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Effects of glucocorticoids on radiological progression in rheumatoid arthritis (Review)

Kirwan JR, Bijlsma JWJ, Boers M, Shea B

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	4
Figure 1.	5
Figure 2.	8
DISCUSSION	9
AUTHORS' CONCLUSIONS	10
ACKNOWLEDGEMENTS	10
REFERENCES	11
CHARACTERISTICS OF STUDIES	13
DATA AND ANALYSES	19
Analysis 1.1. Comparison 1 Glucocorticoids vs comparator, Outcome 1 Erosions at 1 year as proportion of maximum score.	20
Analysis 1.2. Comparison 1 Glucocorticoids vs comparator, Outcome 2 Erosions at 1 year data from 1&2 year studies.	21
Analysis 1.3. Comparison 1 Glucocorticoids vs comparator, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.	21
Analysis 1.4. Comparison 1 Glucocorticoids vs comparator, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.	21
Analysis 1.5. Comparison 1 Glucocorticoids vs comparator, Outcome 5 Joint Space Narrowing at 2 years as a proportion of maximum score.	22
Analysis 1.6. Comparison 1 Glucocorticoids vs comparator, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.	22
Analysis 1.7. Comparison 1 Glucocorticoids vs comparator, Outcome 7 Joint Space Narrowing at 2 years data from 1&2 year studies.	23
Analysis 1.8. Comparison 1 Glucocorticoids vs comparator, Outcome 8 Proportion of patients progressing at Year 1.	23
Analysis 2.1. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 1 Erosions at 1 year as proportion of maximum score.	24
Analysis 2.2. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 2 Erosions at 1 year data from 1&2 year studies.	24
Analysis 2.3. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 3 Erosions at 2 years data from 1&2 year studies.	25
Analysis 2.4. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.	25
Analysis 2.5. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 5 Joint Space Narrowing at 2 years as a proportion of maximum score.	25
Analysis 2.6. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.	26
Analysis 2.7. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 7 Joint Space Narrowing at 2 years data from 1&2 year studies.	26
Analysis 3.1. Comparison 3 Glucocorticoids vs NSAID, Outcome 1 Erosions at 1 year as proportion of maximum score.	27
Analysis 3.2. Comparison 3 Glucocorticoids vs NSAID, Outcome 2 Erosions at 1 year data from 1&2 year studies.	27
Analysis 3.3. Comparison 3 Glucocorticoids vs NSAID, Outcome 3 Erosions at 2 years data from 1&2 year studies.	27
Analysis 4.1. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 1 Erosions at 1 year as proportion of maximum score.	28
Analysis 4.2. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 2 Erosions at 1 year data from 1&2 year studies.	28
Analysis 4.3. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 3 Erosions at 2 year data from 1&2 year studies.	29
Analysis 4.4. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.	29
Analysis 4.5. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 5 Joint Space Narrowing at 2 years as a proportion of maximum score.	29

Analysis 4.6. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.	29
Analysis 4.7. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 7 Joint Space Narrowing at 2 years data from 1&2 year studies.	30
Analysis 5.1. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 1 Erosions at 1 year as proportion of maximum score.	31
Analysis 5.2. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 2 Erosions at 1 year data from 1&2 year studies.	31
Analysis 5.3. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 3 Erosions at 2 years data from 1&2 year studies.	31
Analysis 5.4. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.	32
Analysis 5.5. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 5 Joint Space Narrowing at 2 years as a proportion of maximum score.	32
Analysis 5.6. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.	32
Analysis 5.7. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 7 Joint Space Narrowing at 2 years data from 1&2 year studies.	32
Analysis 6.1. Comparison 6 Studies with less than 26 weeks of glucocorticoid treatment, Outcome 1 Erosions at 1 year as proportion of maximum score.	33
Analysis 6.2. Comparison 6 Studies with less than 26 weeks of glucocorticoid treatment, Outcome 2 Erosions at 1 year data from 1&2 year studies.	34
Analysis 6.3. Comparison 6 Studies with less than 26 weeks of glucocorticoid treatment, Outcome 3 Erosions at 2 years data from 1&2 year studies.	34
Analysis 6.4. Comparison 6 Studies with less than 26 weeks of glucocorticoid treatment, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.	34
Analysis 6.6. Comparison 6 Studies with less than 26 weeks of glucocorticoid treatment, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.	34
Analysis 7.1. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 1 Erosions at 1 year as proportion of maximum score.	35
Analysis 7.2. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 2 Erosions at 1 year data from 1&2 year studies.	36
Analysis 7.3. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 3 Erosions at 2 years data from 1&2 year studies.	36
Analysis 7.4. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.	37
Analysis 7.5. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 5 Joint Space Narrowing at 2 years as a proportion of maximum score.	37
Analysis 7.6. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.	37
Analysis 7.7. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 7 Joint Space Narrowing at 2 years data from 1&2 year studies.	37
Analysis 8.1. Comparison 8 Glucocorticoids vs comparator using modelled SDs, Outcome 1 Erosions at 1 year as proportion of maximum score.	38
Analysis 8.2. Comparison 8 Glucocorticoids vs comparator using modelled SDs, Outcome 2 Erosions at 1 year data from 1&2 year studies.	39
Analysis 8.3. Comparison 8 Glucocorticoids vs comparator using modelled SDs, Outcome 3 Erosions at 2 years data from 1&2 year studies.	39
Analysis 9.1. Comparison 9 Glucocorticoids vs comparator using only studies with modelled SDs, Outcome 1 Erosions at 1 year as proportion of maximum score.	40
Analysis 9.2. Comparison 9 Glucocorticoids vs comparator using only studies with modelled SDs, Outcome 2 Erosions at 1 year data from 1&2 year studies.	40
Analysis 9.3. Comparison 9 Glucocorticoids vs comparator using only studies with modelled SDs, Outcome 3 Erosions at 2 years data from 1&2 year studies.	40
Analysis 10.1. Comparison 10 Glucocorticoids vs comparator using original SDs in studies with modelled SDs, Outcome 1 Erosions at 1 year as proportion of maximum score.	41

