequent data sets for confirmation
- Review of the utility of patient-reported outcomes will be included (ex: are patient-reported outcomes useful in assessing responder status; what do patient-reported outcomes add to the responder assessment; when should patient-reported outcomes be included—always, specific to study, other?).
  - Review of patient global assessment of disease activity if included in trial.
  - Review of patient-reported HRQOL including specific domains of SF-36 and transition question.
  - Review of patient-reported fatigue.
- Review of physician-reported measures of global disease activity and disease flare as well as time to flare.
- Review of glucocorticoid doses and whether attainment of a “clinically meaningful” definition of taper, such as prednisone ≤7.5mg/day, corresponds with a response.

SLE = systemic lupus erythematosus; RCT = randomized clinical trial; HRQOL = health-related quality of life.