EXTENDED REPORT

A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs

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Background: In rheumatoid arthritis (RA), intramuscular (IM) pulsed depomedrone expedites an immediate response to disease modifying antirheumatic drugs (DMARDs). Although IM depomedrone is also widely used to treat disease flares in patients treated with DMARDs, its effect on radiological progression has not been assessed.
Objective: To evaluate the benefits of 120 mg IM depomedrone versus placebo in patients with established RA whose disease was inadequately controlled by existing DMARDs.
Methods: In a 2 year prospective randomised controlled trial patients were assessed using the ILAR/WHO core dataset, disease activity score (DAS28), *x* ray examination of hands and feet scored by Larsen's method, and bone densitometry.
Results: 291 patients with RA were screened, 166 were eligible, and 91 consented and were randomised. Disease activity improved more rapidly in the steroid treated patients than with placebo, but after 6 months no difference remained. A small but significant reduction in erosive damage in the steroid group compared with placebo was also found. More adverse reactions occurred in the steroid treated group than in the placebo patients (55 *v* 42), especially those reactions traditionally related to steroids (16 *v* 2), including vertebral fracture, diabetes, and myocardial infarction. Hip bone density fell significantly in steroid treated but not placebo patients.
Conclusions: IM depomedrone improved disease activity in the short term and produced a small reduction in bone erosion at the cost of a significant increase in adverse events. Despite the initial benefit of IM depomedrone, when patients respond suboptimally to a DMARD they should not be given long term additional steroids but should be treated with alternative or additional DMARDs.

More than 50 years after steroids were first used to treat rheumatoid arthritis (RA)[1] their value is still controversial and their use varies.[2 3] Steroids provide short and medium term symptomatic improvements in RA.[4–6] Their long term value, particularly modification of the disease course, is less certain. Initial trials suggested that high dose steroids decrease erosive damage in established RA,[7] though the evidence was incomplete. Subsequent trials focused on disease modifying effects in early RA.[8] Influential work by Kirwan showed that low dose oral steroids combined with disease modifying antirheumatic drugs (DMARDs) reduce erosive damage in early RA.[9] This was confirmed by others; in particular, Boers *et al* showed that a rapidly reducing regimen of oral steroids slows radiological damage in early RA.[10] There is uncertainty about whether such beneficial effects of steroids persist; some trials suggest they do,[11] whereas others suggest they do not.[12] Concern about steroid treatment focuses on their many well known adverse events.[13] Consequently, few studies have examined their disease modifying potential in established RA, though one study showed an additional radiological benefit in patients receiving oral prednisolone (mean dose 4.5 mg) combined with DMARDs.[14]

Intravenous, intramuscular (IM), or oral pulsed steroids have been used in RA since the late 1980s[1 5 6 7–18] to expedite remission induction by DMARDs. Trials showed that steroid pulses, given at the start of DMARD treatment, improved early responses to all DMARDs except sulfasalazine.[19] IM pulsed steroids have several advantages. The overall steroid dose is substantially less than 7.5 mg prednisolone daily. The standard dose of 120 mg IM depot methylprednisolone monthly, used in several studies to achieve symptom control, gives a plasma level equivalent to 4.7 mg/day oral prednisolone, which decreases gradually to undetectable levels by 3 weeks.[17] This standard dose has similar efficacy to that of pulsed intravenous steroids,[20] without the risk of cardiac arrhythmias or the need for admission to hospital. Compared with oral treatment, IM depot steroids increase the likelihood that patients will comply with withdrawal. Although formal studies have only demonstrated their value in remission induction, pulsed steroids have subsequently been widely used to treat flares or improve clinical response in patients with established RA already receiving DMARDs. Their

Abbreviations: CI, confidence interval; DAS, Disease Activity Score; DMARDs, disease modifying antirheumatic drugs; DXA, dual energy *x* ray absorptiometry; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IM, intramuscular; RA, rheumatoid arthritis; VAS, visual analogue scale

potential for assisting disease modification or erosion prevention in established RA has not been examined.