Analysis 10.2. Comparison 10 Glucocorticoids vs comparator using original SDs in studies with modelled SDs, Outcome 2 Erosions at 1 year data from 1&2 year studies.	41
Analysis 10.3. Comparison 10 Glucocorticoids vs comparator using original SDs in studies with modelled SDs, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.	42
Analysis 11.1. Comparison 11 Glucocorticoids vs comparator sensitivity analyses by quality standards - Concealed Treatment, Outcome 1 Erosions at 1 year as proportion of maximum score.	42
Analysis 11.2. Comparison 11 Glucocorticoids vs comparator sensitivity analyses by quality standards - Concealed Treatment, Outcome 2 Erosions at 1 year data from 1&2 year studies.	43
Analysis 11.3. Comparison 11 Glucocorticoids vs comparator sensitivity analyses by quality standards - Concealed Treatment, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.	43
Analysis 12.1. Comparison 12 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blinding of Patients, Outcome 1 Erosions at 1 year as proportion of maximum score.	44
Analysis 12.2. Comparison 12 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blinding of Patients, Outcome 2 Erosions at 1 year data from 1&2 year studies.	44
Analysis 12.3. Comparison 12 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blinding of Patients, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.	44
Analysis 13.1. Comparison 13 Glucocorticoids vs comparator sensitivity analyses by quality standards - Intention to Treat, Outcome 1 Erosions at 1 year as proportion of maximum score.	45
Analysis 13.2. Comparison 13 Glucocorticoids vs comparator sensitivity analyses by quality standards - Intention to Treat, Outcome 2 Erosions at 1 year data from 1&2 year studies.	45
Analysis 13.3. Comparison 13 Glucocorticoids vs comparator sensitivity analyses by quality standards - Intention to Treat, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.	46
Analysis 14.1. Comparison 14 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blind Assessors, Outcome 1 Erosions at 1 year as proportion of maximum score.	46
Analysis 14.2. Comparison 14 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blind Assessors, Outcome 2 Erosions at 1 year data from 1&2 year studies.	47
Analysis 14.3. Comparison 14 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blind Assessors, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.	47
ADDITIONAL TABLES	49
WHAT'S NEW	52
HISTORY	52
CONTRIBUTIONS OF AUTHORS	52
DECLARATIONS OF INTEREST	52
NOTES	52
INDEX TERMS	52

[Intervention Review]

Effects of glucocorticoids on radiological progression in rheumatoid arthritis

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ABSTRACT

Background

Glucocorticoid use in rheumatoid arthritis (RA) is widespread. Two Cochrane Reviews have been published examining the short term clinical benefit of low dose glucocorticoids compared to non-steroidal anti-inflammatory drugs and demonstrate good short term and medium term clinical benefits. The possibility that glucocorticoids may have a fundamental 'disease modifying' effect in RA, which would be seen by a reduction in the rate of radiological progression, has been raised by several authors.

Objectives

To perform a systematic review of studies evaluating glucocorticoid efficacy in inhibiting the progression of radiological damage in rheumatoid arthritis.

Search methods

A search of MEDLINE (from 1966 to 22 February 2005) and the Cochrane Central Register of Controlled Trials was undertaken, using the terms 'corticosteroids' and 'rheumatoid arthritis' expanded according to the Cochrane Collaboration recommendations. Identified abstracts were reviewed and appropriate reports obtained in full. Additional reports were identified from the reference lists and from expert knowledge.

Selection criteria

Randomized controlled or cross-over trials in adults with a diagnosis of rheumatoid arthritis in which prednisone or a similar glucocorticoid preparation was compared to either placebo controls or active controls (i.e. comparative studies) and where there was evaluation of radiographs of hands, or hands and feet, or feet by any standardised technique. Eligible studies had at least one treatment arm with glucocorticoids and one without glucocorticoids.

Data collection and analysis

Standardised data extraction obtained the mean and standard deviation (SD) of change in erosion scores over 1 year or 2 years. (Where SD for change was not given a conservative estimate was taken from baseline data.) At least two authors selected the studies and extracted the data. Radiographic erosion scores were expressed as a percentage of the maximum possible score for the method used. The results were pooled after weighting in a random effects model to provide a standardised mean difference (SMD).

Main results

The initial search produced 217 citations, and 15 were added from experts, abstracts and review of reference lists. Authors of 4 trials being prepared for publication (and subsequently published) kindly shared their data. After application of eligibility criteria 15 studies and 1,414 patients were included. The majority of trials studied early RA (disease duration up to 2 years), and the mean cumulative dose of glucocorticoid was 2,300 mg prednisone equivalent (range 270 mg - 5,800 mg) over the first year. Glucocorticoids were mostly added to other disease modifying anti-rheumatoid drug (DMARD) treatment. The standardised mean difference in progression was 0.40 in favour of glucocorticoids (95% CI 0.27, 0.54). In studies lasting 2 years (806 patients included), the standardised mean difference in progression in favour of glucocorticoids at 1 year was 0.45 (0.24, 0.66) and at 2 years was 0.42 (0.30, 0.55). All studies except one showed a numerical treatment effect in favour of glucocorticoids. The beneficial effects of glucocorticoids were generally achieved when used in conjunction with other DMARD treatment.

Authors' conclusions

Even in the most conservative estimate, the evidence that glucocorticoids given in addition to standard therapy can substantially reduce the rate of erosion progression in rheumatoid arthritis is convincing. There remains concern about potential long-term adverse reactions to glucocorticoid therapy, such as increased cardiovascular risk, and this issue requires further research.

PLAIN LANGUAGE SUMMARY

Glucocorticoids for rheumatoid arthritis

This summary of a Cochrane review presents what we know from research about the effect of low dose glucocorticoid pills, such as prednisone, on the progress of rheumatoid arthritis. The review shows that:

In people with rheumatoid arthritis, low dose glucocorticoid pills:

- reduce the progression of the disease on x-rays over 1 to 2 years.

This result is based on high quality evidence.

This benefit occurred in people already taking a disease-modifying anti-rheumatoid drug (DMARD) and therefore this benefit is over and above any benefits from the DMARDs.

