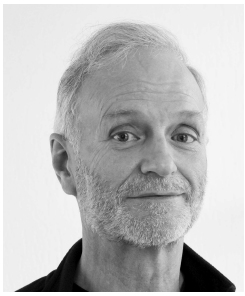
Editorial

Glucocorticoids Are Always Under Suspicion — Is the Perception of Their Risks Unbiased?



In this issue of *The Journal*, Best, *et al*[1] report from their retrospective observational cohort study the associations between the usage of oral glucocorticoids (GC) and the incidence and cost of potential adverse effects (AE) of this medication in rheumatoid arthritis (RA). They included 84,357 patients from a US medical database. The highest cumulative oral GC dose (> 1.8 g prednisone equivalent) during a "baseline period" of 1 year (so on average, > 5 mg of prednisone daily during that year) was associated with an increased risk of any potentially GC-associated AE during the directly following "evaluation period" of 1 year, compared to no GC exposure. In their view, these results suggest that all efforts (such as earlier implementation of GC-sparing treatment) should be made to avoid high-dose and chronic oral GC therapy.

This study adds to the longstanding debate on risks and benefits of GC in RA. North American publications tend to underscore the risks, whereas many European researchers plead that the toxicity of low-dose GC therapy in RA is frequently overestimated, while its benefits are downplayed. This transatlantic divide does not have a parallel in clinical practice: on both sides of the Atlantic, GC therapy is frequently applied. The CORRONA registry, a US-based longitudinal registry of patients with RA (n = 25,000), shows that about 30% of its patients with RA use a GC[2]. In an older US study, 35.5% of 12,749 patients with RA were currently using GC, and the lifetime exposure was 65.5%[3].

Observational studies on AE of GC, like this one by Best, *et al*[1], intrinsically are associated with a number of methodological issues, obscuring interpretation of results. Here, we will address 3 issues:

1. Are all negative events that occur during GC therapy due to GC?
2. May bias by indication play a relevant role in observational studies, and can it be corrected for?
3. What are the (dis)advantages of glucocorticoid-sparing/replacing therapies, regarding risks and costs?

Are all negative events occurring during GC therapy due to GC? The authors analyze potentially GC-related AE. Many of these harms may actually be manifestations of the disease itself or AE of comedications.

Most of the negative effects and events, generally considered as potential GC-related AE, have also been proven to be associated with active RA itself. These include decrease in bone mass[4] and increased risk of fracture[5], aseptic necrosis of bone[6], and reduced muscle mass[7]. Others are glucose intolerance and increased risk of diabetes[8,9], as well as negative effects on lipid levels[10,11] and endothelium[11,12], and increased risk of myocardial infarction[13], stroke[14], poor pregnancy outcome[15,16], and infection[17,18] (Figure 1).

These systemic effects of RA are attributed to the inflammatory mediators produced in the disease process, so that it can be hypothesized that GC reduce the incidence and severity of disease activity–associated effects. In the CAMERA-II study[19], patients with early RA were randomized to 10 mg prednisone daily or placebo, in addition to a tight control and a treat-to-target regimen [stepped-up methotrexate (MTX), and if needed, also adalimumab (ADA)]. In the prednisone strategy group, the mean weight gain after 2 years was 2.9 kg, which was significantly higher than the gain of 1.3 kg in the placebo-prednisone strategy group. Weight gain is generally seen as an AE of GC. However, in an additional analysis[20], the extra weight gain in the prednisone strategy group seemed at least partly attributable to improved disease control by prednisone. In other words, GC reduced active disease-associated weight loss. This effect has also been shown with antitumor necrosis factor therapy[21,22].

Second, we need to consider the possibility that at least some of the AE attributed to GC in observational studies are in fact due to concomitant medications, which will be used, often in higher doses, to treat active disease that also justifies GC therapy. A case in point is comedication with non-

See GC exposure and AE in RA, *page 320*

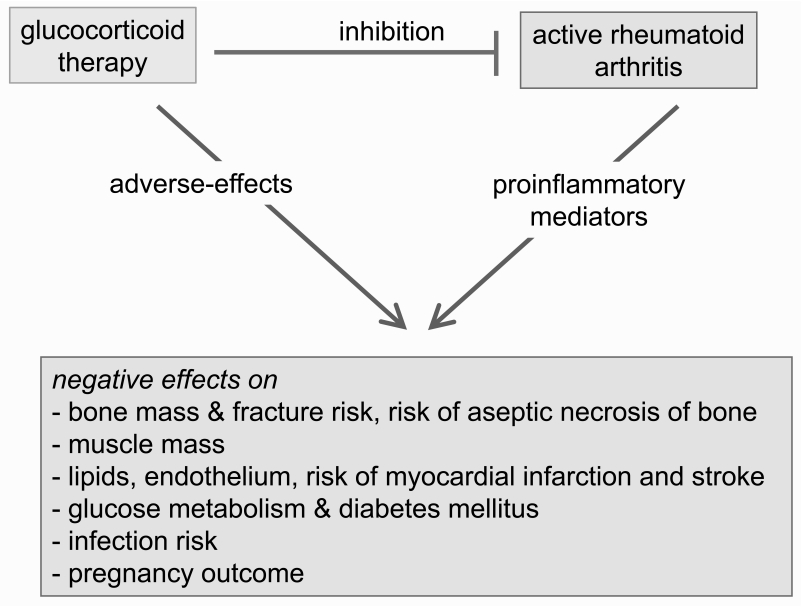


Figure 1. Interactions between glucocorticoid (GC) therapy, rheumatoid arthritis (RA) disease activity, and negative clinical effects. GC therapy may have adverse effects, but it suppresses disease activity and by this mechanism also inhibits negative consequences of active RA. Several negative consequences of active RA match adverse effects of GC.

steroidal antiinflammatory drugs (NSAID) and their risk for cardiovascular events and peptic ulcer[23]. In the study by Best, *et al*[1], the highest statistically significant adjusted incremental costs were observed for ulcer/gastrointestinal bleed, but an adjustment for the possible confounder NSAID use was not possible.

