Corticosteroids in the management of early and established rheumatoid disease

Corticosteroid use in rheumatoid arthritis (RA) remains something of a dichotomy to most rheumatologists. How do we reconcile the promise of disease-modifying activity in early disease with the possibility of significant and potentially long-lasting adverse effects? Is the benefit of the former sufficiently marked to justify the latter? In addition, since the debate concerning corticosteroid use in RA was re-ignited some years ago, ideas about the management of RA have moved on. More intense use of disease-modifying anti-rheumatic drugs (DMARDs), either singly or in combination, and the proliferation of anti-tumour necrosis factor (TNF-α) agents have had an enormous impact on how we now manage RA [1, 2]. Where do corticosteroids fit into our current treatment strategies?

RA has also emerged as an independent risk factor for atherosclerosis over and above those more traditionally recognised (e.g. hypertension, diabetes mellitus, weight and lipid profile) as a link between systemic inflammation and accelerated vascular disease has been demonstrated, both in the general population and in RA [3–5]. Corticosteroids are likely to improve the inflammatory profile but will this be enough to offset their negative effect on traditional risk factors?

Patient choice and opinion, central to the day-to-day management of their disease, is also of prime importance and is a factor often overlooked in the corticosteroid debate [6].

Many of these issues remain difficult to answer but we attempt here to revisit [7, 8] and review the status of corticosteroids in the management of RA in the light of current published evidence.

Corticosteroid use in early RA

The effect of corticosteroids, on both clinical and radiographic parameters, in early RA has been the subject of considerable research effort in recent years [9–14]. However, differences in methodology, variability in the type and dose of DMARD used, differences in corticosteroid dose (5–60 mg) and variable duration (28 weeks–2 yrs) of therapy combine to make it difficult to compare the studies directly and to draw firm conclusions regarding efficacy and toxicity of corticosteroids in early RA.

Efficacy

In a randomized double-blind controlled trial over 2 yrs, Kirwan and the Arthritis and Rheumatism Council Low-Dose Corticosteroid Group [9] reported that progression of erosive change was reduced in early RA (<2 yrs) in those treated with prednisolone (7.5 mg/day) compared with the placebo group. The study, however, was uncontrolled for DMARD use and a variety of agents were prescribed by the supervising clinicians [intramuscular (IM) gold, 8%; penicillamine, 30%; sulphasalazine, 26%; methotrexate, 4%; others, 3%], which may have had a bearing on subsequent X-ray progression. In addition, the two study groups were not particularly well-matched, with the placebo group containing a higher proportion of erosive patients at the outset. Initial clinical benefit was not maintained into the second year of the study and joint destruction resumed when prednisolone was withdrawn [15].

Boers et al. [10] have compared the effect of combination step-down prednisolone (initially high dose and then tapered and stopped at 28 weeks), methotrexate (stopped after 40 weeks) and sulphasalazine with sulphasalazine alone in early RA (<2 yrs) over 56 weeks. Again initial impressive clinical benefit was seen in the prednisolone group, but was not significant after the withdrawal of prednisolone. Analysis of the two groups at 28, 56 and 80 weeks showed that radiological progression was reduced in the combination therapy group. The contribution of methotrexate to reducing X-ray progression may have been significant in this study, but unfortunately a methotrexate/sulphasalazine arm was not included with the result that the true effect of prednisolone is difficult to extrapolate.

In the van Everdingen et al. [11] study of low-dose prednisolone vs placebo in early RA, 40 patients received placebo and 41 received 10 mg of prednisolone. After 6 months, sulphasalazine could be used as rescue—this design does not reflect current rheumatological practice. While radiographic improvement favoured the steroid group, adverse events including weight gain, hyperglycaemia and vertebral fractures were a problem in this group. Capell et al. [12], reporting on behalf of the West of Scotland Early Rheumatoid Arthritis Corticosteroid Therapy (WOSERACT) study, compared the effect of low-dose prednisolone (7 mg/day) compared to placebo on disease activity and X-ray progression in early RA (<3 yrs) in a randomized controlled trial (RCT) over 2 yrs. The study was controlled for DMARD as all patients received sulphasalazine at the outset, with the option of an alternative DMARD later if necessary. The two treatment groups were well-matched for all parameters at baseline due to the technique of minimization [16, 17] in the allocation process. No significant differences in radiological scores, clinical indices or laboratory measurements were observed at baseline or 2 yrs.