These results were true in people that had rheumatoid arthritis for less than 2 years. It seems likely that glucocorticoids would have the same effect in people who have had rheumatoid for 3 to 4 years, but it is not known whether this is true in people who have had it for longer.

The long term effects of glucocorticoids are not known.

What is rheumatoid arthritis and why use glucocorticoids?

Rheumatoid arthritis is a disease in which the body's immune system attacks its own healthy tissues. The attack happens mostly in the joints (especially in the hands and feet) and causes redness, pain, swelling and heat in the joint (inflammation). Glucocorticoids are also known as glucocorticosteroids, or sometimes just 'steroids', although there are many other types of steroids. They are taken as pills for up to 7 months and have already been shown to improve the symptoms of rheumatoid arthritis. There is however still some concern about the long term harms, such as heart problems, when taking glucocorticoids.

Rheumatoid arthritis also breaks down and erodes away the cartilage and bones in the affected joints. This erosion cannot be seen and is measured by x-rays. More erosion on an x-ray usually means that the disease is progressing or worsening. There is some debate about whether glucocorticoids can slow the erosion and the progression of the disease.

What are the effects of glucocorticoids on the progress of rheumatoid arthritis?

The studies looked at people who had rheumatoid for up to 2 years. Low doses of glucocorticoid pills were taken and usually with a disease-modifying anti-rheumatoid drug (DMARD).

Glucocorticoids reduce progression of the disease on x-rays over 1 to 2 years. This result is based on high quality evidence.

Harms were not reviewed. We often do not have precise information about side effects and complications. This is particularly true for rare but serious osteoporosis and long term side effects. Low doses of glucocorticoids may not lead to side effects, but possible side effects may include osteoporosis or heart problems.

BACKGROUND

Glucocorticoid use in RA is currently widespread with up to 80% of patients using prednisone or similar glucocorticoid preparations in many arthritis practices (Byron 1985; Pincus 1992; Pincus 1995; Saag 1996). Despite a relative paucity of published data, several authors have debated the value of glucocorticoids for the treatment of RA (Caldwell 1991; Ramos-Remus 1992; Weisman 1993; Weiss 1989). Two Cochrane Reviews have been published examining the short term (<2 weeks) clinical benefit of low dose glucocorticoids compared to non-steroidal anti-inflammatory drugs (Gøtzsche 1997) and moderate term (about seven months) clinical benefits (Criswell 1998).

In these meta-analyses, the authors focused on disease activity outcome measures routinely included in arthritis clinical trials (Felson 1990). It was recognised that these measures of disease activity are not a substitute for long-term evaluation of disease progression, most often assessed by radiographic changes. The possibility that glucocorticoids may have a more fundamental, 'disease modifying' effect in RA, which would be seen by a reduction in the rate of radiological progression, has been raised by several authors (Byron 1986; Weiss 1989). Meta-analysis has previously been used to evaluate the effectiveness of second-line therapies (so called disease modifying anti rheumatoid drugs, DMARDs), including glucocorticoids (Petiti 1994) but not all published studies were included and several more studies have since been published. We therefore undertook a similar analysis of the ability of low dose glucocorticoids (≤ 10 mg prednisone daily equivalent) to inhibit the radiological progression of RA.

OBJECTIVES

To perform a systematic qualitative review of studies evaluating glucocorticoid efficacy in inhibiting the progression of radiological damage in rheumatoid arthritis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled or cross-over trials.

Types of participants

Adults (>18 years) with a diagnosis of rheumatoid arthritis.

Types of interventions

Prednisone or similar glucocorticoid preparations. We included studies that utilized either placebo controls or active controls (i.e. comparative studies).

Types of outcome measures

Evaluation of radiographs of hands, or hands and feet, or feet by any standardised technique. Information regarding radiographs of other joints was also sought.

Search methods for identification of studies

See: Collaborative Review Group search strategy.

Using "corticosteroids", "glucocorticoids" and "rheumatoid arthritis" as subject headings we performed a computerized

literature search of all clinical studies from MEDLINE inception in 1966 through to 22 February 2005. The Cochrane Central Register of Controlled Trials (CENTRAL) was also searched. There were no language restrictions. The search strategy was:

```
001 exp arthritis, rheumatoid/
002 (rheumatoid adj arthrit$).tw.
003 ((caplan's or felty's or sjogren's) adj syndrome).tw.
004 ankylosing spondylitis.tw.
005 still's disease.tw.
006 or/1-5
007 exp adrenal cortex hormones/
008 adrenal cortex hormones.rn,tw.
009 prednisone/
010 prednisone.tw,rn.
011 corticosteroid$.tw.
012 glucocorticoids.rn,tw.
013 corticosterone.tw,rn.
014 hydrocortisone.tw,rn.
015 cortisone.tw,rn.
016 exp prednisolone/
017 prednisolon.tw,rn.
018 or/7-17
019 6 and 18
020 clinical trial.pt.
021 randomized controlled trial.pt.
022 tu.fs.
023 dt.fs.
024 random$.tw.
025 (double adj blind$).tw.
026 placebo$.tw.
027 or/20-26
028 19 and 27
029 28
```

Data collection and analysis

Data collection

Data from the trials were independently extracted by two reviewers and disagreement was resolved by a third, blinded assessment. Trials were not blinded as to authors or institutions. A standard data extraction form was used to extract the following information: Characteristics of the study population:

- number of male and female participants;
- age;
- disease duration.

Description of experimental and control interventions:

- including concomitant interventions.

Outcomes:

- radiographic scoring system;
- radiographic status at entry;
- change in radiographic status at the nearest evaluations to annual assessments.

Quality Assessment

- Two reviewers independently assessed methodological quality. Disagreement was resolved by a third reviewer.

The quality of the methodology of the trials was rated as 1 point for each answer 'Yes' to the following questions:

- Treatment of allocation randomized?
- Treatment allocation concealed?
- Prognostic similarity?
- Specified eligibility criteria?
- Blind assessors?
- Blind patients?
- Point and variability estimates of primary outcome?
- Intention to treat analysis?