This continuing controversy led us to examine the risks and benefits of IM steroids in a long term randomised control trial of patients with established disease whose existing DMARD was inadequate.

METHODS

Design

We undertook a prospective randomised, double blind, trial which examined the effect of IM steroids given monthly for 24 months. We enrolled patients with established active erosive RA already receiving DMARDs who were currently attending specialist rheumatology clinics in England. Research ethics committees at each collaborating centre approved the trial. All patients enrolled gave informed consent.

Inclusion and exclusion criteria

The inclusion criteria comprised: (*a*) age ⩾18 years; (*b*) RA by the 1987 American College of Rheumatology criteria; (*c*) disease duration of between 2 and 10 years: (*d*) erosion(s) on plain *x* ray examination of the hands, wrists, and feet; (*e*) continuous stable DMARD treatment for at least 3 months (with IM gold, penicillamine, methotrexate, azathioprine, or ciclosporin); (*f*) continuing active disease, with >6 swollen joints and an erythrocyte sedimentation rate (ESR) >30 mm/1st h.

The exclusion criteria comprised: (*a*) end stage joint destruction (Larsen score >100); (*b*) previous or current oral steroid treatment; (*c*) contraindications to parenteral steroids (for example, recent gastric ulcer perforation or bleed); (*d*) serious comorbidity (for example, end stage renal or liver disease); (*e*) patients not taking DMARDs, taking experimental drugs, taking DMARDs that have no effect on *x* ray progression (for example, antimalarial drugs), or taking DMARDs which may interact poorly with IM depot steroids (sulfasalazine[19]).

Treatments

Patients were randomly assigned to receive monthly IM 120 mg depomedrone injections or sterile normal saline (placebo). Injections were given by nurses not involved in assessing patients. Patients continued their DMARDs at the same dose, non-steroidal anti-inflammatory drugs, and analgesics. One allowable DMARD (IM gold, penicillamine, methotrexate, azathioprine, and ciclosporin) could be changed for another at the discretion of the supervising clinician. Intra-articular methylprednisolone was restricted to six injections of ⩽40 mg; they were given to seven patients in the steroid group and six in the placebo group.

Outcome measures

Outcome measures comprised: (*a*) disease activity assessed every 6 months using numbers of swollen and tender joints (out of 28), articular pain (100 mm visual analogue scale (VAS)), patient's and physician's global assessments (100 mm VAS), ESR, C reactive protein, Health Assessment Questionnaire (HAQ) scores, and 28 joint count disease activity scores (DAS28); (*b*) radiological damage in the hands and feet assessed every 12 months using a modification of Larsen's method[21]; (*c*) adverse effects assessed every 6 months, including specific information on fractures, hypertension, hyperglycaemia, weight gain, and infections. Bone density was assessed in the lumbar spine and hip by dual energy *x* ray absorptiometry (DXA) at 0 and 24 months.

