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Systemic Lupus Erythematosus assessment and endpoints review.

Abstract

Systemic Lupus Erythematosus (SLE) clinical trials are complex. To date, three compounds have been approved for this condition. There remains some controversy related to which outcome measures and endpoints are best used for SLE trial design. Unmet needs include residual disease activity, frequent flares, glucocorticoid toxicity, comorbidities and organ damage with low daily quality of life.[1] In this review we provide an overview of the current assessments and endpoints frequently used in SLE clinical trials to obtain an optimal evaluation of outcomes, monitor patients and assess responses to new drugs being developed.

Keywords: *SLE, endpoints, disease activity index, flares, clinical trials*

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Introduction

The six SLE disease activity indices currently used to assess and monitor patients with systemic lupus erythematosus (SLE) in clinical trials are the following: the updated version of British Isles Lupus Assessment Group Index (BILAG 2004), European Consensus Lupus Activity Measurement (ECLAM), Systemic Lupus Activity Measure Revised (SLAM-R), Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), Lupus Activity Index (LAI) and Systemic Lupus Erythematosus Activity Questionnaire for Population Studies (SLAQ), and three SLE responder indices: Responder Index for Lupus Erythematosus (RIFLE), SLE Responder Index (SRI) and BILAG Based Combined Lupus Assessment (BICLA). Three SLE damage indices (patient self-reported questionnaires): Systemic Lupus International Collaborating Clinics/American College of Rheumatology-Damage Index (SLICC/SDI), Lupus Damage Index Questionnaire (LDIQ) and Brief Index of Lupus Damage (BILD).[2] The Lupus Multivariable Outcome Score (LuMOS) was used in two randomized controlled trials of belimumab in patients with SLE.

Outcome measures

According to the Food and Drug Administration (FDA) guidelines for SLE, disease activity should be measured at the beginning and end of the study as well as over the course of the trial in order to reach the primary endpoint (change in Disease Activity Index [DAI] between the baseline and the end of the study) which needs to demonstrate a statistically significant difference between the treatment groups compared with any placebo arm.

Several indices exist, but BILAG is the preferred index, for the FDA, to evaluate reduction in disease activity in SLE clinical trials.

The FDA guidance states that it is important to ensure that the selected DAI accurately assesses disease activity over time and it should also address signs/symptoms not related to SLE and how they will be scored (e.g. hematuria and/or pyuria due to urinary tract infection versus lupus nephritis).

Flares are also used as primary endpoints, so an index to measure flares should measure disease activity over a month's period, rather than at fixed time points, in order to not miss any flare over the course of the trial. The FDA accepts both the BILAG and SELENA-SLEDAI as flare indices.

Recent SLE clinical trials and measurement outcomes of primary endpoints are summarized in Table 1.[3]

Table 1: Recent clinical trials of drugs for SLE (non-organ specific)

Drug	Target	Primary endpoint	Study outcome*	References	Phase/study name
Rituximab	CD20	BILAG	Failure	Merrill, 2010	II/III EXPLORER
Abatacept	CD80/86	BILAG	Failure	Merrill, 2010	IIb
Atacicept	BAFF/APRIL	BILAG	Failure	Isenberg, 2015	IIb APRIL-SLE
Belimumab	BAFF	SELENA-SLEDAI, SFI	Failure	Wallace, 2009	II
Belimumab	BAFF	SRI-4	Success	Navarra, 2011	III/BLISS-52
Tabalumab	BAFF	SRI-5	Failure	Isenberg, 2016	III/ILUMINATE2
Epratuzumab	CD22	BICLA	Failure	Wallace, 2014	IIb EMBLEM
PF-04236921	IL-6	SRI-4	Failure	Wallace, 2014	II
Rontalizumab	INF-α	BILAG-2004	Failure	Kalunian, 2016	II ROSE
Sifalimumab	INF-α	SRI-4	Success	Khamahta, 2016	IIb
Anifrolumab	Type 1 INF-R	SRI-4	Failure	Furie, 2020	III TULIP 1
Anifrolumab	Type 1 INF-R	BICLA	Success	Furie, 2020	III TULIP 2