Infection rate is increased when GC therapy is combined with MTX, leflunomide, or biologicals. Given that effective treatment of RA by GC may allow for lower dosages of concomitant NSAID and other medications[24], it may be hypothesized that GC may contribute to the reduction of the AE of these medications. However, this does not imply at all that GC in RA have negligible AE. In any case, a relevant proportion of the harms occurring during GC therapy is not GC-related, as Best, *et al*[1] also recognize by adding throughout the adjective *potential* to AE of GC.

May bias by indication play a relevant role in observational studies, and can it be corrected for? Most data on the safety of GC are derived from observational studies, and these tend to overestimate AE of medication, especially because of bias by indication[25]. In the absence of randomization, patients with the more severe disease are more frequently prescribed GC and higher doses of comedication, and this inevitably increases the risk of falsely attributing to GC medication the unwanted events that are actually related to higher disease activity (Figure 1), associated comorbidities, and/or comedication. Examples of this bias in the field of GC are plentiful, and this risk of error has actually been highlighted numerous times by appropriate discussion[3,25]. This risk is confirmed by the clear dichotomy between data from observational and those of randomized clinical trials (RCT) of GC. Observational studies show higher rates of AE than the randomized prospective studies, especially regarding infection[26]. Pertinent RCT, which, interestingly, all have been performed in Europe, concluded that the use of low-dose GC in RA is associated with mild toxicity. Of course, RCT have limitations of their own, especially regarding selection criteria, hampering inclusion of a proper representation of the overall patient population and reducing generalizability of study results. Additionally, the published RCT on GC were not focused on toxicity, and had relatively short followups (up to 2 yrs) and small sample sizes (up to n = 250). In Europe, the Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis (GLORIA) study, a big double-blind RCT, is now ongoing (clinicaltrials.gov/ct2/show/record/ NCT02585258), comparing the cost-effectiveness and safety of additional low-dose GC in treatment strategies for elderly patients with RA. This study probably will provide more reliable estimates of the risks of low-dose GC in these patients in daily clinical practice.

We may conclude that confounders, especially bias by indication, do play a relevant role in observational studies on GC. Statistical attempts to correct for these are frequently applied. Best, *et al*[1] performed multivariate analyses using covariates including measures of general health, healthcare costs, and use of disease-modifying antirheumatic drugs (DMARD) during the baseline year. However, statistical corrections can never be considered

equivalent to randomization, because of unknown sources of bias[27].

What are the (dis)advantages of glucocorticoid-sparing/replacing therapies, regarding risks and costs? In RA, all drugs decreasing disease activity are GC-sparing, i.e., they decrease the need for GC. The reverse is also true: effective GC treatment reduces the need for additional DMARD or higher doses thereof. In the CAMERA-II study[19], the treatment strategy with GC was more effective in reducing disease activity and preventing erosive joint damage (DMARD effect, still present at followup after the study[28]), and this allowed for less need for ADA initiation and lower maximum doses of MTX. Elevated serum aminotransferase levels and nausea occurred significantly less frequently in the treatment arm with GC. The same was observed with the total number of AE. Even several years after stopping the experimental treatment, early exposure to GC in RA has been associated with improved outcomes and reduced need for biologicals[28,29,30]. In another study, GC use was also associated with less need for NSAID and other additional therapies[24].

Withdrawal studies, although limited in size and quality, suggest that an important proportion of patients with RA who have their low-dose GC withdrawn after longterm stable remission experiences a flare of the disease, requiring reintroduction of these agents, or increasing the dose of concurrent drugs, or adding another drug to the regimen[31]. Intensified doses of concurrent drugs and alternative medications will increase the risk of AE events and inevitably, the overall cost of treatment. Whether the balance of risks and benefits would favor continuing low-dose GC or replacing it by increased dosages of concurrent medication or initiation of another drug has not been investigated. However, we hypothesize that adding a low-medium dose of GC to a treatment strategy designed to achieve remission, as in the CAMERA-II trial, would be cost-effective.

Observational studies, such as that of Best, *et al*[1], are inherently associated with a high risk of bias by indication and other methodological issues, which tend to artificially inflate the estimated risks associated with low-dose GC therapy in RA. The results of Best, *et al* on potential AE and their cost should be seen in this light. RCT unanimously indicate a milder risk profile of low-dose GC therapy than observational studies, but have limitations of their own. Final answers to this conundrum can only be obtained through a dedicated and properly sized randomized double-blind clinical trial. This should adopt a pragmatic design so as to include patients from daily practice, as in the GLORIA trial, be focused on toxicity, have sufficient duration to incorporate cumulative dose-related GC events, and compare all AE as well as direct and indirect costs of the whole strategy arms.

The advice given by Best, *et al*[1] that all efforts (such as earlier implementation of GC-sparing treatment) should be made to avoid chronic oral GC therapy in RA could only be justified if the GC does not have to be replaced to achieve similar treatment goals (which may include DMARD effects) by other, more expensive medication with a similar or worse risk profile.

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