Glucocorticoid use in rheumatoid arthritis: Benefits, mechanisms, and risks

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Introduction

Glucocorticoids have long been recognized to have beneficial effects in rheumatoid arthritis (RA) (1, 2). Several clinical trials over the last decade have further documented the efficacy of glucocorticoids in relieving inflammation and in preventing radiographic erosions in early RA (3-5). Additionally, research has yielded new insights about the cellular mechanisms responsible for these perceived beneficial effects (6, 7). Despite potential short term benefits, there is a lack of demonstrated long-term efficacy as well as concerns about short and long-term toxicity. Although these concerns have limited enthusiasm for glucocorticoids by many patients and practitioners, in the U.S. it is estimated that 44% to 75% of RA patients use glucocorticoids (8, 9). Confusion and controversy may relate to the fact that toxicity reports are also limited by only modest data quality and quantity. Given growing clinical and basic science evidence supporting the efficacy of glucocorticoids for the treatment of rheumatoid arthritis, their use may further increase. In this review we will examine the latest data supporting the benefits and risks of glucocorticoid use in RA.

Effects of glucocorticoids on RA disease activity and radiographic progression

In 1995, Kirwan conducted a large randomized controlled trial comparing the effects of low-dose glucocorticoids on joint destruction in early RA. Oral prednisolone, 7.5 mg daily was compared with placebo, over a 2-year period in 128 patients. Other treatments including nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs) were allowed. After two years, the number of new erosions was significantly lower in the prednisolone-treated group. This group also had significant improvements in joint inflammation and pain, but only during the first year of treatment with glucocorticoids (5). A follow-up study of this cohort, published in 1998, reported that joint destruction resumed in the prednisolone group after therapy was discontinued (10), which differed from the results reported in the COBRA trial (11) noted below.

The COBRA study (Combinatietherapie Bij Reumatoide Artritis) was a double-blind, randomized trial that compared a combination regimen of prednisone, methotrexate, and sulfasalazine to sulfasalazine alone, in 155 patients with early rheumatoid arthritis. In the combination treatment group, the patients were given 60 mg/day of prednisone for the first week, tapered over the next 6 weeks to 7.5 mg/day and ultimately discontinued after 28 weeks, as well as methotrexate 7.5 mg/day for 40 weeks. Both patient groups received sulfasalazine 2 gm/day. After 28 weeks of the study, the combination therapy group had significantly lower radiographic joint damage and disease activity scores compared to the sulfasalazine only group. Radiographic damage scores were also lower in the combination therapy group at weeks 56 and 80. However, disease activity differences between the two groups gradually diminished, and were no longer significant after the prednisone was discontinued at 28 weeks. Also, no further changes in clinical status occurred after methotrexate was stopped (4). A 4-5 year follow-up assessment of these patients showed continued suppression of radiographic joint damage in the combination therapy group, leading to the conclusion that initial treatment of early RA patients with high dose prednisone with subsequent tapering may provide long-term protection against joint damage (11). The high doses used in this study, while provocative for their role

in disease modification, are infrequently used in most settings due to a heightened risk of even short-term toxicity, as noted below.

The most recently published investigation of the disease modifying effects of glucocorticoids, the Utrecht study, evaluated the use of prednisone 10 mg/day in early RA (defined by a disease duration of less than 1 year). In this double-blind, placebo-controlled, 2-year study, 41 patients received 10 mg/day of oral prednisone and 40 patients received a placebo. At 12 and 24 months, there was statistically significantly greater improvement in grip strength and the 28-joint tenderness scores in the prednisone group than in the placebo group. Use of physiotherapy, NSAIDs, paracetamol, and intra- articular steroids was also significantly lower in the prednisone group. However, at 24 months no difference was seen between the two groups in health assessment questionnaire (HAQ) scores, morning stiffness, joint swelling, or C-reactive protein levels. Radiographic scores of the hands and feet for erosions and joint space narrowing were significantly lower in the prednisone group at both 12 and 24 months (3). This study represents one of the very first efficacy investigations of glucocorticoid monotherapy and is of importance as it demonstrated significant reductions in radiographic progression with prednisone alone. Despite its important contribution, the findings of the Utretcht study have limited applicability since most rheumatologists, including the authors, do not recommend glucocorticoid monotherapy as the only disease modifying therapy for patients with RA, and would include another DMARD, such as methotrexate or a biologic agent. Furthermore, some have suggested that even 10 mg of prednisone is not really a "low dose", this term being generally applied to doses of less than 7.5 mg per day (12).