***Study Outcome: study failure or success in demonstrating the achievement of their primary endpoint.**

Outcome measures preferred for SLE clinical trials are:

SLEDAI (Systemic Lupus Erythematosus Disease Activity Index)

The SLEDAI is a global index which measures disease activity within the last 10 days, including 24 items collecting specific manifestations in 9 organ systems: neurological, musculoskeletal, renal, mucocutaneous, general, heart, respiratory, vascular and hematological that are weighted by the type of manifestation, but not by severity.[4] Disease activity may in theory range from 0 to 105. An advantage of SLEDAI is that it can be used for retrospective studies.

New versions have been developed such as SLEDAI-2K and SELENA-SLEDAI. All three indexes have the same weighting for parameters and organ damage, but have different definitions for each item.

The SELENA-SLEDAI also contains the Physician's Global Assessment scale and a flare index to evaluate worsening signs and symptoms. Activity has been defined on the basis of SLEDAI scores: no activity (SLEDAI=0), mild activity (SLEDAI=1 to 5), moderate activity (SLEDAI=6 to 10), high activity (SLEDAI=11 to 19) and very high activity (SLEDAI≥20).[5]

The SLEDAI-2K collects disease aspects as present or absent and may not reflect partial improvement, which limits its use in clinical trials.[6]

Valid, reliable tools, like SELENA-SLEDAI, exist for assessing disease activity and flare for Systemic Lupus Erythematosus (SLE) patients. However, these tools have been designed to be used in populations under study protocols based on strict inclusion, exclusion criteria. Although they are standardized, physicians who rate the patients should be trained on these assessments in order to minimize the risk of inter-rater variability and increase intra-rater reliability.

BILAG (British Isles Lupus Assessment Group)

An updated version of the BILAG was published in 2005 in an attempt to improve the characteristics of this index and is called the BILAG 2004 Index. It evaluates manifestations over the previous four weeks in a total of 8 organ systems, and 9 in the revised index: constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal and hematological.[6] Activity in each organ system is scored as: A=most active disease; B=intermediate activity; C=mild, stable disease; D=previous involvement, currently inactive; E=no previous activity.[7] (see Fig 1). The BILAG also is used to evaluate the occurrence of flares in patients with SLE. A severe flare is defined as a score of A, new appearance and a moderate flare is defined with a score of B, and a reoccurrence is defined with a score of D or E.

Figure 1[8]

BILAG score	Description
BILAG-A	Requires disease-modifying treatment (prednizone >20 mg/day or immunosuppressant)
BILAG-B	Mild, reversible problems, requiring symptomatic therapy (antimalarial, NSAIDs, prednisone <20 mg/day)
BILAG-C	Stable, mild disease
BILAG-D	No activity in previously affected system
BILAG-E	System never involved

In the past, the classic BILAG was used, as the primary endpoint, in the majority of SLE clinical trials, but currently, it is preferred to use the BILAG-2004 in lupus studies as it is more sensitive to change.

SRI (SLE Responder Index)

SRI is currently one of the most frequently used indices as a primary outcome measure in SLE clinical trials. It is a composite index which combines SELENA-SLEDAI, BILAG and PGA (Physician Global Assessment).

A responder is defined as 4 point or greater improvement of SELENA-SLEDAI score from baseline, no worsening of the physician global estimate (less than 0.3 points increase), and no new BILAG-A or two BILAG-B organ domain scores. SRI responders have to meet all 3 criteria.

After the approval of belimumab by the FDA, with the success of the phase III clinical trials using SRI as a primary endpoint, many other studies adopted this index as their primary endpoint. Using the modified-SRI (excluding both anti-dsDNA and low complement [C3/C4] from the SELENA-SLEDAI component of the score), showed higher response rates.

Interestingly, anifrolumab (anti-type I interferon receptor antibody) failed in one of the phase III clinical trials using SRI4 (23) as the primary endpoint, nevertheless, a phase II clinical trial using SRI4 and another phase III clinical trial using BICLA were successful. These results could be found under the drug clinical efficacy in the corresponding product marketing authorization document.

