Observational studies on glucocorticoids are harmful!

Compose a Response to This Article

Response to Editorial
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The Editor,
Lupus Science and Medicine
BMJ Journals

Dear Madam/Sir,

Our esteemed peer Dr. Boers has editorialised1 on our recently published study of associations of glucocorticoid use with damage accrual in SLE2, suggesting that studies of the type reported are 'harmful'. As this is such a serious accusation, we feel compelled to respond, even though we suspect that in the end the views of the authors and of Dr Boers as serious physician-researchers are in fact highly aligned. Essentially, we do not resile from our view that long-term reliance on glucocorticoids for the control of inflammation in SLE carries harm, and that steroid-reducing regimens for SLE management are urgently needed. At no time in our report, and certainly not in our clinical practice, do we advise against the use of these drugs, though such an imprecation was implied (incorrectly) in Dr Boers’ editorial. Rather,
it is our view that strategies to achieve control of disease activity with reduced reliance on glucocorticoids, such as improving the use of non-glucocorticoid agents or the introduction of novel therapies, are as urgently needed as ever — and that complacency about the chronic use of glucocorticoids in SLE is not an acceptable status quo.

As we stated in the opening remarks, 'The objective of the present study was to quantify damage accrual in a prospectively followed cohort of patients with SLE and determine the association of glucocorticoid use with damage'; similarly, we concluded 'our findings suggest the urgent need for a randomised study comparing the effect on damage accrual of usual care with that of a strategy that stringently limits glucocorticoid dosing'. That our report, like virtually all science that benefits from peer review, was improved in response to reviewers' input is scarcely newsworthy. As peer reviewers we all collectively strive to help authors and readers achieve the best outcome from submitted work, be it through rejection or suggestions for improvement. Moreover, one of the longest paragraphs in our report was an assessment of the limitations of the data and its analysis, and we also clearly state the possibility that glucocorticoid dose is largely, though not completely, a surrogate measure of disease activity. We thank Dr. Boers for restating these in his editorial, although we would have preferred it to have been acknowledged that we had done likewise in our report.

While confounding by indication is a methodological concern in assessment of treatment effects using observational cohort data, there is no single standard dose of steroid applied universally for the treatment of each lupus manifestation. Furthermore, factors other than lupus activity such as musculoskeletal pain due to degenerative joint disease and fibromyalgia, often influence steroid tapering. Accordingly, in real-life cohort data sets, these variations in steroid dosing relative to disease activity score provide an opportunity to tease apart, albeit with limitation, some of the harmful effect of steroids from disease activity itself.

We accept neither the proposition that this study was fatally flawed or that its conclusions are harmful. Rather, we propose the possibility that chronic glucocorticoid exposure has hitherto-unexplored associations with harmful effects that contribute to negative outcomes in SLE above and beyond their largely metabolically-based 'side-effects'. In unpublished studies on MRL/Ipr lupus-prone mice, we have observed that glucocorticoid treatment was associated with accelerated mortality - the mechanism of this effect is as yet unknown, but glucocorticoids induce the release of macrophage migration inhibitory factor (MIF), a protein demonstrated clearly to be harmful in models of SLE by us and other groups3, 4. The most harmful thing we could do is fail to remain open to the possibility that independent of their confounding by indication, glucocorticoids are indeed causing undiscovered dose-related harmful effects with long-term use in SLE. We maintain our view that this is an area of medical science in need of deeper exploration.

D Apostolopoulos, M Nikpour, A Hoi, EF Morand.

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