Editorial

Endpoints for randomised controlled trials in systemic lupus erythematosus

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Although essentially bleak two years ago, today we have a mixed picture of systemic lupus erythematosus (SLE) randomised controlled trials (RCTs). After several trials in which hopeful candidate therapies failed to reach clinical endpoints, belimumab, as the first biologic agent, met the predefined primary endpoint in two large multinational trials (1, 2) and, in 2011, was approved for treatment of SLE in the US and Europe. Whereas these 2 successful RCTs, and the SLE responder index (SRI) endpoint (3), have defined a first path to follow, insights may be gained from examining these trials, as well as the failed ones. Hopefully, this will lead to further improvements and provide the tools needed for more rapidly advancing SLE therapy.

Most other rheumatic diseases, such as rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis, are easier to evaluate in that they have a well-defined range of involvement in one or two organ systems. SLE, in contrast, is very heterogeneous and can affect virtually every organ system, thereby resulting in a wide variety of clinical and biologic manifestations. It is therefore not trivial to capture overall SLE disease activity across all possible organ system manifestations.

Today, this approach mostly relies on long established SLE disease activity scores, such as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (4), European Consensus Lupus Activity Measurement (ECLAM) (5), and British Isles Lupus Assessment Group index (BILAG) (6). Such scores definitely have their value, and, indeed, European Leagues Against Rheumatism (EULAR) and Outcome Measures in Rheumatology (OMERACT) international consensus recommendations include the use of any of these disease activity scores, even for routine follow-up (7-9). Each of these instruments, recently reviewed in detail (10), has their strengths and weaknesses. However, that there is no agreement on utilisation of a single instrument already points to the fact that currently there is no perfect instrument, at least so far.

Among the disease activity scores, BILAG is most different from the others. BILAG as originally designed was not to express disease activity as an overall sum score (11). Rather, involvement of various organ systems is graded based on the necessity for therapeutic intervention (6, 12). Accordingly, BILAG does not include serologic measures, and is designed to be comprehensive, which, in consequence, leads to inclusion of a large number of items to be scored. This makes it ideal for capturing immunological adverse events, *i.e.* new onset SLE disease activity, within RCTs, but largely precludes its use in daily clinical practice.

In contrast, scores like SLEDAI and ECLAM are easier to use, yield a weighted sum score and do include serology. This is helpful in quantitatively assessing disease activity and measuring change. To better capture changes in SLE disease activity both scores also take previous values into account, which is fair as long as intervals between assessments are kept identical, as in RCTs.

However, the weighting that is necessary within each of these disease activity scores can be problematic. In SLEDAI, for example, attributing or not attributing a CNS symptom to SLE will result in a large change of 8 or even 16 points, *i.e.* twice or even 4 times a clinically meaningful change for either worsening or improvement. Nevertheless, SLEDAI, with a more limited number of items is currently the most widely used disease activity score.

In essence, all interventional trials in SLE patients will try to answer one of the two following questions, namely either "Does X prevent SLE flares?" or "Does X effectively treat SLE disease activity?" It appears important that these two approaches are not subconsciously mixed.

If the question is whether a medication prevents (or potentially, as with estrogens, induces) disease flares of any kind, one can make a rather strong argument for BILAG. BILAG appears to gives the best approximation to a 360° look at the disease, and severe BILAG (A) and moderate (B) flares constitute clinically meaningful concepts.

Issues then would be limited to teaching investigators the correct and uniform use of this rather complicated instrument (13), and to check the definitions in a BILAG expert group. Since even the most comprehensive of all scores may have omissions, combining this with a physician assessment of global activity scale is important. Other adverse events are included in every RCT protocol, and more may not be needed.

For the question of response to a medication the answer does not appear as simple. In most trials, SLEDAI and its modifications (SELENA SLEDAI, SLEDAI 2K) have been used to capture this difference. Indeed, clinically meaningful improvements have been defined as ≥4 points and/or ≥50% improvement in SLEDAI 2K (14-17).

In this type of application, the BILAG has a specific problem: although there have been modifications to allow for translating it into a summary score, this is not how it was designed. To derive a summary score means adding up values for "A", "B" and "C" scores valued at 9, 3, and 1, which are not continuous measures. To derive a "global" BILAG score would require weighted numbers across all systems, which presently is not the case. Nevertheless, in a data mining approach, a novel BILAG based responder index has been derived for epratuzumab trials (18), which now must have its value proven prospectively.

