Short-term and Long-term Safety of Glucocorticoids in Rheumatoid Arthritis

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Abstract

Despite over 60 years of use, glucocorticoids continue to be a controversial therapy in rheumatoid arthritis (RA). This stems largely from their measured and their perceived toxicity. However, a paucity of top tier evidence from clinical trials or very carefully controlled observational studies leads to limited evidence supporting potential causal relations between low-dose glucocorticoids and adverse outcomes. Several new studies have contributed to an improved understanding of these associations and they are reviewed here along with highlights from the older body of literature examining these important outcomes.

Although glucocorticoids are very commonly used in Rheumatoid Arthritis (RA), both symptomatic and serious adverse effects dampen patient and physician enthusiasm, particularly for long-term use. Despite these concerns, there is a paucity of data on low-dose glucocorticoid toxicity in RA.1 Most studies of glucocorticoid toxicity tend to be observational. Although the European League Against Rheumatism (EULAR) Task Force on glucocorticoids formulated recommendations for the monitoring of low-dose glucocorticoid-related AEs, many adverse effects, such as psychological or behavioral toxicities, are particularly difficult to systematically assess.2

Several large retrospective reviews suggest that long-term, relatively low-dose glucocorticoid use is a significant independent predictor of numerous, potentially serious adverse events.3,5 Lending further credibility to causality, a glucocorticoid-adverse event association was both dose- and time-dependent (Fig. 1) in a retrospective cohort of RA patients.4 Both cumulative and mean glucocorticoid dose are independently associated with adverse events. There appear to be two distinct dose-related patterns of adverse events6: 1. a “linear” increase with increasing dose was found for a Cushingoid phenotype, ecchymosis, leg edema, parchment-like skin, and sleep disturbance, and 2. a “threshold pattern” describing an elevated frequency of events beyond a certain threshold value was observed for glaucoma, depression and listlessness, and increases in blood pressure. Dosages of 5 mg/day or more were associated with epistaxis and weight gain. A very low dose glucocorticoid threshold was seen for cataract (< 5 mg/day) (Fig. 2).

Whereas less serious adverse effects (e.g., skin thinning and Cushingoid appearance) are often of great concern to RA patients, more debilitating serious toxicities, such as vertebral fractures and cataracts, may be initially unrecognized or asymptomatic.7 What follows is an overview of the most common adverse effects that have been associated with glucocorticoids in RA. International recommendations provide guidance on how to most safely use glucocorticoids.8

Osteoporosis, Osteonecrosis, and Myopathy

Glucocorticoid-induced osteoporosis (GIOP) is a ubiquitous complication of protracted glucocorticoid therapy.9 Comparison of studies examining bone effects of glucocorticoids is made difficult by the differential timing of glucocorticoid initiation, variable dosing regimens, use of different bone mass measurement techniques, and disparities between the sites of measurement.

Observational studies of RA show a mean first-year loss of bone ranging from 1.5 to 20% at the dose range of less than or equal to 10 mg/d prednisone.10 With continued use, bone loss remains greater than normal but decreases to 1.5
to 3% per year dependent on dose, in subsequent years. Although a decline in bone mineral density (BMD) is strongly correlated with fracture risk and BMD is the best overall predictor, the rate of bone turnover, bone quality, and other factors also play important roles and help explain how fractures may occur very early in the course of glucocorticoid use before a significant decline in BMD has occurred. At very low doses, glucocorticoids may actually prevent bone loss in some RA patients because of their inhibitory effects on pro-inflammatory cytokines that modulate osteoclast activity as well as their beneficial effects on functional status, which promotes more weight-bearing activities. However, several studies have failed to demonstrate an association of low-dose glucocorticoid use with low axial BMD, even in the setting of an increased fracture rate. In a 2008 meta-analysis, low-dose glucocorticoid use resulted in a moderate worsening in lumbar BMD compared with controls, whereas femoral BMD was not significantly decreased. When examining the effect of glucocorticoid dose on FRAX calculated fracture probabilities for very low-dose exposure (less than 2.5 mg daily of prednisolone or equivalent), the probability of a major fracture decreased by about 20% compared to the FRAX calculated probability, but for doses between 2.5 mg and 7.5 mg daily, an unadjusted FRAX value can be used as it is routinely calculated by FRAX. Although the risk is clearly less, the presence of biochemical changes in bone remodeling with very low-dose oral or intra-articular therapy argues against a “safe” glucocorticoid dose from the standpoint of bone.

Given the inconsistencies in BMD studies and the knowledge that fractures in glucocorticoid-treated patients occur at a higher BMD and are dependent on other factors, it is necessary to examine long-term studies that evaluate actual fracture incidence. In a large cohort of RA patients, 34% of more than 300 women on a mean dose of prednisone of 8.6 mg/d had a self-reported fracture within 5 years of follow-up. Two case-control studies of hip fractures in patients both with and without RA showed a 2-fold increased risk even after adjusting for the presence of RA. However, randomized controlled trials (RCT) in RA have not confirmed an increased rate of fracture. Although none of these trials have been large or long enough to fully clarify the magnitude of the fracture risk, some have not systematically assessed fractures outcomes in all patients, and in at least one, patients were allowed to use bone protective medications.