Data analysis

Data analysis employed a standard meta-analysis using methods for continuous data developed by Hedges and Olkin (Hedges 1982) and described by Petiti (Petiti 1994). A random effects model was used. The scale for radiographic assessment varied among the studies. Radiographic erosion scores for each study were therefore expressed as a percentage of the maximum possible score for the method used.

Where the mean and standard deviation of the change in radiographic score was provided for the glucocorticoid and control arms, we calculated a standardized mean difference between them. If the standard deviations of the change scores were not available we used the standard deviation of the baseline scores for each group. This provides a conservative estimate of the significance of differences between groups. For some studies we sought clarification from the first author.

We analysed the outcome at one year in all studies included (Comparison 01 subgroup 01), and at one and two years in studies which reported outcomes at two years (Comparison 01 subgroups 02 and 03).

Clinical relevance tables

Clinical relevance tables were compiled under additional tables to improve the readability of the review. Absolute benefit was calculated as the change in the intervention group minus the change in the control group, in the original units. Relative benefit in the change from baseline was calculated as the absolute benefit divided by the change in the control group.

Sensitivity analyses

Sensitivity analyses were determined prior to collection of the data and included:

- including only studies where glucocorticoids were taken with specific anti-rheumatoid drugs (disease modifying anti-rheumatic drugs, DMARD) (Comparison 02)
- including only studies where glucocorticoids were taken without specific anti-rheumatoid drugs (disease modifying anti-rheumatic drugs, DMARD) (Comparison 03)
- including only studies using fixed low dose oral glucocorticoid (up to 7.5 mg prednisolone equivalent daily) (Comparison 04)
- including only studies using step-down treatment (starting at a higher dose and reducing over the following weeks or months) (Comparison 05)

- including only studies with less than 26 weeks of glucocorticoid treatment (Comparison 06)
- including only studies with more than 26 weeks of glucocorticoid treatment (Comparison 07)
- Including only studies with concealed treatment (Comparison 12)
- Including only studies with blinding of patients (Comparison 13)
- Including only studies with intention to treat (Comparison 14)
- Including only studies with blind assessors (Comparison 15)
- examining changes at 1 year and at 2 years (Subgroups 02 and 03 in each comparison)

Secondary analyses

Several trials reported only P-values or nonparametric analyses, and we know that usually the results of radiograph changes show a skewed distribution without providing the mean and standard deviation of the change scores for each treatment group. In such cases, parametric analysis may cause loss of precision. Therefore, as a secondary analysis, we modeled a standard deviation in the following way. We translated the statistical significance (2-tailed P value) of the original trial result or test into a Student's t-score. Using the sample size and the mean or imputed mean we could then calculate a standard deviation for differences in group changes that would have resulted from normally distributed data. These model standard deviations were then used to estimate or calculate the SD of the group change scores, and these were incorporated in this secondary meta-analysis (Comparisons 09-11). The trials to which this was applied are reported in the review of individual trial data below.

RESULTS

Description of studies

As an aid to working we adopted study labels which had meaning at the time, but are now arbitrary. However, we have continued to use the same labels to avoid misunderstanding.

The initial search produced 217 citations, and 15 were added from experts, abstracts and review of reference lists. Authors of 4 trials then being prepared for publication kindly shared their data. These studies have since been published in full. After application of eligibility criteria 15 studies and 1,414 patients were included. The majority of trials studied early RA (disease duration up to 2 years). Two studies (reported in several publications) were published between 1955 and 1960, and are not currently available in the electronic archive. A third was published in 1993. In 1986, Byron and Kirwan (Byron 1986) published a proposal for further scrutiny of the effects of glucocorticoids on x-ray progression. Subsequent studies were published in 1995 (Kirwan 1995; Schaardenburg 1995; van Gestel 1995), 1997 (Boers 1997), 1999 (Hansen 1999), 2001 (Kirwan 2001); 2004 (Capell 2004; Suponitskaia 2004), and 2005 (Choy 2005; Goekoop 2005; Svensson 2005; Wassenberg 2005). Descriptions of the studies are given under 'Characteristics of included studies'. The relationship and cross references between the published studies is illustrated in Additional Figure 1.

Figure 1.

The mean cumulative dose of glucocorticoid was 2,300 mg prednisone equivalent (range 270 mg - 5,800 mg) over the first year. Glucocorticoids were mostly added to other DMARD treatment. Details of individual treatment regimens are set out in the table 'Characteristics of included studies'.

Risk of bias in included studies

The analysis of methodological quality is given in Additional [Table 1](#). In general, recent studies are of high quality. Several studies were instigated in the early years of the introduction of the methodology of randomised controlled clinical trials, and were written for a relatively small audience of clinical specialists who knew each other well. These studies were landmarks at the time of their publication, but the study reports may omit details (such as precise descriptions of the outcome assessments used) that would now be considered essential for a full understanding of the study results.

Effects of interventions

Data extraction

Appropriate outcome data were drawn from each study as shown below under the arbitrary study label used in this review.

Kirwan 1995

Data were available after 1 year of treatment and follow up for 49 patients in the intervention group and 54 patients in the control group. Data were available after 2 years of treatment and follow up for 49 patients in the intervention group and 57 patients in the control group. Data (mean and standard deviation of log transformed scores ($\text{Log}_{10}(x+1)$) were extracted from the text. The principal author clarified the number of patients involved in the calculation of each change score.

Additional data extracted from the text or calculated from the data provided included the proportion of non-erosive hands which had developed erosions. In the prednisolone group these were: at 1 year 26.5% and at 2 years 22.1%. In the placebo group these were: at 1 year 38% and at 2 years 45.6% ($P=0.296$ and $P=0.108$ respectively, Chi-squared test). An additional outcome calculated from the data provided was the proportion of patients who showed progression in year 0-1 (glucocorticoid 14/49, placebo 27/55) and years 0-2 (glucocorticoid 12/44, placebo 28/52). Additional data on the outcome of double blind withdrawal of treatment are available in [Hickling 1998](#). Data on the progress of joint space narrowing in a subset of patients from the study were extracted from [Kirwan 2001](#). There was no significant difference in treatment and control groups for the progress of joint space narrowing.