In contrast, various SLEDAIs and ECLAM disease activity scores have weighted organ involvement. Thus these latter appear better able to measure global changes in overall SLE disease activity. For this purpose, serological parameters are included that may or may not reflect clinical disease activity in an individual patient. While not necessarily a direct focus of therapy, adding immunology measures likely helps in evaluating global disease activity, yielding a better overall assessment.

However, when looking at global disease activity, SLEDAIs or ECLAM may miss uncommon, but important organ system manifestations. If joint symptoms subside, but severe bowel vasculitis newly appears at the same time, this would not be desirable outcome.

To overcome this problem, the SLE responder index (SRI) utilised in the belimumab phase 3 RCTs has combined SLEDAI and BILAG into one instrument (3). Response is measured by SLEDAI, which gives a sensible weighted number of improvement, and the established clinically meaningful difference of ≥4 is used as the decision limit. "Immunological SAEs", in the sense of severe "A" or 2"B" lupus flares are captured by BILAG, and physician global assessment (PhGA) of disease activity was added as another safety parameter.

Thus, this instrument has face validity, and was developed based on data-mining of the failed phase 2 RCT. The additional good news is that the SRI was validated in one and confirmed in the second of 2 pivotal phase 3 belimumab trials. The bad news is that in these 2 large RCTs the differences from placebo (active standard of care) were modest, albeit statistically significant in the 10 mg/kg treatment groups.

This latter fact can be interpreted various ways, and we will have to examine its performance in other trials to fully grasp the relative importance of attaining an SRI response. Nonetheless it is clear that "responders by SRI" reported statistically significant and clinically meaningful improvements in both summary and all 8 domain scores of SF-36 compared with non-responders; also true for FACIT fatigue scores, and that 67% reported they were "better" or "much better" than one year ago in the transition question of SF-36, compared with 33% of non-responders (19). It is not entirely clear at the moment whether the relatively small, albeit significant, difference between placebo vs belimumab, both added to active standard of care (1, 20) was due to the treatment, patient population, or scoring system itself.

Given a variety of secondary analyses, it appears rather unlikely that belimumab has a weak effect only. On the other hand, the belimumab RCTs have mostly included patients with moderate-severe disease activity, but limited to 3 organ systems; BLISS-76 in particular (20). This may have decreased the difference in the response rates between treatment arms. However, by simple regression to the mean, SLE patients with more severe disease might reach even higher placebo response rates.

What could one do to improve this instrument? It appears unlikely that improvement would be measured by BILAG or PhGA; but rather 'lack of deterioration'; not to mention that "treatment failure", *e.g.* use of prohibited increases in immunosuppressives and or corticosteroids would preclude patients from being considered responders. Rather, the instrument that measures success will have to be scrutinised.

Despite all its merits, SLEDAI does not finely graduate success. In most instances, a yes/no answer is given. Suffering or not suffering from arthritis certainly makes a huge difference to patients, but 2 instead of 14 swollen and tender joints will also be of major importance, and this difference would be missed if not indirectly reported by other points, such as changes in serology or scoring ≥50% improvement in individual manifestations.

Moreover, yes/no answers may magnify the effect of small differences in evaluation or even attribution. What if a joint is no longer quite swollen? What if symptoms are attributed to SLE at one time-point, but to a suspected infection at the next? This will lead to further confounding if a particular symptom is heavily weighted in a given score.

To some degree, an advanced instrument for measuring global SLE disease activity may offer a solution. While this probably is worth the effort, it may

become difficult to convince most rheumatologists around the world to use it. In addition, anything more differentiated may also increase complexity and, most probably, work load.

In the meantime, therefore, we think it important to examine other areas where many successful trials have been performed. As in real life, essentially all these approaches focus on major organ manifestations.

In rheumatoid arthritis, the major outcome parameters rely on compound responder indices, including swollen and tender joint counts, but also estimates of disease and parameters of inflammation (21). In contrast to SLE scores, however, these scales generally focus on one organ system only, and they allow for a finer grading of disease activity.

In ankylosing spondylitis, a compound scale focussing on specific problems is used (22). Although all of the individual components appear subjective, given that they are patient reported, this Ankylosing Spondylitis Disease Activity Score (ASDAS) works well and allows for fine grading of disease activity at baseline as well as change during treatment. Finally, in psoriasis, the PASI and its derivatives, compound skin scores, focuses on one organ system only, and yet again allow for fine grading (23). In psoriatic arthritis, it is scored as well as joint involvement, enthesitis and dactylitis (24). Although psoriatic skin lesions and psoriatic arthritis are individually assessed in RCTs, a new composite score is in development (25).