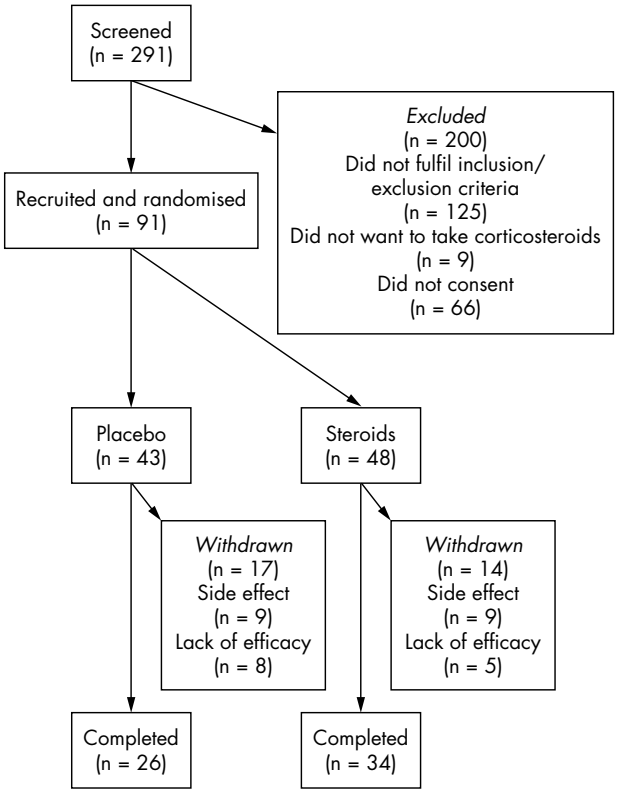

Figure 1 Patients screened, entered, and withdrawn from the trial.

Initial sample size

Our preliminary study showed that 75/91 (82%) patients with RA followed up for 12 months had erosive progression. We consider a clinically relevant outcome would be if this fell to 50% of patients whose erosions did not progress with IM steroids. To show such a difference with a significance level of 5% and 80% power requires 34 patients in each group and a total sample size of 68. Allowing for 25% drop outs a year, the initial sample size must be 85.

Data analysis

Clinical data were analysed on an intention to treat basis using the last value carried forward imputation. For *x* ray findings, all available data were evaluated but missing data were not imputed. Total Larsen scores were reported at each time point and absolute changes in scores were calculated between each time point. To overcome any small imbalances between groups, relative changes (the progression of damage as a percentage of initial damage) were calculated as described by Scott *et al*.[22] The percentage change in the Larsen score was found to be normally distributed when examined by the Kolmogorov-Smirnov test. Parametric statistics were therefore used to analyse the data. Data were analysed using SPSS for windows (SPSS Inc, release 11).

RESULTS

Patients enrolled

Recruitment started in November 1997 and finished in April 2001, with a final assessment in April 2003. Two hundred and ninety one patients were screened and 91 (31%) entered the study (fig 1); 125 patients did not meet the entry criteria (primarily because of lack of disease activity) and 75 did not consent (including nine who did not want steroids). Forty three patients were randomised to placebo and 17 were

Table 1 Changes in clinical assessments over the first 6 months of treatment

	Placebo			Steroids			Comparison of groups (Significance at 6 months)
	Mean	SEM	Significance (0–6 month change)	Mean	SEM	Significance (0–6 month change)	
Swollen joints							
Initial	10.2	0.8	NS	10.2	0.7	<0.01	<0.03
6 months	9.3	0.9		7.0	0.6		
24 months	6.6	0.9		5.0	0.7		
Tender joints							
Initial	10.3	1.1	NS	11.5	1.1	<0.02	<0.06
6 months	10.3	1.3		8.5	1.2		
24 months	9.6	1.4		9.0	1.3		
HAQ							
Initial	1.4	0.1	NS	1.7	0.1	<0.02	<0.02
6 months	1.6	0.1		1.4	0.1		
24 months	1.5	0.1		1.8	0.3		
VAS pain							
Initial	46.2	3.9	NS	45.8	3.6	0<0.01	<0.01
6 months	50.7	4.4		40.3	3.9		
24 months	46.8	4.6		39.1	4.0		
Patients' global							
Initial	49.7	4.2	NS	49.1	3.7	NS	NS
6 months	48.8	4.2		48.2	4.1		
24 months	45.2	4.7		47.3	4.6		
Physicians' global							
Initial	45.9	3.2	NS	42.3	2.9	NS	NS
6 months	41.1	3.8		36.6	3.2		
24 months	37.4	3.8		35.3	3.8		
ESR							
Initial	34.2	4.5	NS	29.3	3.1	NS	NS
6 months	34.1	4.5		27.0	3.4		
24 months	31.3	4.1		30.7	4.2		

Changes within groups compared by paired *t* tests. Changes between groups compared by unpaired *t* tests.

withdrawn (nine owing to side effects and eight owing to lack of efficacy); 10 patients withdrew by 6 months, four between 6 and 12 months, and three between 12 and 18 months. Forty eight patients were randomised to steroids and 14 were withdrawn (nine owing to side effects and five owing to lack of efficacy); 10 patients withdrew by 6 months, one between 6 and 12 months, and three between 12 and 18 months.

