
Low dose glucocorticoids in early rheumatoid arthritis

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ABSTRACT

The use of glucocorticoid therapy in the treatment of rheumatoid arthritis [RA] remains controversial. There has been much data accumulated over the years describing both the risks and benefits of acute and chronic glucocorticoid therapy. Initially there was significant enthusiasm for this type of therapy given the extent of the anti-inflammatory effects. However, use was then modified as chronic therapy with higher doses was associated with frequent reports of important safety concerns. More recently low dose glucocorticoid therapy (e.g. ≤ 5 mg prednisone per day) is being reconsidered in particular for patients with early disease. This paper will review the historical experience with higher dose therapy along with the evolving evidence of an improved benefit to risk ratio with the advent of concomitant therapies to minimize some of the more problematic adverse events associated with chronic use of even low dose glucocorticoid therapy. It is suggested that with appropriate monitoring and careful concomitant prophylactic therapy to prevent osteoporosis, adjunctive therapy using low dose glucocorticoids along with the appropriate disease modifying anti-rheumatic drug may be a reasonable treatment plan for select patients.

Introduction

The treatment of early rheumatoid arthritis (RA) remains controversial. Use of TNF alpha blockade in patients with relatively severe early disease does not lead to substantially improved responses compared with methotrexate alone (1,2). The benefit to risk ratio of all disease modifying antirheumatic agents (DMARDs) requires their judicious use, tailored to the individual patient.

Use of glucocorticoids in early RA has remained controversial. Although well recognized to offer symptomatic improvement, and short term benefit on radiographic disease progression, glu-

cocorticoids are still not regarded as DMARDs. Potentially severe adverse effects associated with chronic administration including weight gain, diabetes, hypertension, cataracts, and osteoporotic fractures have led many to recommend their use in long-term treatment of RA be restricted to patients with early disease. Unfortunately, limited data are available to assess the benefit/risk profile of low dose (prednisone < 7.5 mg daily or equivalent) glucocorticoid therapy in early rheumatoid arthritis, within 2 years of diagnosis. We summarize here the evidence for and against use of low dose glucocorticoids in patients with early RA, and preventive measures for glucocorticoid-induced osteoporosis.

Benefit of low dose glucocorticoids in early RA

Early clinical trials suggested glucocorticoids were "disease modifying" by retarding progression of radiographic damage (3-5). Two failed to show a difference between glucocorticoid treatment and comparators, aspirin and chloroquine, but neither was placebo controlled (3, 4). Despite this evidence, these drugs became widely used in the 1950s, generally in doses of 20-40 mg prednisone, because of their observed acute clinical efficacy (6). When used chronically significant toxicities were recognized, and it was concluded that the adverse events associated with glucocorticoid use generally outweighed any benefits (7). By the late 1950s, clinicians were taught that these drugs had no place in the long term management of RA, except as possibly "bridge therapy" for severe clinical flares or for acute life-threatening manifestations of vasculitis.

During the 1970s some investigators reported and clinicians observed that low dose glucocorticoids [prednisone 5 mg daily] could be chronically administered, with favorable clinical efficacy and an acceptable adverse event profile that differed markedly

from that observed with high-dose therapy. A randomized controlled trial by Harris *et al.* indicated that 5 mg prednisone had greater efficacy than placebo over 24 weeks, although differences were not statistically significant, possibly due to small numbers (8). A meta-analysis by Gotzsche *et al.* demonstrated benefit of "low dose" glucocorticoids, typically prednisone 10 mgs daily, for symptomatic relief in patients with early RA but also those with long term disease (9).

Prior to introduction of the new DMARDs, three randomized controlled trials examining glucocorticoid treatment in patients with RA assessed radiographic progression (10-13). The Kirwan trial reported benefit of oral low dose prednisolone (7.5 mg daily) over 2 years treatment in patients with < 2 years disease duration (10). Despite relatively brief symptomatic benefit over several months, fewer erosive changes (by the Larsen score) were observed in prednisolone treated patients compared with progressive joint destruction with placebo. During the third year, when prednisolone was tapered and withdrawn, the rate of yearly progression in erosion scores approached that of the control group (14) while levels of N propeptide of type III procollagen and pro-MMP-1, lower during prednisolone treatment, increased (15). Overall 71% of patients were receiving second line agents.

