Safety of glucocorticoids – clinical trials

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ABSTRACT
Clinical trials published over the last 5 years support the main conclusion of a comprehensive review on glucocorticoid safety published in 2006: there is little if any solid evidence to support the fear that low-dose glucocorticoids are associated with significant toxicity when used appropriately in inflammatory rheumatic diseases. In fact, most of the recent randomised-controlled research underlines the influence of the underlying inflammatory process in the occurrence of “adverse events” such as osteoporosis, fractures, hypertension and glucose intolerance. This “confounding by indication” is inherent to the field and questions the validity of the observational data, that seems to drive currently common concepts about low-dose glucocorticoid toxicity. Decisive conclusions cannot, in any case, be achieved at this stage because the clinical trials available are of limited duration and dimension and have not been designed specifically to address toxicity.

Toxicity with low-dose glucocorticoids needs to be kept under careful clinical surveillance while we expect such trials to be produced. Meanwhile, the risks of stopping these medications, even on longstanding well controlled disease, need also to be considered, as underlined by withdrawal trials recently published.

Introduction
In 2006, we reported the results of an extensive review of the toxicity of low-dose glucocorticoids (GCs) in rheumatoid arthritis (RA), including unpublished data from four randomised clinical trials (1). The review was focused on RA, but publications regarding other conditions were also reviewed and integrated. The interpretation was submitted to consensus among all co-authors as cooperating experts.

Two main general conclusions were derived from this comprehensive work:

• “Few of the commonly held beliefs about the incidence, prevalence, and impact of glucocorticoid side-effects are supported by clear scientific evidence”.

• “Safety data from recent randomised controlled clinical trials of low-dose glucocorticoid treatment in RA suggest that adverse effects associated with these drugs are modest, and often not statistically different from those of placebo”.

Taking all available information together the expert panel felt that the evidence for increased risk of adverse effects with low-dose GCs was strong enough to justify regular checks on some: osteoporosis, Cushingoid symptoms, adrenal crisis on glucocorticoid withdrawal, growth retardation in children, new onset of diabetes mellitus in subjects at risk or worsening of glycaemia control in patients with the disease, cataracts and glaucoma, peptic ulcer (in combination with NSAIDs) and hypertension. The panel considered that many (if not most) of the side-effects commonly attributed to GCs, such as myopathy, psychosis, hyperlipidemia, and atherosclerosis, were probably very rare, if observed at all, with low-dose therapy.

This may seem an over-optimistic perspective. It is fair to recognise that such conclusions were based more on the absence of evidence for a connection than on reassuring evidence that such a connection does not exist. Recognising this, the report underlined the paucity of good quality evidence, and did not conclude that low-dose GCs are safe but rather that “The overall fear of GC toxicity in RA, as quoted in textbooks and review articles, is probably overestimated, based on extrapolation from observations with higher dose treatment”.

Most of these fears are rooted in observational data, with a variety of doses and regimens, in a variety of different diseases. Very little actually is supported in clinical trials.
Observational studies in this area are bound to reflect confounding by indication, which may undermine the validity of their results. In fact, many inflammatory rheumatic diseases are, per se, associated with an increased incidence of conditions that have been considered side-effects of the GCs used to treat them. Rheumatoid arthritis, independently of GCs, is recognised as a very significant risk factor for cardiovascular disease (2, 3), hypertension (4, 6), osteoporosis and fractures (6, 7) and decreased insulin sensitivity (8). In fact, there is overwhelming evidence that chronic inflammatory diseases in general are associated with a significant increase in cardiovascular risk which seems mediated mostly by the inflammatory process itself (9). The same is probably true for osteoporosis (10). A recent study found a surprising prevalence of 7% of vertebral fractures in children with a variety of auto-immune rheumatic diseases before starting GCs treatment (11). Manifestations of systemic lupus erythematosus (SLE) have even more in common with potential toxicity of GCs: atherosclerosis, hypertension, osteoporosis, psychosis, myopathy, aseptic bone necrosis.

