

Lupus clinical trials: medication failure or failure in study design

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The heterogeneity of lupus poses a significant challenge for clinical trial design. The pleomorphic nature of the clinical manifestations, the severity of the patient population, the ethnicity influence on disease activity, and the difficulties in attempts to perform trials with larger sample size are leading to difficulties and failure in achieving statistical significance for new therapies. Many of the trials exclude patients with renal and central nervous system manifestations in an attempt to detect efficacy in less severe disease states. On this editorial we make some general comments on the trials recently performed.

The EXPLORER trial enrolled 257 patients with moderately to severely active extrarenal lupus. Patients were randomized to receive rituximab plus prednisone or placebo plus prednisone and were followed for 78 weeks. The study failed to achieve primary and secondary endpoints. The LUNAR study enrolled patients with biopsy proven active lupus nephritis. The overall design was similar to the EXPLORER, and the success was defined by renal response at one year. The drug failed primary and secondary endpoints.

"The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial" assessed the effect of abatacept in the incidence of flare rates on a background of oral glucocorticoids. Patients included in the study had to have had a lupus flare within 14 days before entering the trial and on a stable dose of prednisone less than 30 mg/day. One hundred and seventy five patients received treatment: 118 patients were randomized to receive abatacept and 57 to receive placebo. The study did not show differences in flare rates of BILAG A and B events.¹

Belimumab is a human monoclonal antibody that inhibits the B-lymphocyte stimulator (BLyS) and proved more effective than placebo in treating people with serologically active SLE. Efficacy analyses included the SELENA-SLEDAI,

BILAG and SELENA-SLEDAI Flare Index (SFI). The primary endpoint was at week 52 with improvement in several metrics employed, including the Physician Global Assessment (PGA). The success of belimumab in 52 weeks (BLISS-52) may have resulted from a new subanalysis in a subpopulation of patients that improved with treatment. The patients showed to be more in category "B" in disease activity, meaning they had more autoantibodies including higher anti-DNA titer and higher serum immunoglobulin levels.

General key considerations

One of the aspects to be considered in future trials is to analyze whether there is a scientific rationale to focus on the evaluation of treatment efficacy by reducing the number of flares versus decreasing persistent disease activity. SLE patients with periodic flares may differ from those with chronically active lupus; SLE patients from different racial groups may exhibit different pathologies and conditions with a single patient presenting different variations over time. Special attention should be given to ethnicity in future trials as a factor that may affect the outcome. The trial size is also a key challenge. In general, the larger the trial, the greater the likelihood of a therapeutic effect being lost in analyses. Eventually, a small trial could achieve success and have statistically significant results. Other issues that should be taken into consideration are duration of disease, current involvement of specific organ, and previous treatments. Finally, the definition of improvement among outcome instruments used in trials should be universally accepted as the best available. Controversies surrounding the use of the British Isles Lupus Assessment Group Index (BILAG) are based on an intention-to-treat approach according to an extensive series of criteria to classify patients SLE manifestations arising from different organ systems. Finally, there are limitations with the use of BILAG only, for instance, the use of BILAG B as an outcome measure of lupus flare and other indexes should be considered simultaneously as well.²

CONCLUSIONS

Noting the success of trials in rheumatoid arthritis (RA) one could expect that the same should happen in SLE, which did not occur. Hopefully, we should learn from the current failures and create new and different clinical design elements. Looking ahead, the considerations here outlined for future trials should

be able to discriminate between medication failure and failure in the study design.

Morton Aaron Scheinberg, PhD

Clinician and Rheumatologist of the Hospital Israelita Albert Einstein
Scientific Director and Coordinator of Clinical Research of the
Hospital Abreu Sodré – AACD
Habilitation Thesis in Immunology at the Universidade de São Paulo – USP
PhD in Immunology at the University of Boston

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