Response to: 'SLE-DAS: ready for routine use' by Mathew *et al*

It was with great interest that we read the letter 'SLE-DAS: Ready for routine use?' by Mathew and coauthors.[1]

Mathew *et al* commented on our recent article reporting the derivation and validation of the Systemic Lupus Erythematosus Disease Activity Score (SLE-DAS),[2] which demonstrated a much higher sensitivity to change of SLE disease activity, as compared with SLE Disease Activity Index 2000 (SLEDAI-2K).

Mathew *et al*'s main concern is in regard of the SLE-DAS scoring of active lupus nephritis (LN). The SLE-DAS renal component is measured continuously, applying a logarithmic scale of proteinuria absolute value (to be scored only if above 500 mg/day and provided it is attributable to active LN). This is very different of the SLEDAI-2K renal component that comprises four dichotomous variables (proteinuria above 500 mg/day, pyuria, haematuria and urinary casts, each one scored solely as present or absent with a weight of 4 points if present and regardless of severity).[3]

In the derivation of the SLE-DAS, we modelled the renal component using longitudinal data of real patients with active LN from a large, well-characterised tertiary lupus cohort.[4 5] The SLE-DAS with its continuous scoring of the absolute value of proteinuria amends risks of major bias of SLEDAI-2K regarding renal involvement. In patients with active LN, the best predictor of renal outcome is the absolute level of proteinuria.[6] This is a better predictor than simply classifying proteinuria as present when above a threshold of >500 mg/day (or the equivalent urinary protein-to-creatinine ratio >0.5 mg/g), regardless of the level of proteinuria.[6] Moreover, proteinuria is the most sensitive manifestation of active LN. In a comprehensive review of active LN, proteinuria was reported in 100% of patients, while microscopic haematuria was found in about 80% of patients during the disease course, invariably associated with proteinuria.[7] Although active urinary sediment may be present in LN, urinary sediment analysis presents several technical issues limiting its clinical use. The identification and quantification of urinary white blood cells (WBCs), red blood cells (RBCs) and casts in microscopy high power field are imprecise and operator dependent.[6] Furthermore, urinary WBCs and RBCs are non-specific findings as they can originate from multiple sources in the genitourinary tract.[6] Most common causes include urinary tract infection, menses and urinary calculi. In the clinical setting, attribution of urinary sediment abnormalities to active LN or other alternative or concomitant causes is challenging. In addition, active urinary sediment is not a specific marker of active LN, as it was found to be associated both with activity and chronicity indexes in renal biopsies.[8] Importantly, persistent isolated microscopic haematuria in LN has not been associated with a negative outcome.[9 10] In fact, the inclusion of urinary RBCs as part of a composite outcome measure along the absolute level of proteinuria undermined the predictive value of the model, as compared with proteinuria alone.[6] As a result, the inclusion of urinary sediment has been identified as one of the major mistakes in LN management.[11]

Clinical trials of induction treatment of LN with either cyclophosphamide or mycophenolate mofetil consistently reported less than 50% of complete renal response after 6 months of treatment.[12–15] In their letter, Mathew and colleagues reported scoring of SLE-DAS and SLEDAI-2K in a convenience sample of 41 patients with active LN followed up to 6 months after starting induction treatment. This sample is unusual, given that 97.6% of the patients had a complete renal response at 6 months. In this sample, longitudinal changes in SLE-DAS and SLEDAI-2K scores equally identified improvement. We agree that the performance of SLEDAI-2K and SLE-DAS is similar in patients with complete renal response. It should be highlighted that a major advantage of SLE-DAS over SLEDAI-2K is its ability to capture partial, clinically meaningful improvement or worsening in disease activity.[4] This sensitivity to change of SLE-DAS is critical for its usefulness in monitoring individual patients in the clinical setting: regarding active LN, an early but partial improvement of proteinuria is of prognostic value and reflected as a change in the SLE-DAS score, which can be used to guide treatment decisions.

The derivation and validation of SLE-DAS was performed in two real-world, well-characterised cohorts, representative of Caucasian patients.[16 17] In both validation and derivation cohorts, 23.8% of the patients presented moderate/severe disease activity (SLEDAI-2K≥6).[18] It is clear that a disease activity instrument has to be set for a representative population including patients with high, moderate and low disease activity. We agree that SLE-DAS should be further validated in representative samples of different geographic and ethnic patient populations. However, small, convenience samples are subject to sampling bias and can lead to misleading results.

We propose that SLE-DAS can be useful for monitoring disease activity in individual SLE patients in daily clinical practice and guide treatment decisions. For this purpose, the instrument should not include as a factor in its scoring the dosage of glucocorticoids or immunosuppressive drugs: that would lead to a circular reasoning fallacy (ie, the physician decision to increase the prednisone dose leading to an increase in the activity score that in turn 'justifies' the treatment increase). Finally, the derivation of SLE-DAS was modelled considering all clinical and laboratory parameters included in SLEDAI-2K and adding the manifestations comprised in the current definitions of low disease activity and remission,[3 19 20] aiming to provide an accurate, simple and user-friendly global measure that is feasible in daily clinical practice. For those preferring an exhaustive index comprising a wide list of rare manifestations, we suggest the use of British Isle Lupus Assessment Group 2004 that has 97 items,[21] as compared with 17 items in SLE-DAS.

In conclusion, the SLE-DAS was derived and validated as an accurate, continuous global measure of SLE disease activity, able to capture partial clinically meaningful changes in disease activity. It is feasible in daily clinical practice and can be useful to guide treatment decisions in the individual patients. We will soon provide a free and certified SLE-DAS online calculator. Further validation in other patient groups will be further tested in our upcoming study.

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