Mechanism of action of glucocorticoids

Over the past decade many new insights into the cellular mechanism of action of glucocorticoids have been provided (6, 7). Glucocorticoids diffuse freely across the cell membrane into the cytoplasm and bind to the glucocorticoid receptor. This glucocorticoid/receptor complex then binds reversibly to a specific DNA promoter or to suppressor sites in the nucleus, resulting in either the production or inhibition of the transcription of anti-inflammatory proteins.

One of the major proteins for which production is upregulated by glucocorticoids is lipocortin. The anti-inflammatory effects of lipocortin are mediated through its inhibition of phospholipase A2. Phospholipase A2 converts membrane-bound phospholipids into arachadonic acid, with the subsequent intracellular production of prostaglandins, leukotrienes and oxygen radicals.

In addition, by stimulating lipocortin production, glucocorticoids also inhibit production of several other proinflammatory cytokines including interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-3 (IL-3), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) (13). Glucocorticoids have also been shown to inhibit the production of collagenase, elastase, and plasminogen activator in macrophages (14). Glucocorticoids also stimulate the production of a protein that controls the cyclooxygenase-2 (COX-2) gene and downregulates COX-2 activation in inflammatory cells (13). Decreases in T-cell number and function are other proposed mechanisms of the beneficial effects of glucocorticoids in RA (15). More insights regarding the mechanisms by which glucocorticoids exert their effects may lead to their more rational, effective, and safe use.

Adverse effects

General considerations

Following the Nobel Prize-winning discovery in 1948 by Hench and colleagues, glucocorticoids initially were widely used for RA. However, within several years the classical adverse effects of glucocorticoids – including an increased prevalence of hypertension, diabetes, infection, cataracts, and osteoporosis – were frequently noted, particularly at the higher doses being then used, and this markedly limited glucocorticoid use (16). Based on the steadily accumulating evidence demonstrating symptomatic relief of joint inflammation and the potential for glucocorticoids to modify RA disease severity (17), there has been a relative revival of their use. Nonetheless, glucocorticoid treatment of patients with RA should be initiated with caution and conducted under close observation in order to avoid adverse effects. Several strategies are recommended to minimize the occurrence and severity of glucocorticoid-associated adverse events (Table I). Although not all patients will require every screening test or prophylactic agent, these guidelines should be considered where clinically appropriate. Eschewing the use of high dose regimens, the goal is symptomatic improvement and potential disease modification with the lowest possible effective dose (16). Once improvement is achieved, tapering to a more physiologic dosage (less than 7.5 mg/d) should be strongly considered in most patients.

Glucocorticoid-induced osteoporosis

Probably the most common, yet one of the most poorly treated, potentially preventable serious complications of glucocorticoid therapy in RA is glucocorticoid-induced osteoporosis (GIOP). Bone loss is estimated to occur in 50% of patients treated with glucocorticoids for >6 months (18). Bone loss and fractures occur most commonly in postmenopausal women, but men and premenopausal women are not spared these complications (19). Although rheumatoid arthritis itself causes regional and generalized bone loss, glucocorticoids exert an independent deleterious on bone that is dose-dependent (20, 21). A retrospective medical record review of rheumatologists at a large U.S. academic medical center examined osteoporosis risk factor management in 236 RA patients taking glucocorticoids at a mean daily dosage of 8.8 mg ± 3.5. Only 23% of the patients studied had undergone bone density testing, and calcium and/or vitamin D were noted on only 25% of the medication lists. Forty-two percent (42%) of the patients were taking prescription medications for osteoporosis. It is worth noting that men, pre-menopausal women, and pa-

Table I. Strategies for the prevention glucocorticoid adverse events.