Therefore, rheumatic inflammatory diseases carry an increased risk of these adverse events and will also be associated with an increased probability of GC use, which is also associated with the adverse outcome. Higher severity of disease implies higher risk of such events, and also a higher probability of GC use and in higher doses. It may be that the suppressing effect of GCs on disease activity may actually diminish the incidence of the adverse event compared to what would be observed in its absence. However, the risk may still be higher than would be seen in the absence of disease or in the presence of disease that is milder than considered necessary to warrant GCs. In such cases, observational studies would suggest that GCs are doing harm even if they are actually reducing the risk induced by the underlying condition.

Separating the influence of the disease from that of GCs is an impossible task for observational studies at their current stage of methodological development: we can never be sure that all relevant confounding factors have been considered in multivariate analysis – only the ones we are aware of! Observational studies are certainly essential to identify concerns of toxicity, especially those associated with long-term therapy. However, a definite clarification of the role of medication versus co-factors can only be achieved through clinical trials where randomisation overcomes potential confounding introduced by disease severity and other variables affecting the prescription and its effects. Moreover, a definite trial would need to be focused on toxicity (rather than on efficacy), adopt a strict and standardised strategy for identification and registry of side-effects and be of sufficient size and duration to allow for the importance of time and cumulative dose to be reflected. Despite the publication of recommendations for the design of clinical trials on GCs (12), no such a trial has been published and, until then, definitive conclusions on the real toxicity of low-dose GCs cannot be reached.

We scrutinised relevant information from clinical trials and experimental studies published in the six years since the preparation of our previous report (1).

General scope of toxicity
A randomised clinical trial, which would have achieved the inclusion criteria for that review, was published just after the work was finished (13). In this study, 250 patients with early RA were randomised to receive, at the start of their initial treatment with a disease-modifying drug, either 7.5 mg/day prednisolone or no prednisolone for 2 years. The results confirmed significant benefits of this low-dose GCs therapy, both in terms of disease activity and radiographic progression. The authors concluded that this treatment was safe, with very few adverse events leading to withdrawal in both groups. These general conclusions are coincident with the trials included in our 2006 review. And the same holds true when it comes to specific adverse effects: drug treatment was withdrawn temporarily or permanently in 26 patients in the prednisolone group and in 24 patients in the no-prednisolone. Most withdrawals were attributed to the associated DMARD, and prednisolone was judged to be the cause in 5 patients only: one withdrawal due to each of the following causes – diabetes, proteinuria, striae and ecchymoses, weight gain and cushingoid appearance, and weight gain. It is worth noting that 110 of the 119 patients allocated to prednisolone persisted on this therapy for the two years of the trial duration.

Similarly reassuring results were found in the CARDERA trial (14). Four hundred and sixty-seven patients with RA were randomised to receive prednisolone (initial dose 60 mg/day tapered at 34 weeks) in addition to MTX with or without cyclosporine. GCs were associated with significant benefits in terms of disease activity and erosions over two years of follow-up, without “significant differences in serious adverse events between the groups”. In this study, GCs therapy was, however, associated with a significant increase in the risk of developing hypertension (OR: 2.16) and with a more pronounced bone loss at the hip.

Limited data on toxicity of high-dose iv pulse methylprednisolone (IV MP) was offered by a trial (15) of 44 RA patients randomised to receive methotrexate (MTX), alone or in combination with IV MP (1000 mg) or infliximab on day 0 and weeks 2, 6, 14, 22, 30, 38, and 46. This is, to our knowledge, the longest trial of pulsed GCs in RA, with a daily-dose of over 30 mg prednisolone-equivalent/day: most clinicians would expect serious toxicity. The rate of remission was similar with IV MP and infliximab and significantly superior to MTX alone. Regarding safety, the authors summarise in stating that treatment was generally very well tolerated and no severe side effects were observed, except 1 case of MTX-related pneumonitis. The rate of infections was similar in the three groups.