Boers *et al.* demonstrated that combination therapy with high dose prednisone, methotrexate and sulfasalazine was superior to sulfasalazine alone, by clinical responses and radiographic analyses in patients with a median disease duration of only 4 months (11). Despite withdrawal of prednisone and methotrexate at weeks 28 and 40, respectively, less radiographic progression was evident in the combination therapy group at week 28; this benefit persisted through week 80 (16). Mottonen *et al.* demonstrated greater efficacy over 2 years with combination therapy with sulfasalazine, methotrexate, hydroxychloroquine, and 5 mg prednisolone daily than sulfasalazine alone in patients with early RA (4 months disease duration) (12). Further analyses

indicated that a delay of three months was associated with greater long-term radiographic damage in patients receiving monotherapy which was not observed with combination therapy (13). Both trials indicate that combination therapy is more efficacious than monotherapy in patients with early RA, but it is not possible to tease out the specific benefit offered by glucocorticoid administration.

Rau *et al.* confirmed the report by Kirwan *et al.* in another patient population with early RA, demonstrating less radiographic progression in those receiving low dose glucocorticoid therapy (17). These observations have remained controversial, however, as subanalyses of patients receiving glucocorticoids [10 mg prednisone daily] in randomized controlled trials of recently approved DMARDs have failed to show additional benefit on radiographic progression with this concomitant therapy, even in those with early disease (1, 18). And Paulus and colleagues were unable to demonstrate benefit of low dose prednisone treatment [5 mg daily] on radiographic progression in a 3 year blinded controlled trial comparing etodolac to ibuprofen in patients with a mean disease duration of 3.6 years (19).

Recently, Van Everdingen *et al.* compared treatment with prednisone 10 mg daily as monotherapy versus non-steroidal anti-inflammatory agents (NSAIDs) only over two years, using a design which is unlikely to be repeated now that more DMARDs are available (20). Although sulfasalazine was allowed as "rescue" therapy after 6 months, few patients in both groups added DMARD treatment. The 41 patients receiving prednisone showed significantly better symptomatic improvement over the first 6 months than the 40 receiving NSAIDs; with significantly less radiographic progression at 12 and 24 months. However, more adverse events were reported in patients treated with glucocorticoids, including a 3 kg increase in body weight versus none, hyperglycemia in 2 versus 1, and new vertebral fractures (confirmed by x ray) in 5 versus 2 patients in the NSAID group. Gluco-

corticoid administration was associated with better efficacy and more adverse events, although most patients did not report adverse events over 2 years treatment (20).

The above studies indicate that glucocorticoid use in early RA should be re-examined. In two databases in patients with early RA, Paulus *et al.* reported prednisone use in 40-45% of patients (21), Sokka and Pincus in 60% of patients at study visit, including use at some time during the course of disease in 87% (22). Rates of hypertension, diabetes and cataracts appear to be similar in patients receiving low dose prednisone compared with the general population, but this has not been documented (23). However, the major concern with low dose prednisone involves bone demineralization, discussed in greater detail below.

Glucocorticoid-induced osteoporosis

Glucocorticoid-induced osteoporosis is a major problem in patients with RA, as local effects of inflammation and disuse and/or immobilization of joints result in juxta-articular osteopenia. Systemic inflammation, mediated by inflammatory cytokines including TNF-alpha, IL-1 beta and IL-6, increases the differentiation and activation of osteoclasts (24) which leads to increased bone loss and consequently more systemic osteoporosis. Post-menopausal hormone changes also contribute.