Osteonecrosis of bone is a significant problem in patients receiving high-dose glucocorticoids. Osteonecrosis is more strongly associated with peak dose of glucocorticoid rather than cumulative dose, perhaps owing to osteocyte and osteoblast apoptosis. The presence of anti-phospholipid antibodies contributes to osteonecrosis independent of glucocorticoid use. Osteonecrosis is seldom seen with lower doses of prednisone used to treat RA.

Similar to osteonecrosis, the occurrence of myopathy in patients receiving glucocorticoids is very rare at the lower-doses used in RA. Muscle strength and walking speed may be slightly reduced in RA patients on glucocorticoids compared to those not taking them, but this does not account for the

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**Figure 1** Probability of remaining free from adverse events (adverse events) over time while on low-dose (< 5 mg), intermediate dose (5 to 10 mg), or high-dose (> 10 to 15 mg) prednisone compared with a control group.

**Figure 2** Two distinct dose-related patterns of adverse events were observed from self-reported health problems relating to dose and duration of glucocorticoid intake in unselected patients with rheumatoid arthritis from routine practice (N = 1,066). A. Linear pattern, B. Threshold pattern. (Adapted from: Huscher D, Thiele K, Gromnica-Ihle E, et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis 2009, 68:1119-1124.)
differences in overall disease activity and severity. Based on small studies, fluorinated glucocorticoid preparations, such as triamcinolone, may be more strongly associated with myopathy than prednisone.21 In general, myopathy attributable to prednisone requires a higher dose and longer duration of treatment.

**Hypertension, Fluid Retention, and Cardiovascular Disease**

RA patients with essential hypertension require closer surveillance of blood pressure, and may need modification of their anti-hypertensive regimens while on glucocorticoid therapy. In some studies, glucocorticoids at even low or moderate doses have been associated with hypertension, but this may be a reflection of channeling bias due to RA disease severity.22 Glucocorticoids can cause sodium retention. In patients receiving less than 10 mg/day, age and elevated pre-treatment blood pressure likely better explain significant hypertension than the use of glucocorticoids.

Although several observational studies suggest that glucocorticoids at doses of greater than 10 mg/day adversely affect serum lipid profiles, a national sample from the United States was unable to confirm this association.23 Moderate- to low-dose glucocorticoids had no significant adverse effect on lipoprotein levels if other risk factors were controlled.24 Some studies even have suggested that glucocorticoids reverse an unfavorable lipid profile.25 Low-dose glucocorticoid therapy in RA patients generally was associated with an increase in HDL, without increasing LDL or triglyceride—changes which may be favorable.26,27 To date, RCTs have not identified low-dose glucocorticoid therapy as an additional risk factor for dyslipidemia.

Another difficult-to-study potential toxicity of low-dose glucocorticoids is the development of premature atherosclerotic vascular disease. Increasing attention to the importance of accelerated atherosclerotic disease in RA has raised interesting questions about the role of chronic inflammation on the vascular endothelium.28 Although at least one study shows increased carotid plaque and decreased arterial compressibility in RA patients on glucocorticoids,29 there are insufficient data to confirm an independent risk in patients on low-dose glucocorticoids, in particular. A systematic review of low-dose glucocorticoid therapy,30 somewhat in contrast with the lipid findings, found that in four out of six studies low-dose glucocorticoid therapy was associated with major cardiovascular (CV) events, including myocardial stroke, mortality, and a composite index of CV events. Nonetheless, one of the largest and most carefully conducted cohort studies did not find an increased cardiovascular risk with doses less than 7.5 mg prednisone per day.31

**Skin Thinning, Ecchymoses, Striae, Acne, and Hirsutism**

Even at the low dose, skin thinning and ecchymoses represent one of the most common glucocorticoid adverse events. In a self-reported health survey assessing the dose and duration of glucocorticoid intake,6 an increased frequency of bruising was reported even in patients taking less than 5 mg/day of glucocorticoids. Cushingoid appearance manifests as moon facies, truncal obesity, and “buffalo hump,” and is very troubling to patients, but is uncommon at doses below the physiologic glucocorticoid replacement range. Moon facies develop in slightly over 10% of patients receiving even short-term low-dose therapy. Steroid acne and, to a lesser extent, hirsutism and striae are other undesirable dermatologic side effects that can occur even at lower doses. Glucocorticoids also impair wound healing.

**Gastrointestinal Ulceration and Bleeding**

Although glucocorticoids are considerably less toxic to the upper gastrointestinal (GI) tract than nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids slightly increase the risk of adverse GI events such as gastritis, ulcers, and gastrointestinal bleeding. The increased risk of glucocorticoids on GI events is very small. Glucocorticoids are frequently used concurrently with NSAIDs in RA, and the combination synergistically results in a higher risk of GI adverse events. Glucocorticoids cause a nearly 2-fold increased risk of GI adverse events among NSAID users, and the combined use of NSAIDs and glucocorticoids results in more than a four-fold increased risk of GI adverse events over nonusers.

