Lupus serology: off target but still relevant to the treat-to-target strategy in Systemic Lupus Erythematosus.

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Systemic lupus erythematosus (SLE) is a complex autoimmune disorder characterized by the production of autoantibodies and cycles of clinically quiescent disease alternating with unpredictable flares [1]. Disease activity and flares, along with cumulative exposure to glucocorticoids (GCs), predict the development of organ damage associated with declines in quality of life and an increased mortality risk [2]. Targeting remission or a low disease activity (LDA) is associated with a lower risk of flare and damage accrual [3,4]. The treat-to-target (T2T) strategy involves tailoring treatments based on disease manifestations, comorbidities, and patient-specific factors through shared decision-making. Disease activity and treatment adherence are assessed in a tight control process designed to adjust treatment until remission or LDA is achieved [5]. Once the target is reached, maintaining it while preventing flares and minimizing glucocorticoid dosage is critical. An international task force has recently established a framework for implementing T2T in routine clinical care for SLE, identifying priority research areas, including clarifying the role of serological markers, such as anti-dsDNA and C3/C4 complement fractions, in the T2T strategy [5].

The recent analysis of five belimumab RCTs by Gomez et al. provides new data on the importance of lupus serology in the T2T approach [6]. The authors assessed how incorporating normal levels of anti-dsDNA and serum C3/C4 into the original Definitions of Remission in SLE (DORIS) [7] and Lupus LDA State (LLDAS) [4] (Table 1) would alter the frequency of target achievement and their effectiveness in preventing severe and renal flares defined according to the BILAG index.

The study involved 3,645 patients with 45,254 monthly visits. In total, 2,164 severe flares and 2,565 renal flares were recorded by week 52. Additionally, 328 (9%) patients achieved DORIS in 1,871 (4.1%) visits, while 689 (18.9%) patients attained LLDAS in 4,760 (10.5%) visits. Patients who achieved DORIS had a lower risk of subsequent severe flare and renal flares, as well as patients in LLDAS. Combined levels of anti-dsDNA and C3/C4 complement within normal ranges offered greater protection against severe flares in both DORIS (OR 0.051; 95% CI 0.006-0.412) and LLDAS (OR 0.245; 95% CI 0.139-0.433) patients compared to their counterparts with serum abnormalities. Normal serology levels added to DORIS showed a higher protective effect, with an 83% reduction in severe flare incidence (from 4.1 to 0.7 flares per 100 patient-years), compared to 41% reduction in LLDAS (from 5.1 to 3.0 flares per 100 patient-years). Similarly, inactive serology provided better protection against renal flares in both DORIS (OR 0.126; 95% CI 0.028-0.563) and LLDAS (OR 0.352; 95% CI 0.209-0.593)