BICLA (BILAG Based Combined Lupus Assessment)

The BICLA combines BILAG, SLEDAI and physician global assessment.

Response as improvements includes:

- Improvement of BILAG 2004 A to BILAG B/C/D or of BILAG 2004 B to C/D
- No worsening in disease activity: no new BILAG 2004 A and ≤1 new BILAG 2004 B scores
- No worsening of baseline SLEDAI-2K total score
- No worsening in physician global estimate (<10% worsening)
- No treatment failure (defined as nonprotocol treatment, i.e. new or increased immunosuppressive or antimalarial therapy; increased systemic corticosteroids; or premature discontinuation of study treatment)

Other outcomes measures

SLAM (Systemic Lupus Activity Measure) and ECLAM (European Consensus Lupus Activity Measurement) are indices developed for scoring the severity of each organ dysfunction. The concept is good, but the weighting may not be appropriate (e.g. 0.5 points for renal injury in ECLAM equivalent to fatigue), and some domains may not be due to SLE activity such as general malaise, blood pressure, abdominal pain and Raynaud's phenomenon (SLAM).[3]

The SLAM has been modified based on experience with it in multi-observer studies and training of individuals in its use (SLAM-R).

ECLAM index included 15 selected variables and it appears to be an effective instrument for scoring patients with different degrees of disease activity. This is the first SLE disease activity index based on data from a very large number of lupus patients followed at a large number of lupus centres in different countries. It might therefore very well serve as a standardized measure for future European clinical studies.[9] Furthermore, the ECLAM can be used in retrospective studies. Final assessment of the validity, reliability and sensitivity of this index is now underway.

The correlation between change in each index and physician global estimate in descending order was: ECLAM r=0.65; BILAG r=0.61; SLAM r=0.54 and the SLEDAI r=0.52 (all p<0,0001). SLEDAI showed the least sensitivity to change versus physician global assessment.

As shown above all disease activity indices have their own qualities and flaws. This complicates the ability to quantify a decrease or an increase in disease activity and evaluate treatment efficacy for randomized clinical trials (RCTs).

Conclusion

Disease activity in SLE patients occurs in various organs with differing severities. Therefore, it is necessary to find the most appropriate index to assess therapeutic efficacy in SLE RCTs.

A lot of indices have been created and validated over time, although all have limitations when used to assess change in a patient's clinical status. Most SLE indices are used only in clinical trials and they are not used in usual clinical practice.

Composite indices are preferred for RCTs as they cover not only disease activity but also flares, this is the example of SRI and BICLA which introduced the Physician Global Assessment as well.

Currently many clinical trials fail in Phase II or III because of the definition of the primary outcome. Suggestions for improvements in trial design are to avoid including flare rates or steroid withdrawal as a primary endpoint.[11] The most important reason that leads to this is that BILAG flares and SELENA-SLEDAI flares indices do not correlate with each other.

Prompt and accurate SLE flare assessment is needed in routine patient care and in lupus clinical trials, where time to first flare and the frequency and severity of flares should be considered then as secondary endpoints instead of primary.

A review of the literature was performed in Medline to identify randomized controlled trials (RCT) in lupus published during the past decade. A set of criteria was defined a priori to analyze these trials covering different aspects of steroid use in RCTs with regard to eligibility, randomization, post-randomization, steroid use, analysis and reporting.[12] Stratified randomization was rarely used. Steroid dosing during the intervention was reported as a secondary outcome measure in only a few trials. Steroid use variability improves if minimized and sparing effects are defined. Artificial mandated use of steroids and tapering are not used in the usual clinical practices, which is the reason why they fail as primary endpoint.

Many questions remain to be addressed for SLE clinical trial design

- Which is the most appropriate outcome measure?
- Should flare prevention be considered as a primary endpoint?
- Should we use the same index to measure disease activity and flares in a clinical trial?

Keeping patient safety and wellbeing first, an effort should be made in order to achieve consensus on finding the best tool to measure improvement in disease activity for lupus patients.

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