

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 \geq 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.

Diogo Jesus ^{1,2}, Ana Matos,^{3,4} Carla Henriques,^{3,4,5} Margherita Zen,⁶ Andrea Doria ⁶, Luís Sousa Inês^{1,2}

¹Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

²Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal

³School of Technology and Management, Polytechnic Institute of Viseu, Viseu, Portugal

⁴Centre for the Study of Education, Technologies and Health, Viseu, Portugal

⁵Centre for Mathematics, University of Coimbra, Coimbra, Portugal

⁶Rheumatology Unit, Department of Rheumatology, University of Padova, Padova, Italy

Correspondence to Professor Luís Sousa Inês, Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal; luisines@gmail.com

Contributors All authors contributed to the conception, drafting and critical revision of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.



To cite Jesus D, Matos A, Henriques C, *et al.* *Ann Rheum Dis* 2020;**79**:e117.

Received 28 May 2019

Accepted 30 May 2019

Published Online First 14 June 2019



► <http://dx.doi.org/10.1136/annrheumdis-2019-215704>

Ann Rheum Dis 2020;**79**:e117. doi:10.1136/annrheumdis-2019-215794

ORCID iDs

Diogo Jesus <http://orcid.org/0000-0003-3136-0722>

Andrea Doria <http://orcid.org/0000-0003-0548-4983>

REFERENCES

- 1 Mathew A, Chengappa KG, Shah S, *et al.* SLE-DAS: ready for routine use? *Ann Rheum Dis* 2020;**79**:e116.
- 2 Jesus D, Matos A, Henriques C, *et al.* Derivation and validation of the SLE disease activity score (SLE-DAS): a new SLE continuous measure with high sensitivity for changes in disease activity. *Ann Rheum Dis* 2019;**78**:365–71.
- 3 Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;**29**:288–91.
- 4 Jesus D, Rodrigues M, Matos A, *et al.* Performance of SLEDAI-2K to detect a clinically meaningful change in SLE disease activity: a 36-month prospective cohort study of 334 patients. *Lupus* 2019;**28**:607–12.
- 5 Inês L, Rodrigues M, Jesus D, *et al.* Risk of damage and mortality in SLE patients fulfilling the ACR or only the SLICC classification criteria. A 10-year, inception cohort study. *Lupus* 2018;**27**:556–63.
- 6 Dall'Era M, Cisternas MG, Smilek DE, *et al.* Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus nephritis cohort. *Arthritis Rheumatol* 2015;**67**:1305–13.
- 7 Cameron JS. Lupus nephritis. *J Am Soc Nephrol* 1999;**10**:413–24.
- 8 Martínez-Martínez MU, Llamazares-Azuara LMdeG, Martínez-Galla D, *et al.* Urinary sediment suggests lupus nephritis histology. *Lupus* 2017;**26**:580–7.
- 9 Contreras G, Pardo V, Cely C, *et al.* Factors associated with poor outcomes in patients with lupus nephritis. *Lupus* 2005;**14**:890–5.
- 10 Faurischou M, Starklint H, Halberg P, *et al.* Prognostic factors in lupus nephritis: diagnostic and therapeutic delay increases the risk of terminal renal failure. *J Rheumatol* 2006;**33**:1563–9.
- 11 Bose B, Silverman ED, Bargman JM. Ten common mistakes in the management of lupus nephritis. *Am J Kidney Dis* 2014;**63**:667–76.
- 12 Ginzler EM, Dooley MA, Aranow C, *et al.* Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005;**353**:2219–28.
- 13 Grootsholten C, Ligtenberg G, Hagen EC, *et al.* Azathioprine/methylprednisolone versus cyclophosphamide in proliferative lupus nephritis. A randomized controlled trial. *Kidney Int* 2006;**70**:732–42.
- 14 Bertias GK, Tektonidou M, Amoura Z, *et al.* Joint European League against rheumatism and European renal Association-European dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis* 2012;**71**:1771–82.
- 15 Hahn BH, McMahon MA, Wilkinson A, *et al.* American College of rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res* 2012;**64**:797–808.
- 16 Inês L, Duarte C, Silva RS, *et al.* Identification of clinical predictors of flare in systemic lupus erythematosus patients: a 24-month prospective cohort study. *Rheumatology* 2014;**53**:85–9.
- 17 Zen M, Iaccarino L, Gatto M, *et al.* Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. *Ann Rheum Dis* 2018;**77**:104–10.
- 18 Gordon C, Amisshah-Arthur M-B, Gayed M, *et al.* The British Society for rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology* 2018;**57**:e1–45.
- 19 Franklyn K, Lau CS, Navarra SV, *et al.* Definition and initial validation of a lupus low disease activity state (LLDAS). *Ann Rheum Dis* 2016;**75**:1615–21.
- 20 Zen M, Iaccarino L, Gatto M, *et al.* Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. *Ann Rheum Dis* 2015;**74**:2117–22.
- 21 Isenberg DA, Rahman A, Allen E, *et al.* BILAG 2004. Development and initial validation of an updated version of the British Isles lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology* 2005;**44**:902–6.