Four Hot Topics

11 REMISSION AND LOW DISEASE ACTIVITY: THE NEW TARGETS FOR TREATMENT
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In chronic inflammatory diseases such as rheumatoid arthritis, attainment of a specific cut-off of low (or even absent) disease activity has been associated with favourable long-term disease outcomes. Systemic lupus erythematosus (SLE) is a complex, systemic disease where prognosis is determined by a variety of factors including disease activity and exposure to potentially toxic drugs particularly glucocorticoids. To this end, both increased activity (either persistent or exacerbations following a period of inactivity) and continuous intake of prednisone at doses above 5–7.5 mg/day have been correlated with accrual of irreversible dysfunction or damage in a variety of organs.

Delineation of the optimal therapeutic goal in SLE is challenging, which is in part due to the inherent limitations of the available clinical instruments for monitoring the disease. Nonetheless, through an evidence- and consensus-based approach, an international expert panel has recently introduced various definitions of remission in SLE 1 namely: (a) complete remission (with normal serological markers); (b) clinical remission (irrespective of serological markers); (c) complete remission on-treatment (allowing intake of stable maintenance immunosuppressives and/or ≤5 mg/day of prednisone); and (d) clinical remission on-treatment. In the aforementioned definitions, remission is established by combination of absent disease activity (typically, SLEDAI=0 and physician-rated global disease activity [physician global assessment-PhGA] ≤0.5). In addition, an Asia-Pacific collaborative group has proposed lupus low disease activity state (LLDAS) 2 as minimally acceptable disease activity (including serological markers and allowing intake of stable maintenance immunosuppressives and/or ≤7.5 mg/day of prednisone) in patients with SLE. A SLEDAI cut-off of ≤4 with PhGA of ≤1 are included in this definition. Accordingly, a number of observational studies have shown that attainment of either remission or LLDAS is associated with improved patient outcomes such as prevention of flares and organ damage accrual.3 4

However, a number of issues pertaining to the definition of therapeutic target in SLE require clarification. First, although PhGA is useful in monitoring the disease by acting as a ‘safety net’ against the drawbacks of SLEDAI, it is still subject to inter-rater variability.5 Second, existing definitions of remission and LLDAS comprise of a combination of features such as an objective activity index, physician-rated activity and dose of glucocorticoids. The extent to which all these components are prognostically important is not clear and recent studies suggest that SLEDAI=0 alone may suffice for the definition of remission in SLE.6 Finally, it has been a matter of debate whether serology (serum C3/C4, anti-dsDNA) should be included in the definition of treatment targets (remission, LLDAS) or whether the latter should be based on the clinical parameters of SLE activity. This is due to the lack of absolute concordance between clinical and serological activity and the fact, that most patients with stable abnormal serology have favourable long-term prognosis. Further studies in large, well-characterised patient registries will be required to address the abovementioned issues, thus defining the optimal treatment goal in the disease.

Learning Objectives
- Identify factors with an adverse impact on organ damage accrual in patients with SLE
- Demonstrate understanding of the existing definitions of remission and low disease activity state in SLE
- Discuss unresolved issues related to the definitions of remission and low disease activity and their implementations in clinical practice

REFERENCES

BELIMUMAB HELPS LUPUS PATIENTS TO ACHIEVE LUPUS TARGETS
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Remission and low disease activity (LDA) are the most important targets to achieve in systemic lupus erythematosus (SLE) management.1–5 Belimumab is the only biologic drug approved for SLE and whether or not it can help lupus patients to achieve these targets is a critical question. In a post-hoc analysis carried out in patients enrolled in BLISS-52 and BLISS-76, remission and LDA were able to discriminate response to belimumab 10 mg/kg from placebo.5 6 Notably, clinical (c) SLEDAI-2K=0 was the best discriminator4 and, importantly, in a recent multicentre cohort study including 646 patients, cSLEDAI=0 had the best performance in predicting damage accrual compared with all other definitions of remission.7

In real-life the proportion of patients who can achieve a stable low lupus disease activity state (LLDAS) and remission was higher than that obtained in randomised controlled trials, as shown in two recent studies.8 9

A recent Italian multicentre cohort study of 466 patients on the use of belimumab in clinical practice settings, with a median follow-up of 18 months (range 1–60 months), showed that 71.7% of patients achieved LDA, 61.3% SRI-4, and 41.1% remission at 12 months, with these figures being maintained over time.10 The most important independent predictors of SRI-4 response were baseline SLEDAI2K≥10, SLE duration ≤2 years and a baseline SLICC damage index=0. Independent predictors of remission and LDA were baseline SLEDAI-2K <10, baseline SLICC damage index=0 and