Adverse effects	Diagnostic studies	Preventative intervention
Glucocorticoid-induced osteoporosis	DEXA scan	Calcium, vitamin D Risk factor modification* Bisphosphonates Calcitonin Hormonal therapy Teriparitide (?)
Osteonecrosis	Bone radiographs MRI	Early diagnosis and reduced weight bearing
Ophthalmologic (cataract, glaucoma)	Annual eye examination	None known
Gastrointestinal (peptic ulcer disease, diverticulitis)	Monitor CBC Stools for occult blood	Avoid use of glucocorticoids with NSAIDs Proton-pump inhibitors
Cardiovascular (dyslipidemia, atherosclerosis, hypertension)	Lipid profile Monitor blood pressure	Lipid-lowering agent Antihypertensives
Diabetes mellitus	Regular glucose monitoring	Diet and weight control
HPA suppression	Co-syntropin stimulation test	Slower tapering of glucocorticoids
Infectious	PPD, Chest radiograph	Prophylactic antibiotic therapy

HPA: hypothalamic pituitary axis; *weight-bearing exercise, smoking cessation, moderation of alcohol and caffeine intake.

tients with at least one comorbid condition were less likely to undergo bone density testing or receive a prescription medication for osteoporosis treatment (9). Highlighting an international need to better translate research into practice, these findings were actually better than other reports evaluating the same issue in different settings (22, 23).

The deleterious effects of glucocorticoids on bone occur early with varying estimates of 1.5 – 20% losses of bone mineral density (BMD) in the first 6 months after starting therapy, followed by a slower rate of 1-3% per year thereafter (24, 25). The initial bone loss is primarily trabecular bone from sites such as the lumbar spine and greater trochanter. Cortical bone loss from the femoral neck also occurs, but at a slower rate (26). Cortical deformities of the spine were seen in 25% of patients receiving glucocorticoids on a daily basis in one large Dutch study (27). Beyond the increased risk of fractures that results from lowered BMD, glucocorticoids can rapidly increase the fracture risk by other mechanisms such as their direct toxic effect on osteoblasts and osteocytes. Using the General Practice Research Database (GPRD), Van Staa and colleagues studied 244,235 oral glucocorticoid users and 244,235 age- and gender-matched controls and documented an increased risk of all types of fractures beginning at 3 months, including hip fracture (RR 1.61, 95% CI 1.47-1.76) and vertebral fracture (RR 2.60, 95% CI 2.31-2.92) (28).

Glucocorticoids exert negative effects on bone health via multiple mechanisms. GIOP occurs primarily due to decreased bone formation and secondarily as a result of increased bone resorption. Glucocorticoid inhibition of bone formation occurs by an overall decrease in osteoblast number and function. Osteoblast reduction is secondary to a decrease in osteoblastic cell replication and differentiation and the increased apoptosis of mature osteoblasts. Also, glucocorticoids inhibit osteoblast synthesis of type I collagen, the major component of the bone extracellular matrix (29). The increased bone resorption which occurs in GIOP appears to involve the receptor of the activator of the nuclear factor-kB ligand (RANK-L) and osteoprotegerin. RANK-L is an osteoblastic signal that binds to an osteoclast receptor and, in association with colony stimulating factor (CSF)-1, induces osteoclastogenesis. Osteoprotegerin is a decoy receptor that binds RANK-L, preventing it from binding to the osteoclast receptor and subsequent osteoclastogenesis. Glucocorticoids increase the expression of RANK-L and CSF-1 and decrease osteoprotegerin production by osteoblasts ultimately resulting in bone resorption (29).

Glucocorticoid also induces osteoporosis by increasing renal calcium elimination and decreasing intestinal calcium absorption, leading to a negative calcium balance (30). The development of this state of negative calcium balance has long been thought to lead to the development of secondary hyperparathyroidism. The theory has been refuted more recently, however, since serum levels of parathyroid hormone in patients treated with glucocorticoids have not been demonstrated to be in the hyperparathyroid range (31). More importantly, patients exposed to glucocorticoids develop a bone disease fundamentally characterized by decreased bone remodeling, whereas increased remodeling is found in hyperparathyroidism (32).