In a more recent double-blind, placebo-controlled trial over 2 yrs, Wassenberg et al. [13] reporting on behalf of the Low-Dose Prednisolone Therapy Study Group, compared the effect of prednisolone (5 mg/day) with placebo in early RA (<2 yrs) patients who were also started on DMARD therapy, gold sodium thiomalate or methotrexate, at baseline. There was no significant difference in the number of patients on each DMARD between the prednisolone and placebo groups. Radiographic progression was noted to be significantly less with prednisolone than placebo, and interestingly the greatest difference in progression rate was noted in the first 6 months of treatment. However, scrutiny of the baseline characteristics reveals a tendency (not reaching significance) towards more erosive disease in the placebo group, 76.7% compared with 71.3% in the prednisolone group. In addition, >50% of the patients were given gold as their primary DMARD whilst <40% received methotrexate which does not reflect most rheumatologists’ current practice.

Svensson et al. [14] assessed the efficacy of prednisolone (7.5 mg/day) vs placebo in early RA (≤1 yr) in a 2 yr randomized trial. The choice of DMARD was left to the treating physician. In the prednisolone group, 50% started methotrexate and 35%
received sulphasalazine, the corresponding values for the placebo group were 53 and 37%. The study group observed that radiographic progression of erosions was significantly less in the prednisolone-treated group. However, it is not clear if the study was adequately powered as the authors admit that no formal sample size calculation was performed. In addition, 43 patients were excluded from the study because they were considered to need corticosteroid therapy due to highly active disease. Thus, we have no information about a group likely to be highly erosive. Due to these methodological difficulties, the results obtained are difficult to interpret.

In the five recent low-dose prednisolone studies outlined above, there are methodological differences, variation in corticosteroid dose and duration, no uniformity regarding concomitant DMARD therapy and different X-ray scoring techniques used to assess progression of erosions. The definition of early RA itself is wide at between <1–3 yrs. Herein lies the challenge for the clinician. A pragmatic assessment may be that low-dose prednisolone is efficacious in the short-term in early RA, clinically and radiologically, but as yet there is no convincing evidence of sustained benefit which would radically alter routine practice.

**Toxicity**

The side-effect profile of corticosteroids has been well-documented since their earliest use in RA [18, 19]. Physicians are familiar with the characteristic features of weight gain and redistribution, skin thinning, osteoporosis, diabetes, hypertension, cataracts and mood disturbance, albeit at doses we would now consider unsuitable in the routine management of RA. However, little detailed evidence is available regarding the side-effect profile of low dose corticosteroids in early disease. Du Silva et al. [20] in their review of the safety of low-dose corticosteroid treatment in early RA conclude that safety data from recent trials suggests that adverse effects are modest and may not be significantly different from placebo. Others are less convinced [21, 22].

In fact, scrutiny of recent RCTs [9–14] reveals that adverse events have been variously monitored and reported. Significant weight gain was reported by Boers et al. [10], Capell et al. [12], Wassenberg et al. [13] but not by Kirwan et al. [9] or Svensson et al. [14] in the prednisolone-treated groups. Wassenberg et al. [13] noted a mean weight increase of 5 kg in the prednisolone group compared with a mean increase of only 0.3 kg in the placebo group, a finding likely to be deeply unpopular with patients, especially women. Blood pressure measurements remained stable as did bone density in those centers where dual energy X-ray absorptiometry was available. Blood glucose, when measured remained largely unaffected. Lipid profile was observed in only one study [12] and was stable over 2 yrs in those patients in whom it was recorded. Wassenberg et al. [13] assessed for cataract and glaucoma at the beginning and end of their study. Over the 2 yrs, three patients in the prednisolone group and none in the placebo group developed glaucoma. None of these trials systematically monitored effects on the skin. Whilst these are usually not considered serious by physicians, the reality of thin, fragile skin can be considerable morbidity for the patient. Such skin is prone to bruising, tearing and poor healing especially on the exposed areas of the forearm and shin.

The recent RCTs were powered to establish the efficacy of low-dose corticosteroids in early RA and the number of patients included reflect this. Most of the major studies [9, 10, 12, 13] include <100 patients in either their prednisolone or placebo arms and none of these have comprehensively documented weight, blood pressure, blood glucose, lipid profile, bone density/ fractures, infection rate, skin effects, etc. in all the patients. Much larger numbers of patients and a more detailed search for adverse events would be required to adequately assess toxicity. An analysis of non-responders, clinical and/or radiological, would also be valuable. In addition, some individuals may be more susceptible to particular adverse effects than others; age, gender and comorbidity might be relevant here. We should not, therefore, be complacent about the safety of low-dose corticosteroids in early RA.