**Infections**

No studies have adequately explored the risk of infection in patients treated with low-dose glucocorticoids. The association of glucocorticoids with infectious adverse events becomes an even greater concern if glucocorticoids are used in combination with biologicals.32 In the Consortium of Rheumatology Researchers of North America (CORRONA) registry who were prescribed methotrexate, TNF antagonists or other disease-modifying anti-rheumatic drugs, low-dose prednisone use overall was not associated with risk of infection.33 In a nested case control study, the adjusted relative risk (RR) increased from 1.10 (< 5 mg/day) to 1.85 for doses greater than 20 mg/day. While the RR was low at 1.20, the absolute risk was high with one additional infection seen for every 13 patients treated with glucocorticoids for 1 year.34 In a study of RA patients comparing infection risk of biologic therapies to non-biological DMARDs, glucocorticoids were the factor most strongly associated with serious infection outcomes.35 A meta-analysis of 71 controlled clinical trials involving over 2,000 patients randomly allocated to systemic glucocorticoids in the setting of different diseases showed the relative risk for the overall infectious complications was 1.6 (95% CI 1.3-1.9). The rate was not increased in patients given a daily dose of less than 10 mg or a cumulative dose of less than 700 mg of prednisone.36 Similarly, a different systematic review identified 15 studies assessing infection risk of low-dose glucocorticoid therapy in RA patients and...
Glucocorticoid users with diabetes mellitus will commonly have higher blood glucose levels while taking glucocorticoids. However, it is uncommon for frank diabetes to develop as a result of glucocorticoid therapy. Metabolic syndrome is more common in RA, but it has not been proven that low-dose glucocorticoids are clearly associated with this outcome.  

A significant concern of chronic glucocorticoid use is Hypothalamic-Pituitary-Adrenal (HPA) insufficiency. HPA insufficiency is both dose- and duration-specific. Adrenal suppression can be detected in 6 weeks at 10 mg/day or 15 mg/day in 4 weeks. Spontaneous recovery of the HPA axis is normal in patients on less than or equal to 5 mg of prednisone. Subphysiologic doses (< 7.5 mg/d) given for long-term periods also may lead to HPA blunting.

Psychiatric and Mood Disorders  
Patients on even low-dose glucocorticoid therapy report a slight increase in their overall sense of well-being, which appears to be independent of improvement in disease activity. Symptoms of akathisia, insomnia, and depression are also occasionally observed in patients taking low-dose therapy. Memory impairment, particularly in older patients can occur even at low doses. Daily split-dose therapy, in particular, tends to be troublesome because the evening dose promotes sleep disturbances. True glucocorticoid psychosis is distinctly uncommon at doses less than 20 mg/d of prednisone. In a meta-analysis of 11 uncontrolled studies involving 935 adult patients, severe psychiatric reactions were reported in approximately 5% of glucocorticoid-treated patients, and mild to moderate reactions occurred in about 28%.

Cataracts and Glaucoma  
Posterior subcapsular cataracts are a well-described complication of prolonged glucocorticoid use. There is likely no minimal safe dose with respect to this complication, and reports exist of cataract formation even with inhaled glucocorticoid preparations. However, cataracts occur uncommonly in patients taking less than 10 mg/d for less than 1 year. Nearly a third of RA patients taking a mean dose of 8 mg/d for an average of 7 years developed cataracts. Cortical cataracts also have also been associated with glucocorticoid use. In addition to cataracts, glucocorticoid-treated patients can develop increased intraocular pressure, which can lead to visual disturbances. The development of frank glaucoma, particularly with low-dose therapy, is rare and tends to appear in patients who are otherwise genetically predisposed. In the German National Database, glaucoma was found in 3.4% of RA patients who were not exposed to glucocorticoids in past 12 months versus 4.6% of RA patients who were exposed to prednisone doses of 7.5 mg/day or more for more than 6 months.

Conclusions  
The ability to differentiate bad outcomes attributable to glucocorticoids from those occurring due to RA severity, co-therapies, or other comorbidities confounds potential glucocorticoid-adverse event associations. A strong physician selection bias for glucocorticoid use exists, since physicians are more inclined to treat more severe RA patients with glucocorticoids (i.e., confounding by indication). The use of glucocorticoids at variable points in the RA disease course and limited data defining the "threshold" dose for particular adverse events further hinder interpretation of the limited existing data. The few RCTs of glucocorticoid monotherapy in RA suffer from a deficiency found in most clinical trials; namely, insufficient numbers of patients, inadequate duration of follow-up, and non-systematic ascertainment of adverse events. Thus, we are left with limited information on which to make clinical judgment and extrapolations from literature in other disease states. In summary, even at the lower doses commonly used in many parts of the world as an important adjunct to RA management, growing evidence urges cautious monitoring and use of potential preventive strategies to avoid many of these often serious adverse outcomes.

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