The 35 women and eight men who received placebo had a mean (SD) age of 56 (13) years and mean (SD) disease duration of 16 (12) years; 23/38 (61%) were rheumatoid factor positive. The 36 women and 12 men who received steroids had a mean (SD) age of 59 (10) years and mean (SD) disease duration of 13 (6) years; 24/42 (57%) were rheumatoid factor positive. For both groups a mean of one DMARD had previously failed and their baseline disease activity measures were similar (table 1). Fifteen patients had changed their DMARD during the trial—nine in the placebo group and six in the steroid group.

Changes in DAS

The mean (SEM) DAS in the steroid treated group before treatment was 5.48 (SE 0.18) and in the placebo group 5.41 (0.22). Figure 2 shows changes in the values of the DAS.

Within-group analysis of patients taking steroids showed that mean (SEM) values of the DAS fell by 0.65 (0.22) after 6 months ($p<0.01$ on paired *t* test). The DAS remained significantly lower than at the start ($p<0.01$ on paired *t* test) throughout the 2 year study period, with mean (SEM) falls of 0.91 (0.25) at 12 months, 0.76 (0.26) at 18 months, and 0.78 (0.24) at 24 months compared with baseline.

Within-group analysis of patients taking placebo showed that the DAS did not improve significantly during the first 12 months; the mean (SEM) fall after 6 months was 0.08 (0.16) and after 12 months there was a small rise compared with baseline (0.07 (0.27)). In the final year of the study, the DAS improved. At 18 months, the DAS fell by a mean (SEM) of 0.23 (0.20) and at 24 months by 0.47 (0.21); these changes were significant ($p<0.05$ on paired *t* tests) compared with the initial value.

Between-group analysis showed that the decrease in the DAS during the first 6 months with steroids (mean 0.65) was significantly greater than with placebo (mean 0.08; $p = 0.038$ on unpaired *t* test). No significant difference was seen subsequently.

Changes in core dataset assessments

Within-group analysis showed that with steroids there were significant falls (by paired *t* tests) in swollen joint counts, tender joint counts, HAQ, and VAS pain scores (table 1). With placebo treatment, no core dataset variables showed a significant change.

Between-group analysis of changes over the first 6 months showed significant differences in favour of steroids (by unpaired *t* tests) in four of the core dataset variables: swollen joint counts, tender joint counts, HAQ, and VAS pain scores (table 1). By 24 months there were no sustained differences between placebo and steroid treated groups in any of the core dataset variables.

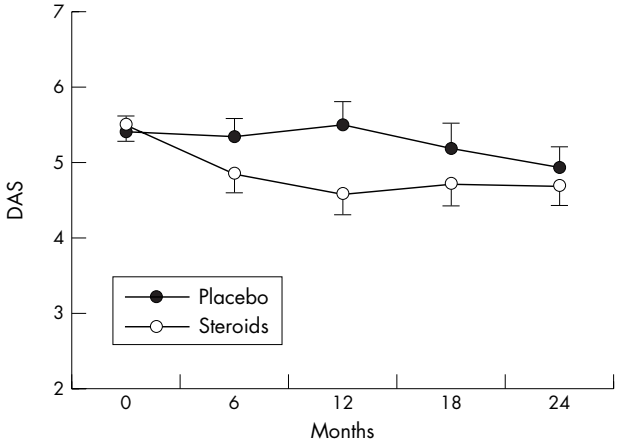

Figure 2 Changes in the DAS over 24 months. Mean values (SEM) shown for placebo and steroid treated groups.

Changes in Larsen score

x Ray assessments were available in 62 cases: 30 patients in the placebo group and 32 in the depomedrone group. Figure 3 shows these changes.