Glucocorticoids also lead to decreased sex steroid production which contributes to the development of GIOP. Some of the reported mechanisms include: decreased gonadotropin output, reduced ACTH release from the anterior pituitary leading to the reduced production of adrenal androgens, and the direct inhibition of testicular and ovarian steroidogenesis (33).

Osteonecrosis

Although there are many causes for osteonecrosis, glucocorticoids represent a major risk factor. Osteonecrosis is most frequently seen in patients with systemic lupus erythematosus taking prednisone doses greater than 15 mg/day (34), and is uncommon in patients taking the glucocorticoid doses most frequently used in RA (< 10 mg/day) (35, 36). Previous treatment with high doses of glucocorticoids, even if only for brief periods, has also been associated with the development of osteonecrosis (37).

Ophthalmologic side effects

The development of posterior subcapsular cataracts is a well recognized complication of long-term glucocorticoid use, although study data supporting this complication is less robust for low dose therapy (38). Cortical cataracts have also been associated with glucocorticoid use (39). Cataract formation has been reported with both oral and inhaled steroids and with dosages as low as 5 mg/day (40). Wolfe and colleagues reported a significantly increased risk of cataracts in their analysis of 819 RA patients taking 5 mg/day of prednisone for 3 yrs (OR = 2.7, 95% CI 1.7 – 4.4) (41). Increased intraocular pressure with minor visual disturbances also occurs in chronic glucocorticoid users (42). Glucocorticoids are not thought to be a direct cause of glaucoma; however, they may hasten the onset in those already at increased risk. In light of the ocular risks, it is advisable that all long-term glucocorticoid users have periodic eye examinations.

Gastrointestinal side effects

Glucocorticoid use has been associated with an increased risk of adverse gastrointestinal (GI) complications including ulcers, bleeding, and perforation (43). The relative risk directly attributable to low dose glucocorticoids is small, being estimated to be between 1.1 and 1.5 (44). The most significant increase in risk occurs with the combination of glucocorticoids and NSAIDS, for which case studies have shown a 2- to 4-fold higher risk of an adverse event (43-45). Rheumatoid arthritis itself may increase the risk of peptic ulcer disease and its complications (46). In one study using the UK General Practice Research Database as its source, glucocorticoid users were found to a relative risk of 1.8 (95% CI, 1.3 – 2.4) for an upper GI complication in comparison to non-users (47).

In addition to upper GI issues, a recent study evaluated the association between sigmoid diverticular abscess perforation and glucocorticoid use. In this case-controlled study, 64 patients were compared with 320 controls matched for age, sex, geographic location, and socioeconomic status. The study revealed that a rheumatologic diagnosis was significantly more common in the cases than in the controls (48% vs 17%; $p < 0.001$). A significantly higher proportion of cases than controls were receiving glucocorticoids (16% vs 0.6%; $p < 0.001$) and NSAIDs (42% vs 26%; $p = 0.008$). After multivariable adjustments, glucocorticoid treatment was strongly associated with diverticular perforation (OR 31.9; 95% CI 6.4 – 159.2; $p < 0.001$), as was a diagnosis of a rheumatic disease (OR 3.5; 95% CI 1.9 – 6.7; $p < 0.001$) (48).

Cardiovascular side effects

Chronic glucocorticoid use has been associated with dyslipidemia and atherosclerosis in several conditions including systemic lupus erythematosus (SLE), asthma, and organ transplant recipients (49-52). In lupus patients, the adverse lipid profile effects appear to occur only at prednisone doses greater than 10 mg/day (53).

Several studies have suggested that RA patients have increased atherosclerotic disease and mortality due to cardiovascular events (54-57). Increased cardiovascular deaths in RA patients are thought occur due to endothelial damage and hypercoagulability as a result of chronic inflammation. Studies evaluating the effects of glucocorticoids on lipids and atherosclerosis in RA patients have yielded mixed results, with reports of beneficial, neutral, and adverse effects (58-60). At this time, the existing evidence does not show a strong association between low-dose glucocorticoids and cardiovascular disease in RA.

