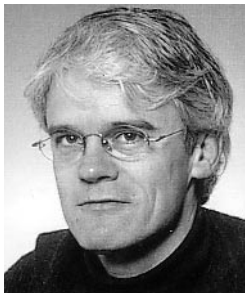
Editorial

Studying the Benefit/Risk Ratio of Glucocorticoids in Rheumatoid Arthritis



This month's *Journal* features a highly interesting observational study on patterns of glucocorticoid (GC) use in rheumatoid arthritis (RA) from the National Databank for Rheumatic Diseases[1]. In this patient population, one-third of patients are currently using GC, and two-thirds are exposed to these agents over the period of observation ("lifetime"). This shows that, despite the appearance of biologic agents, a majority of patients require treatment with GC at some point.

Importantly, GC treatment is a dynamic process, with lots of patients stopping or starting these drugs each year. This shows that physicians constantly scrutinize the need for ongoing treatment, although the study also demonstrated that the indication-setting to start or stop GC was highly variable between individual practices. Finally, GC use was associated with RA severity and poor outcome: mortality, work disability, and total joint replacement were all higher in current users versus past users, and past users versus nonusers. In the final paragraph of the abstract, the authors warn of the limitations of these observations: "the ability to discern causal associations is severely limited by confounding by indication."

This author group cannot be accused of being "soft on steroids." In an editorial published in 2005 in *The Journal*, Caplan, Russell, and Wolfe positioned themselves firmly in the camp of GC opposition[2]. Their editorial was written to accompany several papers. One discussed in a balanced way the problems of interpreting data on cardiovascular side effects of GC (GC worsen lipid profiles in general, but may improve the profile in active RA due to suppression of disease activity)[3]; another described new understanding and potential for the development of better (more selective) GC. Worrisome was the biased and offhand way the editorialists discounted positive evidence and played up negative evidence. They ended with the statement: "The fundamental question is whether we need more data in order for physicians to weigh this decision [...to balance the benefits and potential risks associated with GC use...] more competently." The implicit answer was "no," but now my n-of-one observational study suggests the addition of the fourth author, Kaleb Michaud, and perhaps some tweaking in the review process, has done much to soften their tone and create more balance in their views on GC, opening the way for the current publication.

BENEFIT/RISK RATIO OF GC: QUALITY OF THE EVIDENCE

The risks of GC in RA are "well known" and yet our knowledge of benefits and risks is still appallingly limited[4]. This is not the place to list or summarize the available evidence; it doesn't get better on repetition. Suffice it to make the following points: (1) "general" knowledge of GC is of limited use in RA because the disease itself may cause many of the outcomes that are associated with GC (for example, osteoporosis and cardiovascular disease). (2) There are only a few randomized trials of GC in RA, and these are powered for benefit, i.e., they are too short and too small for adequate risk assessment. (3) Observational studies on GC harm have mostly been of such low quality that they are useless to quantify the risk or study a dose-response relationship. For instance, in *The Journal* we summarized the best studied side effect of GC, i.e., bone loss: up to 1998 it was backed by prospective documentation of not more than about 300 patients in the whole world literature[5]! Ironically, the authors fail to quote our reference in what they term this "most intensely studied outcome." Here, the quality of evidence has substantially improved with the publication of several large trials on the prevention of GC-induced osteoporosis[6], but now we unfortunately ignore this evidence and the resulting guidelines, failing to protect our patients as we should[7].

See Corticosteroid use in RA: prevalence, predictors, correlates, and outcomes, *page 696*

CAUSE OR MARKER? LIMITATIONS OF OBSERVATIONAL DATA

Rather than make "the same mistakes with increasing confidence," as Ted Pincus is fond of saying, I would like to use this excellent example of an observational study to list the methodological challenges and suggest a way forward. What then, are the methods of this study? The National Databank performs an ongoing data collection where physicians voluntarily submit data on a selection of their patients, and this process is repeated over the years. In this way, several years of followup data are available for many patients in many settings. For this study, the huge sample (over 20,000 patients) allowed extensive statistical modeling. Recruitment continues, and physicians are requested not to select patients as to severity. Data collection is thus prospective and standardized, both key requirements to limit information bias. It is not an inception cohort, as patients are not recruited at a uniform and early stage of disease. As in all observational studies, issues of differential dropout, information, and selection bias can never be completely addressed or corrected for.

The main and, at first glance, paradoxical finding of the study is the confirmation that so many patients use GC, despite the fact that this use is strongly associated with poor outcome. If GC truly causes poor outcome, why in heaven's name would anyone consider prescribing or taking these agents at all? In their previous editorial, the authors suggested physicians perhaps do not take the literature on the possible harm seriously enough. Another suggestion they make for the popularity of GC is the effect on symptoms, although in their perception GC are about as strong as hydroxychloroquine,

Finally, they suggest any benefit is immediate, but harm takes a long time to develop. In my view, the main explanation remains firmly in confounding by indication. It is an insult to think physicians and patients aren't well aware of the potential risks of longtime GC use, but they note that in some situations nothing (not even hydroxychloroquine!) works as well as GC. Given the perceived dangers, GC use will be limited to the more severe cases, which have a higher chance of poor outcome regardless of treatment. In this way GC use becomes a marker rather than a cause for poor outcome. By documenting the dynamic nature of GC use, with many yearly stops and starts, the current study also does away with the notion that GC use is an addiction, i.e., that patients cannot quit once they are on the drug. If GC do have disease-modifying properties, as many (but not the authors) believe on the basis of a firm body of literature[8], it is likely that these properties are best applied aggressively at the beginning of the disease. However, if GC are used as a last resort and at the lowest possible doses, the benefit/risk ratio may be adversely altered.