Intergroup analysis

Mean changes in the Larsen score over 12 months with IM depomedrone were −0.59 (median 0.00) compared with 2.77 (median 0.00) with placebo. Mean changes in the Larsen score over 24 months with IM depomedrone were 0.28 (median 0.00) compared with 6.27 (median 0.00) with placebo. These differences were not statistically significant. However, the groups were not strictly comparable as patients receiving steroids had higher initial Larsen scores than those taking placebo. Consequently, an additional analysis was undertaken, in which the change in the Larsen score was expressed as a percentage change in the initial Larsen score (fig 3B). This showed that the mean percentage change in the Larsen score was 12% (95% confidence interval (CI) 1% to 20%) in the placebo group and −5% (95% CI −15% to 6%) in the patients receiving steroids ($p = 0.028$ on Student's *t* testing). This level of significant difference between the groups ($p = 0.03$) remained when an analysis of covariance was undertaken that included the initial Larsen score in the model. There were no significant differences between groups over 12–24 months using percentage changes in the initial Larsen score.

Intragroup analysis

Within-group analysis of the patients taking placebo showed that the mean Larsen score rose significantly over the first 12 months by an average of 2.77 (95% CI 0.02 to 5.51; $p = 0.048$ on Student's paired *t* test and median change 0.00) from an initial mean of 37.1. Between 12 and 24 months it rose by an average of 3.50 (95% CI −1.28 to 8.28, $p = 0.14$ on Student's paired *t* test and median change 0.00). Over 24 months Larsen scores increased by an average of 6.27 (95% CI −0.30 to 12.84; $p = 0.061$ on Student's paired *t* test and median change 0.00).

Within-group analysis of patients taking steroids showed that the mean Larsen score fell over the first 12 months by an average of 0.59 (95% CI −4.34 to 3.15 and median change 0.00) from an initial value of 46.6. Between 12 and 24 months it rose by an average of 0.88 (95% CI −1.83 to 3.58 and median change 0.00). Over 24 months it rose by an average of 0.28 (95% CI −3.54 to 4.11 and median change 0.00). Unlike the placebo group, none of these differences were significant (Student's paired *t* tests), suggesting that steroids had a positive effect.

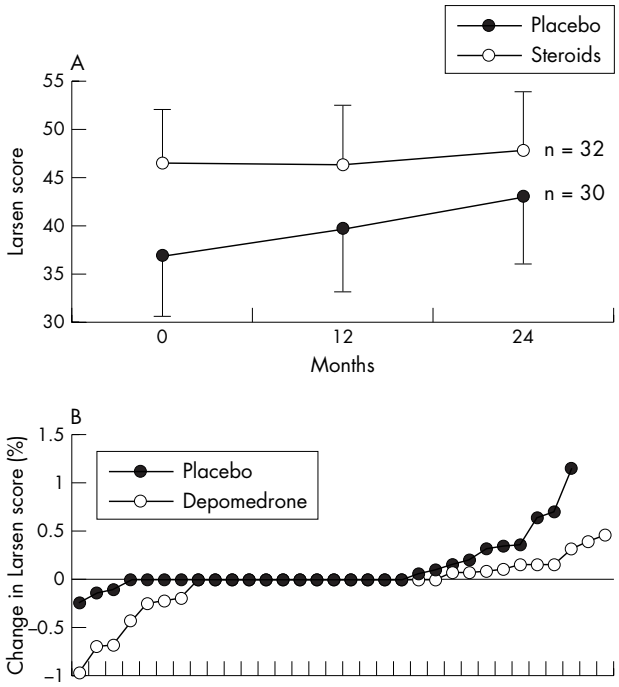

Figure 3 Changes in Larsen score in placebo and steroid treated patients. (A) Mean (SEM) changes over 24 months; (B) percentage changes during the initial 12 months. Each circle represents an individual patient treated with placebo or steroids.