Increased hypertension has been observed in about 30% of patients using glucocorticoids (61, 62). Fluid retention has been postulated to partially account for this observation, although the full mechanisms involved remain unclear and are likely to be highly dose-dependent (62). The risk of hypertension with glucocorticoid use appears to be greatest with doses greater than 10 mg/day (61). Blood pressure should be closely monitored and aggressively treated in patients with pre-existing hypertension, cardiac, or renal disease receiving concomitant glucocorticoid therapy.

Metabolic and endocrine side effects

Hyperglycemia and diabetes mellitus are potential complications of even low dose glucocorticoids. Persons at the highest risk for these adverse effects include those with existing glucose intolerance and those who are obese, elderly, or have a family history of diabetes. The Utrecht study evaluated the use of prednisone 10 mg/day over 2 years in 41 patients with early RA and compared the results to 40 placebo-treated patients. Serum glucose measurements significantly increased in the prednisone group from 92 ± 11 mg/dl to 106 ± 34 mg/dl ($p = 0.01$). Hyperglycemia as defined by the World Health Organization developed in 2 patients in the prednisone group and in 1 in the placebo group (3).

An increased risk of the need to initiate hypoglycemic drugs is seen in patients who take glucocorticoids (63). Glucocorticoid-induced diabetes usually responds to dose reduction and may fully reverse after cessation of glucocorticoid use (64). In general, all RA patients receiving glucocorticoids should have their glucose levels checked prior to the initiation of therapy and periodically thereafter.

Long-term glucocorticoid treatment also commonly causes hypothalamic-pituitary-adrenal (HPA) suppression with secondary adrenal insufficiency. Although not fully described and understood, this is thought to occur after the use of as little as 10 mg/day of

prednisone for 4 to 6 weeks. HPA suppression may occur more rapidly with higher doses of glucocorticoids or with twice-a-day dosing. Symptoms of adrenal insufficiency after glucocorticoid use include arthralgias, myalgias, fatigue, nausea, vomiting, and hypotension. In cases of suspected glucocorticoid-induced adrenal insufficiency, a co-syntropin stimulation test may help to confirm the diagnosis. In general, when tapering patients to the reduced glucocorticoid dosages typically used in the treatment of RA (≤10 mg/day), the safest approach is a slow dose reduction of approximately 1 mg every 1 to 2 weeks (65).

Infectious disease as a side effect

Glucocorticoids increase susceptibility to all classes of infectious agents in a dose-dependent fashion (66). The increased risk of infections is believed to occur through multiple alterations in host defenses including altered cellular and humoral immunity, decreased phagocytosis and intracellular killing, and the inhibition of cytokine release. Infections with atypical organisms and herpes zoster appear to occur more commonly in persons taking glucocorticoids (36, 67). *Pneumocystis carinii* infections may occur more frequently in patients using moderate doses of glucocorticoids (68), although confounding by indication (i.e., sicker RA patients who are already more prone to infectious complications are more likely to be treated more aggressively with glucocorticoids) is a concern with this and other putative infectious toxicities believed to be associated with glucocorticoid use. Studies evaluating the incidence of infections in RA patients taking low dose glucocorticoids have not shown significantly increased risks of infection (41, 69). However, in the current era of RA treatment, patients will likely be receiving other immunosuppressive agents in addition to glucocorticoids, making it imperative that one maintain a high index of clinical suspicion for infection in patients with unusual symptoms.

Conclusions

Glucocorticoids continue to be an important and highly prescribed component of the treatment regimen for patients with rheumatoid arthritis. An increasing body of literature from well-designed clinical trials supports the efficacy of glucocorticoids for both short-term symptomatic relief and as a disease-modifying agent. Basic science research is also yielding increasing insights regarding the mechanisms by which glucocorticoids cause both beneficial and deleterious effects. One of the most serious and well-described adverse effects of glucocorticoids is osteoporosis. Unfortunately, this also remains the most under-treated potential complication. Glucocorticoids have other potential negative side effects; however, the data supporting the true incidence of what are popularly upheld to be adverse events at the low doses commonly used in the contemporary treatment of RA is scant and, in many cases, controversial. Thus, balancing the benefits of symptomatic improvement and disease modification with the true risk of side effects remains the major challenge of glucocorticoid use in RA. Through judicious use and with close monitoring for potential side effects, lower doses of glucocorticoids can be safely used by many RA patients.

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