Osteoporosis
Trials published on GCs are too small and/or short in duration to allow definitive conclusions regarding osteoporosis and, especially, fractures. However, the
results of all these RCTs show a much lower rate of GCs-induced bone loss than would be expected from current general reviews and recommendations. In the BARFOT study, discussed above (12), there was no difference in bone loss between those receiving 7.5mg/day prednisolone over two years and those who did not! This was further analysed in 150 patients with markers of bone metabolism (16). The authors concluded that low-dose prednisolone actually avoided bone loss induced by rheumatoid inflammation at the hip. This was not observed on the spine where a small but significant negative impact of prednisolone on vertebral BMD was observed in this subgroup (not significant in the overall population). A strong positive correlation was found between bone resorption markers and disease activity, as indicated by CRP and IL-6, emphasising the importance of inflammation in osteoporosis.

Similar results have been reported from the BeSt trial (17) – the combination strategy including highdose GCs was not associated with increased bone loss over one year in early RA. Also in this study, joint damage and joint damage progression were associated with high BMD loss.

Such observations emphasise the link between disease activity and generalised bone loss. These observations underline the need for caution when interpreting the cause of bone loss observed in the presence of GCs.

Strategies to prevent glucocorticoid-induced osteoporosis have been recently reinforced with the demonstration that yearly zoledronic acid (18) is an efficient alternative. The results with prasertone in SLE were less optimistic (19).

**Cardio-vascular and glucose metabolism**

Analysis of data from the BeSt trial offers some interesting insights into the relationship between rheumatoid arthritis, GCs and hypertension (4). Results show a striking positive correlation between indices of disease activity and levels of both systolic and diastolic blood pressure, not only at baseline but throughout the two years of the study. The group receiving combination therapy including high-dose prednisolone did not show a tendency towards higher blood pressure. Actually, the diastolic blood pressure was significantly reduced in this group, compared to sequential monotherapy. Interestingly, the use of anti-TNF stood out with a remarkable beneficial effect upon blood pressure, exceeding the improvement expected on the basis of disease activity alone. Such observations again suggest the existence of important interactions between the inflammatory response, blood pressure regulation and cardio-vascular risk.

The impact of GCs upon atherosclerosis and endothelial function in patients with concomitant inflammatory disease was addressed in a subset of 67 patients within the BARFOT study referred above (20). In the prednisolone group, 21 patients were treated for 2 years and 13 continuously for five years before vascular evaluation (intima-media thickness, intima-media area and atherosclerotic plaque formation of the carotid and flow-mediated dilation of the brachial artery). Neither of these measures differed between patients treated with and without prednisolone. Prednisolone was, in this trial, associated with higher levels of total cholesterol and a trend towards higher blood pressure (for treatment longer than 4 years). Age, blood pressure, HDL cholesterol and creatinine were correlated with the vascular parameters. The impact of disease activity was not addressed in this report.

A very elegant study, now in press (8), demonstrates that RA disease activity is strongly related with abnormalities in glucose metabolism, irrespective of GCs. Cumulative dose of GCs also had an independent negative effect on glucose tolerance and insulin sensitivity.

**Infection**

A systematic literature review looked at the evidence regarding the risk of infection associated with low-dose GCs (≤10mg/day prednisolone equivalent) in RA (21). Of the 1310 screened reports, the literature analysis identified 15 eligible reports. Of the eight reports that studied all types of infection, six articles found no association between risk of infection and low-dose GCs. One of the reports described a significant association severe infections (OR = 8 [1–64]) and another indicated a dose-dependent association: RR = 1.32 for doses <5 mg/day 1.95 for doses between 6 to 10 mg/day.

Of three trials evaluating the risk of bacterial infection: one showed an increased risk (HR = 1.7 [1.5–2.0]) while two did not, in doses up to 10mg/day. None of three studies studying postoperative infection risk nor any of the two reports looking at herpes zoster found a significant association between infection risk and low-dose GCs. The authors of this systemic literature review stress the scarcity of good quality data preventing sound conclusions.

However, their results are globally in line with the conclusion of a meta-analysis of 71 trials involving about 2000 patients with various underlying diseases: GCs exposure was associated with an overall relative risk of infection of 1.6 (22) but the risk was not significantly increased with doses below 10 mg/day, especially in rheumatic diseases.