Adverse effects

The patients receiving steroids reported 55 adverse reactions; patients receiving placebo reported 42 adverse reactions. Six adverse events were classified as serious (four with active treatment and two with placebo), though only two of these (vertebral fracture and iatrogenic Addison's disease (both occurring after 18 months' steroid treatment) were considered related to treatment.

Adverse reactions traditionally associated with steroid treatment occurred in 16 cases in the steroid group, comprising four cases of hypertension requiring antihypertensive treatment (defined as either systolic blood pressure ⩾160 mm Hg or diastolic blood pressure ⩾100 mm Hg on at least two occasions), facial swelling (three cases), bruising (three cases), osteoporosis (two cases—one with vertebral fracture, one case of *t* score ⩽2.5 on DXA scan), diabetes mellitus (one case noted initially by a random blood sugar of >12.1 and confirmed by a raised fasting blood sugar >7 mmol/l), myocardial infarction (one case), hypercholesterolaemia (one case defined as fasting serum cholesterol of >7.1 mmol/l), and iatrogenic Addison's disease (one case diagnosed by a consultant endocrinologist after a long adrenocorticotropic hormone test and a cranial magnetic resonance imaging scan). By contrast, only two placebo treated patients had such adverse effects (one with hypertension and one with weight gain). The difference was significant ($p = 0.0008$, χ^2 test).

Results of bone density measurements, evaluated over 2 years using DXA scans, were available in 29 patients treated with placebo and 32 treated with steroids. In the placebo group, the mean lumbar spine T score remained stable (initial −0.60, final −0.61, change −1%, $p = 0.87$ by paired T test); though the mean hip T scores fell (initial −1.35, final −1.44,

change −6%, p = 0.06 by paired T test) this change did not reach statistical significance.

In the steroid treated group mean T scores fell in both the hip (initial −0.84, final −0.97, change −15%, p = 0.046 by paired T test) and the lumbar spine (initial −0.39, final −0.46, change −18%, p = 0.052 by paired T test) though the change in the latter just failed to reach significance.

DISCUSSION

This study shows that in patients with established RA whose disease is inadequately controlled by existing DMARDs, the addition of IM depomedrone temporarily reduces their disease activity and has a small beneficial effect on reducing bone erosion. However, this limited benefit is associated with a significant increase in steroid related side effects, including osteoporosis. Overall, we consider the risk-benefit analysis does not favour the use of long term IM depomedrone in this group of patients and that its use should be reserved for the established indications of induction of remission and short term treatment of flares. Patients, such as those in this study, who are inadequately controlled by DMARDs should not be given supplementary steroids except in the very short term, but instead should be treated with an alternative DMARD, an additional DMARD (sequential combination treatment), or a biological agent.

When IM depomedrone was given to patients with established RA whose disease was active despite DMARD treatment, swollen joint counts, pain scores, HAQ scores, and the DAS were reduced. However, the clinical benefits did not persist beyond 6 months. The improvement seen with depomedrone, including reduction in the DAS, is less than that seen in trials in which new DMARDs are started, but is of a similar degree to that previously reported in systematic reviews of low dose oral steroids.[23] The notable exception is improvement in the HAQ score, which improved to a degree similar to that reported on starting treatment with sulfasalazine, methotrexate, and other DMARDs.

The changes in *x* ray damage are more difficult to interpret. Although randomisation resulted in different initial Larsen scores between groups, long term observation of patients with established RA, like those in the current study, suggests that such a difference is unlikely to have influenced the progression of *x* ray damage.[24] However, as the progression of newly (not previously) damaged joints declines with disease duration,[25] the situation is relatively complex. Calculating the progression of damage as a relative change (as a percentage of the initial damage), which was an approach suggested nearly 20 years ago,[22] overcomes any small imbalances between groups. Using this approach, we found that *x* ray scores significantly deteriorated in the placebo but not the steroid group. We also found that using absolute changes there was a significant within-group progression of *x* ray damage with placebo treatment but not with steroid treatment. These findings are compatible with the observations of Kirwan and others that steroids slow *x* ray progression in early RA.[9 10 26]