Even low dose glucocorticoid administration results in more trabecular than cortical bone loss, and leads to an increased risk for vertebral fractures and some types of hip fracture (24-30). Unfortunately, reported studies of the effect of glucocorticoid administration on bone mineral density are confounded by inclusion of different patient populations (pre- and post-menopausal women and men) as well as a variety of inflammatory diseases. Michel *et al.* followed 395 patients with RA for an average of 6.7 years; those receiving prednisone > 5 mg daily had a 34% probability of sustaining a vertebral fracture over 5 years (25). Low risk groups included men and patients

receiving < 5 mg prednisone daily.

Verhoeven and Boers demonstrated that non-RA patients taking higher doses of glucocorticoids (20 mg prednisone daily) lost bone mineral density faster than those with RA, whether or not they were receiving low doses of glucocorticoids (7 mg prednisone daily) (30). They concluded that bone loss in RA was related both to extent and severity of disease as well as concomitant doses of glucocorticoids. Saag *et al.* reported more effects on bone mineral density with higher daily doses of prednisone (29). In 62 patients with RA, Laan *et al.* showed more rapid loss of trabecular than cortical bone, both in the lumbar spine and distal radius in the 26 receiving low dose glucocorticoids daily (26). Laan *et al.* confirmed these original findings in another group of 40 RA patients, approximately half of whom initiated prednisone 10 mg daily with subsequent taper between weeks 12-24 (27). In patients receiving prednisone, trabecular bone loss without change in cortical bone mineral density occurred. Interestingly, when prednisone treatment was discontinued, some reconstitution of trabecular bone mass was observed.

Recently Haugeberg *et al.* studied a population based cohort of RA patients over 2 years, 48% of whom were receiving glucocorticoids and 37% concomitant anti-resorptive therapy, including bisphosphonates, calcitonin or hormone replacement (31). Current use of glucocorticoids (dose undefined) was independently associated with an increased risk for loss of bone mineral density in the total hip, although this risk was decreased in patients receiving anti-resorptive therapies. The data suggest that bone mineral density loss attributed to glucocorticoid administration appears to plateau after one year of treatment (24, 32). Although by no means definitive, available data indicate that low dose glucocorticoids (< 5 mg prednisone daily) appear to be less deleterious than higher doses (33).

Treatment of glucocorticoid-induced bone loss

A variety of treatments have been attempted to prevent bone loss due to

glucocorticoid administration, including: salmon calcitonin, bisphosphonates including etidronate, residronate, alendronate, and synthetically derived parathyroid hormone peptide (34-37). Every other day use of glucocorticoids has not prevented bone mineral density loss (36). Concomitant treatment with calcium and vitamin D are important, but do not increase relative bone mass (34, 35). Further addition of calcitonin decreases bone loss, without resulting in a positive effect on femoral neck or distal radius bone mineral density (38-40). In comparison, concomitant administration of bisphosphonates appear to improve as well as prevent glucocorticoid induced osteoporosis (41-47). Treatment with alendronate significantly reduced radiographically confirmed vertebral fractures by 90% over 2 years in patients receiving prednisone 7.5 mg daily, approximately 1/3 of whom had RA (47). In patients treated with glucocorticoids daily, 40% of whom had RA, risidronate administration significantly reduced vertebral fractures by 70% (46). In postmenopausal women with RA receiving prednisolone 2.5 mg daily, 2.5 mg risidronate prevented bone loss in the lumbar spine but not femoral neck (45).

Together these data suggest that when glucocorticoids are administered to patients with RA, concomitant treatment with a bisphosphonate should be considered in addition to ensuring an adequate intake of vitamin D and calcium. These studies have not specifically examined patients with RA, much less early RA, and only one restricted enrollment to patients receiving low dose glucocorticoids. Although administration of bisphosphonates has been demonstrated to significantly decrease loss of bone mineral density, other potential adverse effects of glucocorticoid therapy including development of cataracts, hyperglycemia, hypertension and increased incidence of infections, are not affected (28).