THE WAY FORWARD

So where to go from here? If even large-scale observational studies of this quality are powerless to assess and quantify treatment-related risks, what can be done? I see 3 potential routes, 2 of which should be possible in this dataset, although the authors disagreed during the review process.

First, a large, pragmatic, placebo-controlled, randomized trial should be started, preferably in patients with early RA. Randomization is the only way we know that will balance out known and unknown prognostic factors, thus preventing confounding by indication and other factors. "Pragmatic" means the opposite of the ubiquitous phase-3 design of the registration trials funded by industry: thus all patients should be eligible, and the protocol should be hassle-free, with a minimum of data collection (but of excellent quality!), and it should allow the physician maximum freedom to continue routine practice. Such a trial will have excellent generalizability, dispelling the notion that generalizability can only be achieved in observational studies. It is true the trial should run over several years, say 5, but not 10 or more. If the sample size is large enough, sufficient numbers of good and bad "longterm" outcomes will occur in this time period. Most of quail at the thought of a trial with thousands of patients running many years. However, if cardiologists, oncologists, and gynecologists (and others) can do it, why not rheumatologists? Costs should be borne by a large funding agency and not industry. This is a trial we owe to ourselves!

Second, in the current dataset "pseudo-randomization" has occurred and this can be used to create a virtual trial. A prominent finding in the study was the high variability between physicians in their propensity to prescribe GC, as assessed by the mean disease activity level of the patients versus the mean use of GC in each practice. This variability is not really a random process, but comes pretty close if we look at the dispersion in Figure 2 of the study. Thus one could for example define "GC believers" as the physicians in the highest tertile of GC use, and "GC deniers" in the lowest tertile. We can now set a disease activity level range such that in the practice of the believers, most patients with this level will start GC, but in the practice of the deniers, most patients will not start GC. Now, we form 2 groups: patients with the same disease activity but either starting (from the believers' practices) or not starting GC (from the deniers' practices; non-start defined as the first timepoint at which these patients achieved this disease activity level). Then we follow the fate of these 2 groups of pseudo-randomized patients from their GC start (or non-start) forward in time, and note their outcomes.

Third, patterns of GC use should be examined in true inception cohorts: not cohorts starting at the moment of GC initiation, but starting at an early and uniform stage of the disease. An inception cohort is probably present as a subset in the current National Databank database, and the patterns

in this cohort could be compared with the results of the current study. Although such an approach further limits information and selection bias because patients and their information are collected before most treatment decisions have been taken. Please note this approach by itself does not prevent confounding by indication: the treatment decisions of interest are still based on indication-setting, i.e., not subject to randomization. Inception cohorts that start as continuation from randomized trials are better, because at least in the initial stages the treatment decisions are randomized. Unfortunately, the current batch of trials is small in number and sample size.

In sum, this superb observational study allows highly interesting insights into the patterns and associations of current GC use in RA. I urge the authors to commit themselves to the additional analyses of the current dataset as suggested above, and our rheumatology community to commit itself to a large pragmatic trial. Then, and only then, will faith be replaced by evidence as a guide towards effective and safe use of GC.

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REFERENCES

1. Caplan L, Wolfe F, Russell AS, Michaud K. Corticosteroid use in rheumatoid arthritis: prevalence, predictors, correlates, and outcomes. J Rheumatol 2007;34:696-705.
2. Caplan L, Russell AS, Wolfe F. Steroids for rheumatoid arthritis: the honeymoon revisited (once again) [editorial]. J Rheumatol 2005;32:1863-5.
3. Davis JM 3rd, Maradit-Kremers H, Gabriel SE. Use of low-dose glucocorticoids and the risk of cardiovascular morbidity and mortality in rheumatoid arthritis: what is the true direction of effect? J Rheumatol 2005;32:1856-62.
4. Da Silva JA, Jacobs JW, Kirwan JR, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis 2006;65:285-93.
5. Verhoeven A, Boers M. Limited bone loss due to corticosteroids; A systematic review of prospective studies in rheumatoid arthritis and other diseases. J Rheumatol 1997;24:1495-503.
6. Lodder MC, Lems WF, Kostense PJ, Verhoeven AC, Dijkmans BA, Boers M. Bone loss due to glucocorticoids: update of a systematic review of prospective studies in rheumatoid arthritis and other diseases [abstract]. Ann Rheum Dis 2003;62 Suppl 1:94.
7. Saag KG, Gehlbach SH, Curtis JR, Youket TE, Worley K, Lange JL. Trends in prevention of glucocorticoid-induced osteoporosis. J Rheumatol 2006;33:1651-7.
8. Kirwan J, Bijlsma J, Boers M, Shea B. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007;1:CD006356.