The value of using steroids, whether parenteral or oral, longer term in RA remains controversial. They control disease activity over the medium term, as shown by a meta-analysis of studies with an average duration of 7 months.[4] They can prevent bone erosion in early disease, as shown by the initial studies of Kirwan[9] and Boers *et al*,[10] a subsequent positive trial of oral steroids in early RA by van Everdingen and colleagues,[26] and the long term follow up of Landewe *et al*.[27] In contrast, the follow up to the Kirwan study demonstrated that withdrawal of steroids led to a resumption of erosive damage and cartilage loss,[28] suggesting that the benefit was temporary. Conn in a largely positive editorial focused on the benefits of steroid treatment in controlling disease activity and on the limited gastrointestinal damage steroids induced if used without non-steroidal anti-inflammatory drugs[29]; he acknowledged their osteoporosis-inducing effect, but felt it could be managed using bone protection agents. In contrast, a paired editorial by Saag raised substantial concerns about long term steroid use.[13] Further evidence against routine steroid use in RA comes from a more recent study by Capell *et al*,[30] which showed that low dose oral prednisolone conferred no radiological or clinical benefit in patients maintained by a DMARD over 2 years. The difference between this and previous studies showing positive results[9 10 26] might be its assiduous use of alternative DMARDs where the primary standardised DMARD (sulfasalazine) had failed. This implies that changing or adding a standard DMARD may produce the same benefits as steroids but at a lower risk so that steroids, even at a low dose, should be reserved for short term use only.

Although the patients in our study received only low doses of methylprednisolone (4 mg daily, equipotent in glucocorticoid effect to 5 mg prednisolone daily), more adverse events occurred in the steroid group than the placebo group, which was entirely be accounted for by reactions associated with glucocorticoids (16 such events in 48 steroid treated patients compared with 2 in 43 placebo patients). These steroid related adverse effects included hypertension in four cases, osteoporosis in two cases (with one vertebral fracture), diabetes mellitus in one case, and a cardiac infarction in one case. These results were consistent with previous studies, such as that of Saag *et al*,[31] which have shown that despite an important confounder effect from disease severity the use of low dose steroids in RA increased adverse events in a dose dependent fashion. Although it is difficult to balance side effects with benefits,[32] the level of increase of steroid related adverse events seen in our study could only be justified if the benefits of the treatment were major and unequivocal, which was not the case. In her more recent study, Capell also concluded that low dose steroids increased the risk of side effects such as hypertension and osteoporosis as indicated by the increased prescription of antihypertensive agents and osteoporosis drugs for steroid treated patients.[30] In that study, considerable care was taken to mitigate steroid adverse events by the intensive use of interventions designed to reduce them, but the authors observed that long term steroid related sequelae cannot be entirely prevented even with the most effective interventional regimens.

Osteoporosis, an important and potentially preventable adverse event, was examined in detail in our study by performing a DXA scan before and after treatment in the majority of patients. This showed a substantial fall (15–18%) in bone density in the steroid treated group, whereas there was little or no change in the placebo group. This was disappointing because previous work using a similar IM steroid regimen in polymyalgia rheumatica[33] showed that bone density was more affected by the high level of inflammation than by low dose steroids. However, as the patients with polymyalgia were only treated for 1 year and initially had a very marked acute phase response, such differences are not so surprising. Our current study in RA supports the increasing body of evidence suggesting that glucocorticoid treatment, however administered and whether continuous or recurrent, has the potential to induce osteoporosis, which is dependent on dose and duration of treatment.[34 35] Patients in our study were not treated routinely with bone protective agents as this was not standard practice at the time; however, clearly, if such a steroid regimen is contemplated in any patient in the future, appropriate bone protection is required according to current guidelines.

In conclusion, IM steroid treatment produces only a transient clinical benefit. Although it may have a small protective effect against erosions, the level of steroid related adverse events precludes its use as a long term treatment strategy.

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