Svensson 2005

Data from this study were kindly provided by the lead author and have subsequently been published. Data were available at 1 and 2 years of treatment and follow up. An estimate of the number of patients with available change scores on x-rays after 1 year and 2 years was made based on the ratios of patients in the treated and control groups at baseline and 2 years. This estimate was: prednisolone group had 102 at year 1 and 107 year 2; control group had 112 at year 1 and 118 year 2.

Additional data included the development of erosions in previously unaffected joints. Medians (inter-quartile ranges) for year 0-1 were: prednisolone group 0 (0-1); control group 0.5 (0-2); P (Mann-Whitney) = 0.004. For year 0-2 these were: prednisolone group 0.5 (0-2); control group 1.25 (0-3.25); P (Mann-Whitney) = 0.007.

Goekoop 2005

Data from this study were kindly provided by the lead author and have subsequently been published. We included Group 1 (sequential monotherapy) as the control group and Group 3 (the same treatment strategy as the COBRA (I) study shown below) as the glucocorticoid group. [Other groups not included in this analysis were step up DMARD therapy and methotrexate plus infliximab therapy.] Data were available at 1 year of treatment and follow up. An estimate of the number of patients with available change scores on x-rays was made based on comments in the draft manuscript on the number of dropouts. This estimate was: prednisolone group 121; control group 115.

Choy 2005

Data from this study were kindly provided by the lead author and have subsequently been published. Data were available at 1 and 2 years of treatment and follow up. The report did not include a standard deviation for the change scores, but provided 95% confidence intervals from which the standard deviations were calculated.

Boers 1997

Data were available after 56 weeks of follow up for 70 patients in the intervention group and 65 patients in the control group. Data were available after 80 weeks of follow up for 65 patients in the intervention group and 56 patients in the control group. We calculated a model SD of the difference scores for a secondary analysis (as described in statistical methods). We used these model SDs as an estimate for the SD of the change score, and assumed this would be the same for both groups. Additional information on long term follow up is available in [Landewe 2002](#).

Schaardenburg 1995

Data were available after 2 years of treatment and follow up for 28 patients in the intervention group and 28 patients in the control group. Data were extracted from Table 2 in the study report. The report did not include a standard deviation for the change scores. No further information was available from the authors, so we used the standard deviation for the baseline scores instead.

Empire 1955

Data were available after 2 years of treatment and follow up for 35 patients in the intervention group and 31 patients in the control group. Data were extracted from Table XII in the study report. Standard deviations were calculated from the standard error of the mean and the sample size. Additional data available included number of joints developing radiological involvement over 1 year. In the cortisone group the mean was 2 (SE 0.8) and in the control group it was 3 (0.7), the difference being 1.0 (0.9), $P>0.05$.

Hansen 1999

We used the analysis based on intention to treat. Data were available after 1 year of treatment and follow up for 43 patients in the intervention group and 39 patients in the control group. The report did not include a standard deviation for the change scores, nor information from which an estimate could be made. We therefore chose an arbitrarily large value three times the value of the mean. We calculated a model SD of the difference scores for a secondary analysis (as described in statistical methods). We used these model SDs as an estimate for the SD of the change score, and assumed this would be the same for both groups.

Harris 1983

Effects of glucocorticoids on radiological progression in rheumatoid arthritis (Review)

Data were available after 6 months of treatment and follow up for 18 patients in the intervention group and 16 patients in the control group. Data were extracted from Table 6 in the study report. Additional data included the proportion of patients who deteriorated over the six months of the study. In the prednisolone group it was 1/18 (5.6%) and in the placebo group it was 4/16 (25%) ($P=0.11$, Chi squared).

Joint 1959

Data were available after 2 years of treatment and follow up for 41 patients in the intervention group and 35 patients in the control group. Table VIII in the report provided the number of patients falling into categorical scores (on a Likert scale) for pre-treatment and one year post-treatment assessments. From this we constructed a table showing the most conservative interpretation of individual patient change scores, and hence calculated a mean and standard deviation for change scores over 1 year. The data provided do not allow the derivation of combined hand and feet scores for individual patients. Mean change scores were therefore available for year 0 to year 2, but no standard deviations. We estimated these standard deviations as the same proportion of the mean as was calculated for the year 0 to year 1 change scores. We calculated a model SD of the difference scores for a secondary analysis (as described in statistical methods). We used these model SDs as an estimate for the SD of the change score, and assumed this would be the same for both groups.

Additional data available included change over 2 years in the number of patients in each group with 'moderate to severe abnormality' on x-ray. These were converted to the increase in number of patients as a percentage of the maximum number available to increase. In the prednisolone group this was 9.6% (2.5/26) averaged over hands and feet, and in the analgesic group it was 50% (10/20) ($P=0.002$, Chi squared). Additional data for 3 year follow up is available in [Joint 1960](#).

Wassenberg 2005

Data from this study were kindly provided by the lead author and have subsequently been published. Data were available at 1 year of treatment and follow up for 68 patients in the intervention group and 72 patients in the control group. Data were available at 2 years of treatment and follow up for 70 patients in the intervention group and 72 patients in the control group.

Suponitskaia 2004

Data were available at 1 year of treatment and follow up. The report did not include a standard deviation for the change scores. We used the standard deviation for the baseline scores instead. (We thank S Volkov for translation of text within the body of the paper.) We calculated model SDs for the change scores for a secondary analysis (as described in statistical methods) based on $P=0.04$. We then calculated the SD of the difference between groups.

van Gestel 1995

Data were available after 18 weeks of treatment and at 20 and 44 weeks of follow up for 20 patients in the intervention group and 20 patients in the control group. Median (inter-quartile range) change in erosion scores were provided at 20 weeks: prednisolone group: 2 (0-4); placebo group 2 (1-5). At 44 weeks these were: prednisolone group: 3.5 (0-8); placebo group 5 (2-10). The study reports a t-test P value for these comparisons at 20 weeks of 0.48 and at 44 weeks of 0.48. The authors were unable to provide data about mean and SD change scores. We calculated model SDs for a secondary analysis

(as described in statistical methods). We used these model SDs as an estimate for the SD of the change score, and assumed this would be the same for both groups.

van Everdingen 2002

Data were available after 1 year of treatment and follow up for 39 patients in the intervention group and 35 patients in the control group. Data were available after 2 years of treatment and follow up for 39 patients in the intervention group and 35 patients in the control group. Data were extracted from Table 1 in the study report, the report text and Figure 03 in the study report. The report did not include a standard deviation for the change for erosion scores or joint space narrowing scores. We estimated these standard deviations as the same proportion of the mean as was reported for the total Sharp score. These were as follows: Erosion score - years 0-1: intervention 9.75; control 12.32; Years 0-2: intervention 15.81; control 21.08; Joint space narrowing score - years 0-1: intervention 4.88; control 4.82; Years 0-2: intervention 7.19; control 7.03.