The debate regarding use of low dose glucocorticoids in early RA

Based on the data reviewed, low dose glucocorticoid treatment results in less

erosive disease in the first two years of RA, presumably by inhibiting osteoclast activity at the pannus-bone interface. Yet this same glucocorticoid dose has also been shown to result in loss of general bone mineral density, also modulated by osteoclast differentiation and activation. The biologic processes that govern these opposing effects may well be different. Although unproven, it is possible that the beneficial effects of low dose glucocorticoid therapy on bone erosions may act synergistically with demonstrated effects of the available DMARDs in inhibiting radiographic progression.

The debate regarding use of low dose glucocorticoids in early RA continues. Boers reviewed compelling arguments for the use of glucocorticoid therapy in RA, citing the early studies in the UK (3-5) and the landmark study by Harris *et al.* demonstrating that discontinuing treatment resulted in disease flares (8, 48, 49). More importantly, persistent radiographic benefits observed in patients receiving combination therapy in the COBRA trial argue that we should positively consider the use of low dose glucocorticoid therapy in early RA. Not only may beneficial effects on disease progression persist after stopping treatment, but many of the observed adverse effects are limited, manageable and reversible, and may be less than in patients with less disease control.

Morrison and Capell argue against this position, extending arguments presented by others (50, 51). They pointed out that many studies indicate that initial symptomatic benefits attributed to glucocorticoid therapy are not sustained (9, 52-56). These findings are supported by the two meta-analyses cited above (9, 29). Even reported efficacy of 'induction' and or 'bridging' therapy with glucocorticoids in several randomized controlled trials does not convincingly argue that they offer additional clinical benefit (10-15, 54-57).

At this time, many potential adverse effects of low dose glucocorticoid treatment are treatable. There appear to be major differences in outcomes with long-term glucocorticoid administration in low doses compared with even

limited use of high doses. (29,48). Perhaps the best analogy is presented by Pincus *et al.* comparing low dose glucocorticoid therapy to an evening glass of wine that may prolong life, whereas high doses are similar to an entire bottle of wine, that is harmful (23). Physiologic, rather than pharmacologic, doses may address potential deficiencies in the hypothalamic-adrenal-pituitary axis, with inadequate adrenocorticotrophin hormone responses to corticotrophin-releasing hormone in RA being documented by several groups (58-60).

Estimates of the benefits and risks of glucocorticoid use will vary among individual patients and individual clinicians, affected by variables such as age, disease severity, co-morbidities, skin fragility, and intrinsic assessment of risk. The physician's responsibility is to provide the best information for an informed decision by the individual patient and individual physician.

While van Everdingen *et al.* demonstrated less radiographic progression with low dose prednisone – approximately 8 modified Sharp units/per year compared with 15 units/year in the placebo group – this apparent benefit did not approach the observed effect with any of the presently available DMARDs. Treatment with methotrexate, leflunomide, and the three TNF-alpha inhibitors have all demonstrated progression on the order of 0-2 Sharp units/year (1, 2, 61). As these DMARDs have shown better radiographic outcomes, it would seem logical that glucocorticoids should only be used as adjunctive therapy. Although shown to provide improvement in signs and symptoms, use of glucocorticoids in early RA has not been associated with increased remissions or "cure". It is also not clear whether low dose glucocorticoid therapy improves radiographic outcomes unless it is used soon after diagnosis and over at least 2 years' treatment.

Conclusions

In view of data summarized above, there appear to be clear benefits in improving the signs and symptoms of active RA with low dose glucocorti-

coids in many patients, and demonstrated structural benefit evident for at least two years in patients with early disease. How important that structural benefit is in the context of currently available DMARDs including methotrexate, leflunomide, TNF-alpha blockers, IL-1ra, or sulfasalazine remains to be determined. As many of the potential adverse effects of low dose glucocorticoids can be treated and osteoporosis obviated with concomitant therapy with bisphosphonates, it is logical that in the "right" patients use of low doses of prednisone is justified. Within the first 2 years of disease, short term use of low doses of glucocorticoids appear to offer more benefit than risk, but this benefit appears to diminish over time. Unfortunately it is not clear what the exact range of this "window of opportunity" is to recommend how long such therapy should be continued.

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