Layman's version of "Safety of low- to medium-dose glucocorticoid treatment in rheumatoid arthritis: myths and reality over the years"

Tania Santiago and Jose Antonio P. da Silva

Annals of the New York Academy of Sciences, 2014

Introduction

Glucocorticoids (GCs) are a cornerstone in the treatment of rheumatoid arthritis (RA). Although research has proven GCs to be very effective, the possible risks of adverse events means that the lowest possible dose for the shortest time should be used. It is difficult however, to tell whether possible adverse events (AEs) are associated with using the GCs, or with the disease itself. This is, for instance, the case when looking at the possible AEs of osteoporosis, glucose intolerance and cardiovascular disease.

The aim of this study is to:

1) provide an update of evidence from recent research using randomized controlled trials (RCTs) studying the safety of GC treatment in RA

2) present an overview of the problems encountered with two different research study-designs in considering the safety of GC treatment in RA. Firstly randomized clinical trials (RCTs) and secondly nonrandomized observational studies.

In a Randomized clinical trial investigators randomly allocate participants who fit the criteria they have chosen for the study (e.g. age, female, length of time the participant has had RA,) into e.g. *treatment groups* and non- treatment *control groups.* The *treatment group* receives the intervention that is being studied, whereas the *control group* does not receive the intervention, instead they may be given a placebo (i.e. a fake intervention). The results are assessed by comparing the outcomes in the *treatment group* compared with the *control group*.

In a nonrandomized **observational study** investigators cannot randomize participants; the treatment each participant receives is not determined by the investigator; the outcomes may have an element of bias because e.g a participant is also clinically depressed and loses weight - is the weight loss because of the intervention or because of the depression, or perhaps something else?

Evidence from recent trials

In 2006, a review by Jose Antonio P. da Silva, which looked at 4 randomized controlled trials (RCTs), concluded that safety data from the research suggests that adverse events caused by low-dose GC treatment (less than 7.5 mg per day) are modest, and often not very different from adverse events patients experienced when given a placebo treatment (a fake treatment).

Since the review of the 4 RCTs, 3 additional clinical trials also provided data about the safety of low- and medium- dose GCs. Both the treatment group and the placebo-group had some patients who reported new-onset diabetes (less than 1% in both groups), osteoporosis, and cardio-vascular effects, but the numbers of patients were too low to be statistically significant. That means these adverse events are not caused by the GC treatment but by random chance. In these trials, low-dose GCs are associated with an increase of body weight and glaucoma (3 patients of the 93 patients developed glaucoma in the prednisone group, as opposed to none in the control group) over 2 years. However, in one study, the weight gain under GC treatment was explained as due to recovery of weight lost

earlier in the disease process, when the disease was more active. Another factor is that when the disease-activity is less, the patient's physical mobility will increase, which could promote weight loss. Therefore, further studies are needed to e.g. explore body weight change in RA when using GC treatment.

Where is the evidence for fear coming from?

The outcomes of adverse events because of GC treatment in both RCTs and the observational studies are uncertain.

RCTs of GCs in RA are of limited size and duration, are designed for efficacy and frequently demonstrate inconsisting reporting of safety outcomes. Many studies report conflicting findings on GC treatment in RA: the risk of fracture in patients with RA remained (significantly) high after excluding patients who had taken oral GCs. That means that RA itself is a risk factor for osteoporosis fracture, irrespective of GC use, and despite the argument that GC treatment can cause bone mineral density loss, resulting in a higher risk of fractures. Results of other studies highlight a complex interplay of three factors: 1) RA affects negatively certain metabolic pathways such as glucose, osteoporosis and cardiovascular events, 2) GCs work effectively on the disease-activity which may diminish that negative effect, but 3) GCs itself impairs these metabolic pathways.

Conflicting results of RCTs and a lack of clear research data, also for other adverse events caused by GC use, leads to the conclusion that many of the negative but commonly held beliefs about the incidence, prevalence and effects of low-dose GC use are not supported by clear evidence. However, the limitation of the available clinical trials need to be taken into account when analyzing the evidence: absence of evidence for serious toxicity is not the same as evidence that such toxicity is absent. *RCTs tend to underestimate the true risk of GC treatment*.

The outcomes of **observational studies** may also be difficult to interprete. Outcomes of observational studies can be uncertain, which can be attributed to different dosages, comorbidity (if a patient has more than one disease), adherence (does the patient take the drug as prescribed?) recruitment methods etc. GCs are mostly used by patients with an active disease, therefore the chance of poor outcomes of these patients is higher, but that outcome may not be attributed to the GC treatment. In a study all negative risk factors, found from the data, had a higher prevalence among GC users than in patients that did not use GCs, such as smoking, educational level, disability, comorbidity etc. Therefore, it is not possible to judge whether the poor outcomes in the group of patients that used GCs was attributed to the GC treatment or to the negative risk factors. *Observational studies tend to overestimate the true risk of GC treatment*.

Conclusion

There is no evidence that low-dose GCs are associated with significant toxicity in early RA over 2 years, besides weight gain and probably glaucoma (this is not to say that we have evidence that there is no significant toxicity). These conclusions are not definite, therefore further RCTs about the safety of GCs are required.