Capell 2004

Data were available at 1 and 2 years of treatment and follow up. Median and inter-quartile ranges were provided. We enquired about mean and SD change scores and the authors kindly supplied the mean and standard deviation of log transformed scores ($\text{Log}_{10}(x+1)$). We used the log transform of the maximum scores to derive the percentage of the maximum possible score.

Glucocorticoid dose

The mean cumulative dose of glucocorticoid was 2,300 mg prednisone equivalent (range 270 mg - 5,800 mg) over the first year. Glucocorticoids were mostly added to other DMARD treatment. The details of the treatment comparisons are listed in 'Characteristics of included studies'.

Disease duration

From the table of characteristics of included studies it can be seen that 5 studies did not report disease duration. Of the other 10, 1 had a median of 13 years and all the others had disease duration of less than 2 years. Therefore the results of this analysis apply principally to patients with short disease duration (<2 years).

Meta-analysis result

Erosions. All studies except one ([Capell 2004](#)) showed a numerical treatment effect in favour of glucocorticoids. Figures section 01 shows the results from all studies (glucocorticoids vs. comparator). Figure 01-01 shows that the SMD in favour of glucocorticoids for change in erosions at 1 year was 0.39 (95% CI 0.27 to 0.52). Taking only those studies reporting two years of treatment (Figure 01-02) shows that the SMD in favour of glucocorticoids for change in erosions at 1 year was 0.41 (95% CI 0.29 to 0.66) and at 2 years was 0.42 (0.30, 0.55).

Joint Space Narrowing. Seven studies provided data about the progression of joint space narrowing (2 [[van Gestel 1995](#), [Boers 1997](#); [Goekoop 2005](#)] over 1 year only, 1 [[Kirwan 2001](#)] over 2 years only, and 3 [[Schaardenburg 1995](#); [Svensson 2005](#); [van Everdingen 2002](#)] over 1 and 2 years). Figure 01-03 shows that the SMD in favour of glucocorticoids for change in joint space narrowing at 1 year was 0.36 (0.18, 0.53) and at 2 years was 0.31 (0.14, 0.49). Using only the studies including data for 1 and 2 years these figures are 0.31 (0.04, 0.58) for 1 year and 0.31 (0.13, 0.50) for 2 years.

Proportion of patients progressing. There were 4 studies in which the proportion of patients progressing during the study was given. The relative risk in favour of glucocorticoids was 0.60 (0.48, 0.74).

Clinical relevance

The change in scores in the original units is given in Additional Table 2 for the comparator arm and for the glucocorticoid arm of each study. Absolute benefit was calculated as the change in the control group minus the change in the intervention group, in the original units and relative benefit in the change from baseline was

calculated as the absolute benefit divided by the change in the control group (also included in Additional Table 2). The proportion of benefit gained by glucocorticoids in reducing the progression of erosions from an average (95% CI) of all the studies over 1 year was 59.8% (45.4%, 74.1%). Using data only from trials lasting 2 years, the proportion of benefit gained by glucocorticoids in reducing the progression of erosions from an average of all the studies over 1 year was 67.2% (48.9%, 85.4%) and over 2 years was 61.3% (46.5%, 76.1%). These data are illustrated in Additional Figure 2. It should be noted that the beneficial effects of glucocorticoids were generally achieved when used in conjunction with other DMARD treatment.

Figure 2.

Sensitivity Analysis

The results from the sensitivity analysis of erosive progression and joint space narrowing can be viewed in the Comparison sections 02 to 08, each dealing with subsets of the trials as set out in the methods section above.

There were statistically significant reductions in the progression of erosions over 1 year and over 2 years in all subgroup analyses, irrespective of concomitant medication and length of study. Glucocorticoids were advantageous when studies in which they were given in conjunction with and compared to DMARDs plus NSAIDs were analysed. This was also true when only studies of low dose glucocorticoids were included. There was a significant benefit when step-down glucocorticoids taken with DMARDs plus NSAIDs were compared to DMARDs plus NSAIDs. There was a significant benefit when glucocorticoids were compared with NSAIDs in patients not taking DMARDs. Significant benefits were shown with treatment for less than 26 weeks and treatment for more than 26 weeks. Thus all groupings of the treatment combinations showed

a significant reduction in the progression of erosions in patients treated with glucocorticoids.

As a second measure of radiographic progression the effect of glucocorticoids on joint space narrowing (JSN) was examined. As described above, JSN was reduced at 1 year in all glucocorticoid treated patients compared to all not treated with glucocorticoids. This was true at 1 year and 2 years in studies lasting two years. A similar result was found for the other subgroup analyses, although for some (step down glucocorticoids plus DMARD plus NSAID, studies with less than 26 weeks of glucocorticoid treatment) the difference between the groups was not always significant.

Analysis by quality

Several of the studies were published at a time when study reports were not routinely required to include the quality information. The quality standard with the greatest variability in reporting was Concealed Treatment. Of the 15 studies, only 12 provided information on which to judge concealment of treatment, and in only 6 studies was concealment of treatment adequate. An analysis

of erosions at 2 years using only studies with concealed treatment (Comparison 12-03) showed an SMD in favour of glucocorticoids of 0.51 (95% CI 0.74 , 0.28). This is greater than with all studies taken together.

