Observational studies on glucocorticoids are harmful!

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In this issue, Apostopoulos *et al*¹ report yet another observational study on the association of glucocorticoid (GC) treatment with a bad outcome, in this case damage accrual in SLE. Unsurprisingly, the association is present, and ‘independent’ of potential confounders. Unsurprisingly, the authors argue for a causal relationship. So what is new, and why are studies such as these harmful?

First, let me apologise for this cynical start, and stress that I am convinced this research has been performed with the best of intentions. However, strong language is needed because I think observational studies on GC are taking a very dangerous turn: where previously associations were sought with adverse outcomes ‘typically’ associated with GC exposure, now studies are emerging that seek associations with core disease outcomes: in this case SLE morbidity/damage, in other cases even death. For example, in rheumatoid arthritis interstitial lung disease, researchers found that steroid use was related to increased mortality.² And in each instance, the suggestion is put forward that GC treatment is actually worsening the disease outcome, and should be reduced or avoided altogether. As a result, the treat-to-target recommendations for SLE included ‘steroid-sparing’ as a possible target, and regulatory guidance has identified steroid-sparing as a possible outcome for clinical trials. Because these recommendations are mostly based on biased associations rather than evidence of causality, I am extremely worried that we are putting patients at risk, by limiting application of what is in many cases still a life-saving treatment.

The truth of the matter is that trials on GC beneficial and adverse effects are not being done, and that observational studies (invariably only focusing on GC adverse effects, both related and unrelated to the disease)

are hopelessly and irretrievably confounded by indication. In brief, patients with the most severe disease are preferentially treated with GC, and this leads to the associations found in observational studies, regardless of the beneficial effects of GC.³ As any student of epidemiology knows, strong confounding cannot be corrected for by statistical techniques. So unless the medical community gets its act together and performs properly powered double-blind randomised trials to validly study the balance of benefit and harm of GC, we can continue to agonise over the associations seen in observational studies for another century, without coming to a resolution.

In the meantime, and until such trials are completed, we should refrain from giving strong (and very likely, wrong) advice based on weak observational data (even though there is a lot of it) to astute clinicians who continue to carefully treat their patients with this life-saving class of drugs. There is an element of masochism here, because the same researchers who lament the use of GC and advise against it, are clinical experts in the disease, and (thankfully!) have no qualms in treating their severe patients with GC in adequate doses. Otherwise, how can it be that in the centre that cares for the patients in this study, no less than 75% were on GC? My conviction is that GC dose is probably the best indicator of disease activity and severity in many chronic diseases treated with this drug.

As a result of peer review, Apostopoulos *et al* improved their analysis strategy where possible, changed all the terms suggesting a causal relationship to associations and most importantly, changed the main conclusion from one suggesting ‘continued reliance on GC is harmful’ to one suggesting a large randomised trial on the balance of benefit and harm of GC in SLE is urgently needed.

I urge the lupus community to act on this conclusion, and stop repeating the same mistakes (ie, doing weak observational studies) with ever-increasing confidence.

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