patients compared to those with abnormal anti-dsDNA or C3/C4 levels. Normal serology led to an 85% decrease in renal flare incidence, from 8.5 to 1.3 per 100 patient-years in DORIS, and a 47% reduction, from 7.9 to 3.7 per 100 patient-years in LLDAS, compared to targets met with abnormal anti-dsDNA or C3/C4 levels. These findings confirm that achieving DORIS and LLDAS reduces the risk of flares, including renal flares, and suggest that the inclusion of normal serology enhances their flare-preventing effect, particularly in patients who are in remission. However, further investigation in properly designed studies is needed to determine if adding serological remission to the DORIS and LLDAS definitions enhances patients' protection against the risk of accumulating organ damage. On the one hand, the study results are noteworthy because proved a short-term protection against flares in patients with moderate to severe disease activity (median SLEDAI-2K, 10.0 IQR 8.0-12.0; median PGA 1.5, IQR 1.1-1.9), high rate of serologic activity (71.3% anti-dsDNA antibodies positive, 57.7% low levels of C3 and/or C4), and high baseline prednisone dose. On the other hand, extrapolation of the results from this study to other patient groups should be taken with caution. Belimumab RCTs were conducted before the development of the treat-to-target concept in SLE, and there was no mandated glucocorticoid tapering protocol in place. As a result, achieving treatment target was elusive for most patients, and normal anti-dsDNA and C3/C4 complement levels were found in only 544 (29.1%) DORIS visits and 1,879 (39.5%) LLDAS visits. Observational studies in different cohorts have reported a higher rate of treatment target achievement, but a similar rate of serologic remission associated with achieving the treatment target [3,8]. These data suggest that achieving serological remission, associated with DORIS and LLDAS, remains challenging and should still be regarded as off-target in the T2T approach. Therefore, escalating treatment to achieve serological remission in patients who have already reached their treatment target is not recommended unless future studies provide substantial evidence of long-term success. Nevertheless, lupus serology may still be valuable in the T2T strategy to help tailor optimal follow-up intervals after achieving the treatment target, and for patients who plan to taper and discontinue GCs. A recent multicenter retrospective study highlighted that serological activity at the time of GC withdrawal did not influence flare risk, but, when assessed as a time-varying factor, both high anti-DNA binding and hypocomplementemia predicted increased flares [9]. Indeed, the increase in anti-dsDNA values and the decrease in C3/C4 levels are reported as more significant than a consistently abnormal absolute value in predicting flares [10,11]. Accordingly, seroconversion, rising autoantibody levels, or declining trends in C3/C4 should

result in more frequent follow-up visits, enabling clinicians to anticipate flare-ups and manage them promptly, until future research defines more effective monitoring strategies.

Gomez et al. also reported that, when analysed separately, high anti-dsDNA and low C3/C4 levels exhibited different associations with DORIS and LLDAS in conferring greater protection against flare risk. The flare-preventing effect of DORIS primarily stemmed from patients who tested negative for anti-dsDNA, especially for severe flares (OR: 0.042; 95% CI: 0.005-0.331) and to a lesser extent for renal flares (OR: 0.126; 95% CI: 0.028-0.563). Some laboratory issues in measuring anti-dsDNA and complement fractions as biomarkers of SLE activity have clinical implications that should be considered before implementing lupus serology in the T2T algorithm. The C3 and C4 serum levels do not necessarily reflect complement activation, especially C4. Laboratory assays for anti-dsDNA revealed significant differences in the biologic characteristics of the antibodies detected and their association with global and renal SLE activity [12]. Despite utilizing an ELISA assay, which has lower accuracy compared to other techniques in detecting anti-dsDNA levels related to immunological activity, Gomez et al. employed a systematic serology evaluation with consistent measurements conducted over time in centralized laboratories, which represents a strength of the study.

What are the implications of these results for clinical practice? The T2T strategy should not involve normalizing serological values in SLE patients. Physicians should consider including lupus serology, particularly rising anti-dsDNA or declining complement levels, to personalize monitoring intervals and to assess the risk of treatment withdrawal. Considering the potential benefits for patient outcomes, the community should explore the effects of preventive treatment adjustments in cases with persistent, particularly worsening, isolated serological activity, as well as the flare-preventing effects of treatment protocols that not only induce clinical remission but may also restore abnormal lupus serology.

Table 1. Definition of DORIS Remission and Lupus Low Disease Activity State (LLDAS) in SLE.

	REMISSION (DORIS)	**LLDAS**
SLEDAI-2K	Clinical SLEDAI-2K = 0*	SLEDAI-2K≤4 No activity in major organ systems No new item on the SLEDAI-2K
Physician Global Assessment (range 0-3)	<0.5	≤1.0
Prednisone (equivalent dose)	≤5mg/day	≤7·5mg/day
Immunosuppressive treatment	Stable	Standard maintenance dose

* Excluding lupus serology (anti-dsDNA antibodies and complement levels). LLDAS: Lupus Low Disease Activity State; DORIS: Definitions of Remission in SLE; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index;

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