The quality standard which was next most variable in reporting was Blinding of Patients. Only 11 studies provided information on which to judge patient blinding, and in only 7 of these had patients been blinded. An analysis of erosions at 2 years using only patient blinded studies (Comparison 13-03) showed an SMD of 0.36 in favour of glucocorticoids (0.63, 0.10). This result is similar to the results of all studies combined.

The quality standard which was next most variable in reporting was Intention to Treat analysis, where 12 studies provided enough information on which to judge the analysis, and of these 9 studies reported this analysis. An analysis of erosions at 2 years using only these studies (Comparison 14-03) showed an SMD in favour of glucocorticoids of 0.33 (0.54 , 0.11). This result is similar to the results of all studies combined.

For the quality standard Blind Assessors, 13 studies provided enough information on which to judge and 12 included blinded assessors. An analysis of erosions at 2 years using only assessor blinded studies (Comparison 15-03) showed an SMD of 0.40 in favour of glucocorticoids (95% CI 0.56, 0.24). This result is the same as the results of all studies combined.

Other quality criteria were satisfied by 13 or 14 of the studies, and omitting the studies which did not satisfy the criteria made almost no difference to the analyses.

Secondary analyses

In the secondary analyses using modeled SDs for some trials (as described in methods), there were changes in only three informative studies (Boers 1997; Hansen 1999; Suponitskaia 2004). In general these changes resulted in a larger SMD in favour of glucocorticoid treatment. For example, for all studies SMD for erosions at 1 year changed from 0.39 (Comparison 01, Outcome 01) to 0.42 (Comparison 09, Outcome 01). When only the three studies themselves are considered, SMD for erosions at 1 year changed from 0.35 (Comparison 11 Outcome 01) to 0.47 (Comparison 10, Outcome 01).

DISCUSSION

There is a variety of valid methods for assessing the progression of radiographic damage in RA. For this analysis we placed all study results on a comparable scale by re-scoring each published result so that it was expressed as the percentage of the maximum possible score for the radiographic method used. It is seldom, if ever, that maximum scores are achieved in practice, so the absolute values of this rescaling are not a good representation of the severity of radiographic damage. Furthermore, whenever there was a choice of method for defining the outcome within a study, we chose to take the most conservative estimate of the difference between the patients treated with glucocorticoids and those on comparator treatment. Finally, our principal analysis included all studies with all types of glucocorticoid administration, even though it is possible (or even likely) that the efficacy of glucocorticoids depends on the detailed way in which it is administered (e.g. route of administration, use of concomitant medications).

Our secondary analysis applied a novel approach to redefining the results of three contributory studies so that they reflected, in our opinion, a more realistic representation of the effect of treatment on outcome. This increased the SMD in favour of glucocorticoids by 35% (from 0.35 to 0.47) in the studies concerned and by 8% when all the data were taken together.

Even using the conservative approach of our primary analysis, the results show a significant benefit in the reduction of radiographic erosion progression for glucocorticoid treatment compared to other treatments in patients with relatively early, active RA. This result is similar to that obtained by Jones and colleagues (Jones 2003) who analysed 4 of the 5 trials that were published at that time, although only 3 were included in the meta-analysis calculations (Empire 1955; Joint 1959; Kirwan 1995), together with a study of pulsed intravenous methylprednisolone (Hansen 1990). Our sensitivity analyses looked at several different ways of combining the studies, and in all cases a similar benefit for glucocorticoid therapy was demonstrated. This was also found by Jones (Jones 2003). Further, two other measures of radiographic progression - joint space narrowing and the number of patients who showed progressive change, also demonstrated a similar substantial benefit for glucocorticoid treatment. While not all individual studies showed a statistically significant benefit for treatment, all but one showed glucocorticoid treated patients to have a better radiographic outcome than comparator groups.

The SMD reported here is a conservative estimate because of the nature of the measurements made on the radiographs. Nevertheless, the proportion of benefit gained by glucocorticoids in reducing the progression of erosions from an average of all the studies over 1 year was 67.2% (CI 48.9%, 85.4%) and over 2 years was 61.3% (CI 46.5%, 76.1%). Furthermore, this benefit was achieved in patients who were (mostly) already receiving DMARD treatment. It therefore represents a gain over and above any benefits from DMARDs alone.

It should be recognised that the link between radiological benefit and overall long term functional benefit is not firmly established, and it does not necessarily follow that patients will gain long term functional benefit. However, taking different approaches, two authors (Kirwan 2001A; Scott 2000) have concluded that there is an important link between them.

The potential for high doses of glucocorticoids to cause adverse effects is well known, but the doses used in many of the studies reported here were low. There have been no studies seeking radiological benefit for high dose glucocorticoids, and such studies are unlikely in view of these known adverse effects. The potential for adverse effects at low dose is much less clear. This has been reviewed in detail elsewhere (Da Silva 2006) in a paper which includes results reported in RCTs included in this meta-analysis, but also ranges much more widely in the literature seeking evidence applicable to low dose glucocorticoids in rheumatoid arthritis. The conclusions of that review were that published reports on low dose glucocorticoid treatment in rheumatoid arthritis show that few of the commonly held beliefs about their incidence, prevalence, and impact are supported by clear scientific evidence. Safety data from recent randomised controlled clinical trials of low dose glucocorticoid treatment in RA suggest that adverse effects associated with this drug are modest, and often not statistically different from those of placebo. The most immediate concern, reduced bone mineral density, can also now be readily treated.

Therefore, we believe the evidence that glucocorticoids given in addition to standard therapy can substantially reduce the rate of erosion progression in rheumatoid arthritis is convincing, and that the use of such treatment should be made readily available to patients. Nevertheless, there remains concern about potential long-term adverse reactions to glucocorticoid therapy, such as increased cardiovascular risk, and this issue requires further research.

AUTHORS' CONCLUSIONS

Implications for practice

Even in the most conservative estimate, the evidence that glucocorticoids given in addition to standard therapy can significantly reduce the rate of erosion progression in rheumatoid arthritis is convincing. There remains concern about potential long-term adverse reactions to glucocorticoid therapy.