**Chronotherapy**

The studies on the newly developed modified release tablets for prednisolone, have not added significantly to our knowledge on the safety of GCs because there was no placebo-group in the trials. These tablets allow the medication to be released in the GI tract at about 2 am, if taken orally at around 10 pm, thus delivering the drug at the time when circulating endogenous glucocorticoids are at their lowest levels and inflammatory mediators, such as IL-6 are at their highest. Of note, the fact that night-time prednisone over 12 months did not induced significant changes in the corticotropin-releasing-hormone test in comparison to immediate release prednisone administered in the morning (23). Such observations indicate that prednisolone need not be given in the morning to avoid the risk of serious unbalance of the HPA axis. The overall safety profile was found to be similar between both preparations in a 13-week trial whose primary endpoint was duration of morning stiffness (24).
Osteonecrosis
Osteonecrosis has been considered a rather common side-effect of GCs, especially in SLE. An interesting trial including 60 newly diagnosed SLE patients (25) suggests that warfarin may reduce by around 30% the incidence of osteonecrosis of the femoral head (ONF) induced by high-dose GCs. Although the rate of osteonecrosis seems extremely high in this study (33% of 58 control hips over five years), the results offer hope that such a serious adverse event can be partially prevented.

The adverse effects of stopping GCs
Common wisdom and even authoritative recommendations (26) suggest that GCs should be used for the lowest possible dose and tapered as soon as possible. Although the same argument could be presented to every single drug in every single medical condition, it is interesting that GCs seem to deserve it much more than any other medication. This, obviously, reflects the fear of side effects but it also incorporates some disregard for the positive effects of GCs. Stopping GCs has a cost: the loss of benefit, including well-established disease modification in RA. This has been overcome in most reviews by the statements that: 1. The benefits of GCs are short lived and 2. Stopping GCs is followed by a rebound flare. The latter argument is strange: Most clinicians would agree that disease aggravation after stopping a given drug is a sign that it was working! Do we ever question it with any other drug but GCs?

The former argument has been clearly dismissed by objective evidence of efficacy of longterm low-dose GCs in RA, in randomised withdrawal trials. In the report by Tengstrand et al. (27), fifty-eight patients with RA treated with 5–7.5 mg prednisolone daily for at least 2 years were randomised either to withdraw or to continue GC treatment. The patients were followed prospectively for 2 years with respect to disease activity, functional ability and bone mineral density of the lumbar spine and hip. 15 of the 26 patients failed to withdraw GC because of increased disease activity and deteriorating function. A higher mean DAS28 during the study (as observed in those who tried and failed to stop GCs) was associated with loss of bone mass in the trochanter. The group that continued with unchanged GC treatment did not deteriorate in BMD during the 2 years: in fact their Z-scores improved significantly. It is probable that these good results on BMD were favoured by supplementation with calcium and vitamin D. Pincus et al. (28), also found that stopping longterm GCs (used in stable doses of 1 to 4 mg/day in patients with stable controlled disease), was followed, in a large proportion of patients, by increased inflammatory activity.

Taken together, the results of these two trials suggest that tapering or withdrawing GC treatment is not an obligatory path: the decision must take into consideration the risks as well as the benefits of continuing the medication for the individual patient. Withdrawal should not be forced at the cost of higher disease activity and all the associated adverse consequences associated with it.

Clinicians may also wish to consider, in this setting, recent suggestions that longterm GC use is associated with a reduced risk of lymphoma in RA (29).

Conclusions
The evidence to support clear conclusions regarding the toxicity of GCs remains limited in quantity and, especially, in quality. Although RCTs are indispensable to avoid the confounding by indication that inevitably degrades the validity of observational studies, they also have limitations, in terms of duration, inclusion criteria and, above all, lack of focus and methodological rigor regarding toxicity. However, this is the best evidence we have, and, as far as low-dose therapy, it looks a lot more reassuring than current medical opinion would suggest.

These are, nevertheless, questionable data and interpretations, and definite conclusions will not be possible before properly designed trials focused on safety issues are available.

References
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