**Corticosteroid use in established RA**

Corticosteroids are widely used for short/medium-term symptom relief during disease flares or induction of DMARD therapy in patients with established RA. Several studies using a variety of agents [e.g. oral prednisolone, IM or intravenous (IV) methylprednisolone] in combination with DMARDs support this practice [23–26] but conclude that the beneficial effects (clinical and radiological) are short-lived. One 6 month RCT of sulphasalazine combined with pulses of methylprednisolone or placebo showed no differences between the two groups [27]. In addition, Saag et al. [28] reported in a historical cohort of RA patients that low-dose (>5 mg/day) long-term prednisolone is associated with the development of adverse events in a dose-dependent fashion; although, they noted that disease severity was an important confounding factor.

Choy et al. and the Intramuscular Methylprednisolone Study Group [29] conducted a 2 yr RCT to establish the benefits of IM depomedrone vs placebo in patients with established RA (mean disease duration 16 yrs) whose disease was inadequately controlled by their existing DMARDs. After screening and consent, 91 patients were followed up. The steroid group (n = 48) received 120 mg IM depomedrone monthly (equivalent to ~5 mg prednisolone/day) whilst the placebo group (n = 43) received IM sterile normal saline. Improvement in disease activity was better initially in the steroid-treated group but by 6 months no difference remained. A small but significant reduction in progression of erosive change was noted in the steroid group. However, more adverse events occurred in those patients receiving steroids compared with placebo (55 compared with 42) and this was especially marked in those effects particularly associated with corticosteroid use (16 compared with two). The following were noted in the steroid group: hypertension (n = 4), facial swelling (n = 3), bruising (n = 3), osteoporosis (n = 2, one patient with vertebral fracture), diabetes mellitus (n = 1), myocardial infarction (n = 1), hypercholesterolaemia (n = 1) and iatrogenic Addison’s disease (n = 1). In contrast, only two placebo-treated patients had similar effects: hypertension (n = 1) and weight gain (n = 1).

The authors conclude, in the light of the significant side-effect profile, that despite the initial benefits of IM depomedrone, RA patients should not receive long-term steroids in addition to their DMARD(s) when their disease is sub-optimally controlled but should instead be treated with additional or alternative DMARDs. This view is supported by Durez et al. [30] who demonstrated in their short-term (6 weeks) randomized comparative study of IV pulse methylprednisolone vs infliximab in RA patients (median disease duration 10 yrs) with active disease despite methotrexate that TNF blockade is superior to pulsed steroid therapy.

**Does route of administration of corticosteroids matter?**

Furtado and colleagues [31] studied 69 RA patients with 6–12 swollen joints and randomized them to polyarticular injection (6–8) with triamcinolone or equivalent doses of IM triamcinolone. Over 6 months, the intra-articular (IA) group had significantly better American College of Rheumatology 20, 50 and 70 responses, and fewer adverse events than IM group. Blood
Corticosteroids and cardiovascular risk

Since the inception of most of the recent RCTs of low-dose prednisolone in the treatment of early RA, evidence revealing an association between accelerated atherosclerosis and RA has been accumulating and has been recently reviewed [5]. In addition to traditional risk factors such as hypertension, lipid profile, weight, etc. systemic inflammation is likely to play an important part in the aetiology of atherosclerosis. Conventionally, corticosteroids have been thought to exacerbate cardiovascular morbidity through negative effects on traditional risk factors, but the true direction of their effect is likely to be a more complex interaction, perhaps offset by their beneficial effects on inflammatory markers [32]. More work is needed before we can be sure. Clarification is particularly important for those of us who treat populations already at high cardiovascular risk [33].

Summary

The use of corticosteroids in RA is clearly something of a clinical balancing act, the key to which would seem to be judicious timing. Early initiation of DMARD therapy in new onset RA, with escalation as required to achieve disease control, is the essence of current good practice. Corticosteroids used early and for short periods, either orally or parentally, are an effective adjunctive measure. The caveat being that detailed information about their side-effect profile in this setting is lacking. In established RA, however, the evidence suggests that corticosteroids should be reserved for short-term use during flares of disease activity or as bridge therapy until the efficacy of a DMARD is established. Longer use cannot be justified as the clinical and radiological benefits are relatively small and adverse events not inconsequential.

Despite some continuing uncertainties and reservations, the results of recent RCTs have undoubtedly refined our use of, and subtly altered the position of, corticosteroids in the management of both early and established RA. They remain, therefore, one of our most powerful and useful therapeutic interventions and it is our responsibility to use them wisely.

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