

# Letter to the Editor (matters arising from published papers)

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## Comment on: Auto-antibodies to double-stranded DNA as biomarker in systemic lupus erythematosus: comparison of different assays during quiescent and active disease

SIR, We read with great interest the recent report by de Leeuw *et al.* [1] on the comparison of seven different assays for detecting anti-dsDNA antibodies in SLE. Firstly, they demonstrated that RIA by the Farr assay and enzyme-labelled anti-isotype assay (EliA) had the higher rate of anti-dsDNA detection (both 95%) in 58 samples from 29 patients with active LN. Afterwards, the diagnostic accuracy of RIA by the Farr assay and EliA was tested in 40 SLE patients with active disease (SLEDAI > 4), 152 with quiescent disease (SLEDAI ≤ 4) and 214 disease controls. In active disease the sensitivity was equal using Farr or EliA, with 37 out of 40 (93%) positive for anti-dsDNA using Farr and 38/40 (95%) by EliA. In quiescent SLE the sensitivity was higher using Farr (79%) than EliA (41%), with 120 patients out of 152 being positive for anti-dsDNA by Farr and 62/152 by EliA. Anti-dsDNA were detected in 19 out of 214 diseases controls using EliA (specificity 91%) and in 101/214 (specificity 53%) with Farr. Finally, Farr and EliA were retrospectively compared for their ability to predict flare in 34 SLE patients. Both of them showed a 25% increase in anti-dsDNA levels, in about 70% of patients, during the 6 months before flare. Nephritis flares were more often preceded by increase in anti-dsDNA levels (Farr: 82%, EliA: 93%) than non-nephritic flares (Farr: 66%, EliA: 43%). The authors concluded that, besides the advantages of being automated, fast and non-radioactive, EliA had results comparable to the Farr assay.

Recently, we investigated the role of anti-dsDNA as predictors of flares in SLE and the potential role of a preventive therapeutic intervention based on serial anti-dsDNA assessment [2]. We recorded 7 renal and 52 non-renal flares in 46 anti-dsDNA (RIA by Farr) positive SLE patients [2] selected from our prospectively followed-up cohort [3]. Overall, 5/7 (71.4%) renal flares and 31/52 (59.6%) non-renal flares were preceded by an increased anti-dsDNA >20% level in the 6 months prior to flare occurrence. Moreover, we retrospectively evaluated different therapeutic approaches, according to different physicians' behaviour within our cohort, in 64 patients who showed an increase in anti-dsDNA level ≥50% (measured by Farr) without clinical signs of disease activity. In all, 15 out of

64 patients received a modification of treatment, consisting of intensification in immunosuppressive therapy with increased dose of steroids in 10 cases, and 49/64 did not. In the former group no patients had flare, whereas in the latter group 16 (32.6%) patients developed flare within 6 months since the increase in anti-dsDNA levels, thus suggesting that a precautionary intensification in immunosuppressive treatment could be effective in preventing flares ( $P=0.013$  by Fisher's exact test) [2].

Results from a literature review highlighted that steadily increased anti-dsDNA levels have no utility in predicting SLE flares. Several longitudinal studies reported that an increase in anti-dsDNA levels may precede flare within 6 months. Fewer studies claimed the effectiveness of a flare-preventive intensification in immunosuppressive treatment driven by rising anti-dsDNA levels. The greatest amount of evidence and the most convincing came from studies using the Farr assay to quantitatively measure anti-dsDNA [2, 4]. The mechanism of anti-dsDNA production, which is also related to their pathogenicity and to disease activity, implicates a quantitative variation over time [5, 6]. They can disappear with treatment in some patients or widely fluctuate in others [7], even in the absence of clinical activity configuring the serologically active clinical quiescent disease pattern [8].

Therefore, to monitor anti-dsDNA levels a well-balanced assay in terms of specificity and sensitivity, as demonstrated for RIA by the Farr assay, might have greater utility than a highly specific and less sensitive assay, as controversially claimed for EliA. Our main cautionary message is that the apparently advantageous lower anti-dsDNA positivity in SLE quiescent disease, as those detected by de Leeuw *et al.* using EliA, may be indeed unfavourable in identifying early anti-dsDNA increases that precede a disease flare. Therefore, we would point out that more extensive evidence is needed before EliA could be considered at least equally effective as the Farr assay in quantitatively monitoring anti-dsDNA levels and, then, in driving the decision making process for precautionary increase in immunosuppression level to prevent SLE flare. On the other hand, we found that our results are quite consistent with the findings of de Leeuw *et al.* using the Farr assay, corroborating the role of anti-dsDNA as a useful biomarker for both diagnosis and follow-up of SLE when assessed using RIA.

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