Comments on the article: "Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial"

We recently have read with great interest the article written by Mathian *et al* entitled "Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial" published in 19 December 2019.[1] The study assessed development of flares in patients with systemic lupus erythematosus (SLE) with clinically inactive disease course on maintenance versus withdrawal of 5 mg/day prednisone over a 12-month period. This study showed that withdrawal of this low-dose glucocorticoid was associated with a fourfold increase in the risk of flares. Although this study is impressive and provides the strongest evidence regarding the efficacy of low-dose prednisone in the prevention of the disease flares, there are some concerns that may endanger the validity of the study.

First, as this study aimed at comparison of risk of flares patients with SLE experience in each of the two groups, it was expected that all factors determined so far in the literature, to be associated with increased risk of the disease flares, be considered and compared between the groups, if it is possible. African-American race (OR of 1.8 compared with Caucasian ethnicity), disease onset ≤25 years (HR of 2.14) and serum BLyS levels ≥2 ng/mL (HR of 1.5–1.9 to experience severe flares in the following 12 months) are risk factors not considered in the current study.[2–4] As confounding potential of these factors cannot be ruled out in this study, the causative relationship between withdrawal of prednisone and higher flare risk would be in question. Although the serum BLyS levels of the study participants at the baseline could not be evaluated anymore, the first two mentioned factors could simply be measured and added to the study. Adjustment of these potential confounding factors remarkably increases the credibility of the results in this study.

Second, masking the nature of the treatment course known as blinding is a critical methodological feature of randomised clinical trials (RCTs). A pilot study with a close design with similar purpose conducted by Galbraith *et al* showed that blinding is totally applicable in this setting by over-encapsulation of both prednisone and placebo tablets.[5] Since there was no placebo group, the findings of this open-label trial could have been influenced by two problems. First, some of the patients in the withdrawal group might have failed their adherence to immunosuppressive drugs following discontinuation of prednisone, as they might have thought that their disease status is better than the other group and it is not necessary to strictly follow the medications. The second problem is that some other patients might develop emotional stress after discontinuation of prednisone rooted from this fact that they are not receiving maintenance treatment anymore while a majority of other patients undergo long-term low-dose glucocorticoid treatment. As both these events, poor compliance to treatment and emotional stress are considered to be associated with an increased risk of flares, blinding should had been performed.[6]

Notwithstanding the foregoing, this study has provided a fascinating evidence and it is the sole RCT study conducted with appropriate population size concerning long-term use of maintenance glucocorticoid in patients with SLE. However, whether to administer or discontinue this low-dose glucocorticoid requires further studies to validate the results of the current study. Also, there is a need for studies that assess other dimensions of withdrawal of glucocorticoids in patients with SLE, as the goal of low-dose corticosteroid maintenance is not just to prevent the disease flares.

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