Should SLE be seen differently? Probably not, since, after all, the reason for instituting more agressive therapy than antimalarials or low dose corticosteroids is significant organ involvement of whatever kind. It is not the concept of "overall disease activity", but CNS manifestations, renal flares, arthritis, thrombocytopenia, or the extent of skin vasculitis that trigger most decisions. Why could we not, in analogy to the SRI, combine the best available instrument measuring disease activity in the most relevant organ manifestations on the one hand with BILAG and PhGA on the other?

To do so, we would have to use specific instruments for the leading organ systems. This would probably include swollen and tender joint counts and perhaps a visual analogue scale for joint pain, blood counts and differential blood counts for haematological parameters, the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), maybe supplemented by a more subjective patient related scale, for skin disease, and probably psychometric tests for CNS disease.

In many ways, SLE nephritis is a good example for this exact approach. One specific organ system is in focus. The hard parameters within these trials, namely renal failure and doubling of serum creatinine, are intuitive, but require prolonged observation for their attainment. In consequence, some established "early markers" have surfaced, which can be used for shorter term estimates, but with some insecurity as to the long term result.

In fact, several long-term SLE nephritis trials, such as the NIH cyclophosphamide series, the Euro-Lupus trial (26), and, despite lower numbers in follow-up, the maintenance trial (27) have been very successful, shaping lupus therapy worldwide. The much shorter mycophenolate mofetil induction trial (28) still showed clear-cut benefit.

Likewise, the Aspreva Lupus Management Study (ALMS) trial likely gave the correct answer, namely that mycophenolate mofetil is equivalent to cyclophosphamide, and better in patients of African origin according to *post hoc* analyses (29, 30). In the maintenance phase, mycophenolate mofetil was superior to azathioprine, after re-randomisation (31). For abatacept, despite short follow-up and without combination with cyclophosphamide as in murine models (32), the negative outcome presented at the 2011 ACR meeting (33) was balanced by a more positive analysis using outcome measures employed in other RCTs (34). Essentially, the LUpus Nephritis Assessment with Rituximab (LUNAR) trial was the only one to fail despite clinical evidence for efficacy of the agent, and the specific problems of this RCT have been thoroughly analysed (35, 36).

The major downside of such an approach focusing on organ disease may lie in the lower prevalence of less common organ system manifestations. This can cause significant recruitment problems, and several RCTs, including a membranous lupus nephritis trial with infliximab, have failed because of them. Recruitment remains an important issue, especially in a time of increasing numbers of SLE trials.

The likely answer is to not overspecify required disease manifestations. Refractory skin disease is easier to find than refractory subacute cutaneous LE (SCLE) only, and refractory haematological manifestations may be more realistic than specifically requiring haemolytic anaemia, for two examples.

One more important aspect remains to be stressed: in addition to further improving survival and organ manifestations, it is essential to analyse how various treatment options impact the health related quality of life (HRQoL) of SLE patients, as already defined in the 1999 OMERACT consensus (9, 37), and reiterated in the 2010 EULAR recommendations (7). After all, patients with SLE, and especially those with SLE nephritis, report much lower scores in all domains of the Medical Outcomes Survey Short Form 36 (SF-36) questionnaire than healthy individuals (38, 39). In addition, specific problems, fatigue in particular, importantly afflict the vast majority of SLE patients (40), and will largely be overlooked by SLE disease activity scores .

While there may be reluctance to further complicate an assessment of response by inclusion of HRQoL measures, any RCT in SLE should include a generic and a disease-specific HRQoL instrument (9, 41-44). It will be of major importance to analyse outcomes across RCTs in this regard, and current examples indeed show significant, and sometimes unexpected, benefit (19).

Taken together, a cautiously optimistic view appears appropriate today. For safety and flare trials as well as for general efficacy RCTs, respectively, BILAG centered and SRI responder indices appear to provide useful endpoints, although further refinement of these would help. For more focused trials, which more closely mimic real life, organ specific endpoints may be the

optimal solution, possibly in combination with BILAG and PhGA, as shown by the SRI, or at least to include additional safety information. In addition, HRQoL measures should be included in any SLE trial. Hopefully, these additions and changes will give us the tools to allow well informed decisions on whether or not new therapy is effective. In the longer term, however, a new disease activity score for use in RCTs as well as in daily practice is where we need to go.

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