Outcome assessments for flares in SLE trials have been both overly sensitive and non-specific, depending on the instrument being used. The article in this issue of *Rheumatology* by Thanou *et al.* [1], from a well-respected SLE centre, discusses proposed modifications to the classic Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA)-SLEDAI Flair Index (SFI). The SFI is defined by an increase in the SLEDAI of 3 or more points (mild or moderate flare) or a 12 point increase (severe), a 0–3 visual analogue scale (VAS) with anchors for the physician global assessment (none, mild, moderate or severe flare) with an increase in 1 (for mild/moderate) or 2.5 (for severe) and adding NSAIDs or HCQ (for mild) or steroids, but no more than 0.5 mg/kg/day and/or adding a new immunosuppressant (for severe) [2, 3]. The SFI was developed prior to the use of new medications in SLE, such as MMF, belimumab and other biologics. Medications that were changed would be considered a flare but may be added as a standard of care, such as initiation of HCQ as usual care or changing one immunosuppressive to another due to side effects. It is important to try to determine clinically relevant flares for SLE clinical trials, so this article is an important step forward, adding an ability to separate mild to moderate flares and more concordance between flares and the physician global assessment.

Ninety-one patients with SLE who were seen at the lupus clinic [1] and had the SLEDAI [4] and BILAG [5] calculated were included in the study. The conventional SFI (cSFI) was compared with an experimental version (eSFI) where medication criteria were not used and separated the mild/moderate flare category into its components by judgement based on patient charts where the physician global assessment was obtained or scored post hoc [1]. The eSFI had face validity where moderate flares had higher physician global assessments and BILAG scores compared with those rated as mild. With the elimination of medication, three-quarters of severe flares and nearly one-third of mild to moderate flares decreased with respect to severity. Thanou *et al.* [1] found that the downgraded severity flares had lower global assessments and lower scores with respect to SLEDAI [4] and BILAG [5] scores and fewer organs/domains considered flaring. One-quarter of medication changes happened when no flare was assigned; however, nearly 9 of 10 drug changes in the cSFI, where a severe flare was scored, were rated by the physician global assessment as no flare or mild or moderate flare. Thus this modification (where medications were eliminated) resulted in improved discrimination compared with the cSFI.

Some may have a contrary opinion, asking why any rule should be used to determine flare severity; as physician judgment of flares and rating them as mild, moderate, severe or even inconsequential may suffice, or using a scale such as a physician VAS of flare, where training could occur for evaluators within a trial.

Measurement of flare is important in clinical trials, as is measurement of improvement, and the two may not be scaled to detect important differences between groups in a study. The SLE responder index (SRI) was developed for measuring improvement in SLE trials. The SRI requires a 4 point decrease in SELENA-SLEDAI score (improvement), no new BILAG A and no more than one new BILAG B score (i.e. no major organ worsening, although there can be some worsening) and no worsening of the physician global assessment (i.e. ≤ 0.3 point worsening out of 3) [6]. Ideally the percentage of flare would be [100 – percentage responding – percentage with no flare and no response] and the percentage responding would be (1 – percentage flaring – percentage without a response or flare). The SFI has a problem partially due to the SLEDAI, where an organ-specific flare can become much worse and not be considered a more severe flare. For instance, significant worsening of renal, muscle, joint, skin, serositis, CNS, cytopenias and serology would not score higher if present already.

Determining increases or decreases in steroids may be an important outcome in SLE trials (i.e. finding a treatment with steroid-sparing effects is desirable), but the eSFI does not account for treatment changes. However, this can be captured in studies if steroids are part of the outcome measurements (percentage that reduce or increase steroids by a certain amount). Potential insensitivity to improvement or relevant worsening of the SLEDAI may have resulted in negative treatment differences where important differences may have been present, whereas many BILAG flares were not considered flares by the physician. Dichotomous outcomes in the SLEDAI lose sensitivity (a feature is present or absent) and there is not incremental change within organs [4, 5, 7].

SLE studies have used instruments that were either insensitive to changes in flaring and improving or had many flares detected (several of which were clinically not relevant) and thus non-specific. Perhaps a composite scoring system that is specific (detects real but major flares) but
Insensitive is not the best way to evaluate worsening/flaring in SLE.

In clinical trials and in following up patients there needs to be sophisticated techniques for analysing patients if they have flared more than once. There can be a flare rate per patient, mean change per patient, only the first flare counted, etc. These issues have not been standardized for most rheumatological diseases, such as counting digital ulcers in SSc (number of new ulcers, number of ulcers per patient, total ulcer burden, time to first ulcer or healing, etc.) [8]. Different analyses can vary the interpretation of treatment efficacy. Data for flares in SLE are often skewed when a minority have multiple flares. This is also true for radiographic progression in RA biologic trials, where 15% progress radiographically and thus mean X-ray change is not an accurate representation of the data, whereas the percentage progressing over a certain threshold change may be [9].

Therefore the article by Thanou et al. [1] can help trialists determine whether to include a responder and flare index and to use the SFI with or without the proposed modifications. However, relevant flares in organs with pre-existing disease activity will not be detected, so, in order to understand therapy in SLE, we need a finely tuned instrument to detect both improvements and flares that are clinically important.

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