Response to: 'Performance of the systemic lupus erythematosus disease activity score (SLE-DAS) in a Latin American population', by Rodríguez-González *et al*

It was with great interest that we read the letter 'Performance of the Systemic Lupus Erythematosus Disease Activity Score (SLE-DAS) in a Latin American population'.¹

Rodríguez-González *et al* commented on our recent manuscript reporting the derivation and validation of Systemic Lupus Erythematosus Disease Activity Score (SLE-DAS),² which demonstrated a much higher performance to detect clinical meaningful changes of SLE disease activity, as compared with SLE Disease Activity Index 2000 (SLEDAI-2K).³

In their letter, Rodríguez-González *et al* reported a cross-sectional monocentric cohort study of 227 Mexican Mestizo SLE patients, in which they found a very high positive correlation between the SLE-DAS and the SLEDAI-2K ($\rho=0.92$, $p<0.0001$). These results are consistent with our published data in which we identified a very strong correlation between the SLE-DAS and the SLEDAI-2K in both the derivation and the external validation cohorts ($\rho=0.940$ and 0.943 , respectively, $p<0.0005$ for both).²

Moreover, Rodríguez-González *et al* analysed the correlation of SLE-DAS and SLEDAI-2K in subgroups of patients defined according to the severity of disease activity. It is important to note that they used the SLEDAI-2K score as gold standard to define categories of quiescent/low disease activity (defined as SLEDAI-2K <6) and moderate/severe (SLEDAI-2K ≥ 6). This methodology is problematic, because of the very limited sensitivity to change of SLEDAI-2K, which is due to the dichotomous scoring of each item, ignoring the severity of the abnormalities.⁴ For this same reason, the accurate definition of remission and lupus disease activity categories cannot be solely based on the SLEDAI-2K score. This issue is recognised by the expert-derived proposals for definition of SLE clinical remission and low disease activity, based in a SLEDAI-2K score ≤ 4 but all requiring additional conditions to define those targets.⁵⁻⁷

Rodríguez-González *et al* reported that the Spearman correlation was very high ($\rho=0.90$) in patients with SLEDAI-2K <6 . On the contrary, in patients with SLEDAI-2K ≥ 6 , the correlation was much lower ($\rho=0.46$). These results were misinterpreted by Rodríguez-González *et al*, since they are fully expected and desirable, due to the much better performance of SLE-DAS. The SLEDAI-2K has an important limitation due to the dichotomous scoring of each item, that causes a ceiling effect. On the contrary, the SLE-DAS can identify differences in cases with diverse levels of activity in individual parameters within the same SLEDAI-2K score.

To clearly represent the ceiling effect limitation of SLEDAI-2K and its inability to capture changes in disease activity, that it is overcome by SLE-DAS, we present four clinical scenarios in the figure 1. As it is illustrated in the clinical scenario A, a patient presenting positive anti-dsDNA, low complement levels and leukocyte count below $3 \times 10^9/L$ is scored with a SLEDAI-2K of 5 points, regardless of having $2.9 \times 10^9/L$ or $0.1 \times 10^9/L$ white blood cells. The same limitations are represented with thrombocytopenia, arthritis and lupus nephritis in the clinical scenarios B, C and D, respectively. Contrarily, as the SLE-DAS considers the severity of each manifestation, it captures partial improvement and worsening changes and can better distinguish cases with different clinical severities and treatment requirements.

Figure 1 SLE-DAS and SLEDAI-2K scores of four different SLE clinical scenarios. Scenario (A) SLE-DAS and SLEDAI-2K scores with low complement levels, increased anti-dsDNA and different levels of leukocytes count. Scenario (B) SLE-DAS and SLEDAI-2K scores with low complement levels, increased anti-dsDNA and different levels of platelets count. Scenario (C) SLE-DAS and SLEDAI-2K scores with different numbers of swollen joints. Scenario (D) SLE-DAS and SLEDAI-2K scores with low complement levels, increased anti-dsDNA and different levels of proteinuria. Thresholds for low disease activity (LDA) are presented, considering the SLEDAI-2K LDA used by Rodríguez-González *et al* in their letter (SLEDAI-2K <6) and the estimated threshold for SLE-DAS LDA (SLE-DAS ≤ 3.77). SLEDAI-2K, SLE Disease Activity Index 2000; SLE-DAS, SLE disease activity score.

Moreover, Rodríguez-González *et al* reported that despite both SLEDAI-2K and SLE-DAS showed a statistically significant association with C3 serum levels, only SLEDAI-2K presented a statistically significant association with C4 serum levels. These associations are of uncertain clinical meaning, taking into consideration the low performance of SLE biomarkers for monitoring disease activity. Importantly, two recent literature reviews concluded that there is no consistent association between the complement levels and the occurrence of disease flares, because low complement levels may be related to variations in genetic polymorphisms, synthesis variability and auto-antibodies that may activate complement in vivo irrespective of disease activity.^{8,9}

In conclusion, this letter by Rodríguez-González *et al* corroborates the overall very strong correlation between the SLE-DAS and the SLEDAI-2K in an independent cohort of Latin American patients with Mexican Mestizo ethnicity and highlights one of the major advantages of the SLE-DAS over the SLEDAI-2K, that is overcoming the ceiling effect issue of SLEDAI-2K with its ability to distinguish cases with true differences in lupus disease activity despite having the same levels of SLEDAI-2K score.

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