This review suggests that in patients with active rheumatoid arthritis of less than two years duration who require treatment with DMARDs there would be a substantial reduction in joint destruction by the addition of a suitable low dose or step down glucocorticoid regimen. It seems likely that patients with a disease duration of

3 or 4 years would also benefit, but it would be inappropriate to extrapolate into longer disease durations without more firm evidence of benefit.

Implications for research

The cost-effectiveness and relative risk-benefit ratios of new treatments for rheumatoid arthritis (such as biological therapies) that (delete: might) reduce radiographic progression can only be established in respect to reduction in radiographic progression if they are compared in head-to-head studies against treatment with DMARDs and glucocorticoids. Concerns about potential long-term adverse reactions to glucocorticoid therapy require further research.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Boers 1997

Methods	Double blind randomised placebo controlled trial
Participants	Early rheumatoid arthritis (median duration 4 months)
Interventions	Sulphasalazine (2 g/day) & methotrexate (7.5 mg/week for 40 weeks) & prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day and stopped after 28 weeks) vs sulphasalazine (2 g/day)
Outcomes	Modified Sharp score hands and feet. Max erosion = 280, max JSN = 168
Notes	Prednisolone equivalent dose 2345mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Capell 2004

Methods	Randomised controlled trial
Participants	Active RA (defined) < 3 years starting DMARD
Interventions	NSAID, fixed regimen SSZ & Prednisolone 7mg daily vs NSAID, fixed regimen SSZ & Placebo for 2 years
Outcomes	Modified Sharp score hands and feet. Max erosion = 280, max JSN = 168
Notes	Prednisolone equivalent dose 5110mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Choy 2005

Methods	Double blind randomised placebo controlled trial
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Effects of glucocorticoids on radiological progression in rheumatoid arthritis (Review)

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Choy 2005 (Continued)

Participants	Established active erosive RA (Mean disease duration 13 years)
Interventions	NSAID, DMARD & IM Depomedrone 120mg monthly vs NSAID, DMARD & Monthly IM placebo for 2 years
Outcomes	Modified Larsen hands and feet, maximum = 140 (Check this)
Notes	Mean prednisolone equivalent dose 900 mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Empire 1955

Methods	Randomised controlled trial
Participants	RA with 3 or more inflamed joints, age <60
Interventions	NSAID, standard DMARD regimen, Prednisolone 15mg daily x 30 then lowest symptom free dose vs NSAID, standard chloroquine then other DMARD regimen for 2 years
Outcomes	Progression of radiographic damage at 1 year
Notes	Prednisolone equivalent dose 5475mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Empire 1957

Methods	Randomised controlled trial
Participants	RA with 3 or more inflamed joints, age <60
Interventions	Cortisone Acetate at lowest symptom free dose vs Aspirin at lowest symptom free dose
Outcomes	Progression of radiographic damage at 3 years
Notes	Prednisolone equivalent dose

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Goekoop 2005

Methods	Randomised controlled trial of 4 treatment strategies
Participants	RA of less than 2 year and active disease (defined)
Interventions	NSAID, SSZ, MTX 7.5 22 weeks, Pred 60 to 7.5 over 6 weeks then 7.5 22 weeks vs sequential monotherapy and 2 other regimens
Outcomes	Modified Sharp score hands and feet. Max erosion = 280, max JSN = 168
Notes	Prednisolone equivalent dose 2345mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hansen 1999

Methods	Randomised controlled trial
Participants	Active RA (defined) about to start or change DMARD
Interventions	NSAID, DMARD & Prednisolone 30mg daily then decreasing then lowest symptom free dose vs NSAID & DMARD for 1 year
Outcomes	Larsen score in hands Max = 140
Notes	Prednisolone equivalent dose 2200mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Harris 1983

Methods	Double blind randomised placebo controlled trial
Participants	Active RA (defined) of less than 1 year
Interventions	Constant NSAID, DMARD & Prednisolone 5mg vs Constant NSAID, DMARD & placebo for 6 months
Outcomes	Progression of erosions in hands single score for progression in both hands (0-3) at six months.
Notes	Prednisolone equivalent dose 840mg

Risk of bias

Bias	Authors' judgement	Support for judgement
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Effects of glucocorticoids on radiological progression in rheumatoid arthritis (Review)

Harris 1983 (Continued)

Allocation concealment?	Low risk	A - Adequate
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Joint 1959

Methods	Randomised controlled trial
Participants	RA with 3 or more inflamed joints, age <60
Interventions	Prednisolone 20mg daily then lowest symptom free dose vs Aspirin 6g daily or phenylbutazone 400mg daily then lowest symptom free dose
Outcomes	X-ray severity score 1 and 2 years - hand data only used so far!
Notes	Outcomes recalculated for inclusion

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Joint 1960

Methods	Randomised controlled trial
Participants	RA with 3 or more inflamed joints, age <60
Interventions	Prednisolone 20mg daily then lowest symptom free dose vs Aspirin 6g daily or phenylbutazone 400mg daily then lowest symptom free dose for 3 years
Outcomes	X-ray severity score 3 years
Notes	Prednisolone equivalent dose 12971 mg over 3 years

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Kirwan 1995

Methods	Double blind randomised placebo controlled trial
Participants	Active RA less than 2 years not taking glucocorticoids
Interventions	NSAID, DMARD, & Prednisolone 7.5mg daily vs NSAID, DMARD, & placebo for 2 years
Outcomes	Larsen score in hands Max = 140

Kirwan 1995 (Continued)

Notes Mean prednisolone dose 5475 mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Kirwan 2001

Methods Double blind randomised placebo controlled trial

Participants Active RA less than 2 years not taking glucocorticoids

Interventions NSAID, DMARD, & Prednisolone 7.5mg daily vs NSAID, DMARD, & placebo for 2 years

Outcomes Larsen score in hands Max = 140. Joint space narrowing score Max = 80

Notes Subgroup analysis of 28 patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Schaardenburg 1995

Methods Randomised controlled trial

Participants Active RA, age ≥ 60

Interventions NSAID, standard DMARD regimen, Prednisolone 15mg daily x 30 then lowest symptom free dose vs NSAID, standard chloroquine then other DMARD regimen for 2 years

Outcomes Erosions and JSN scored in hands and feet on 5 point scale in 50 joints - maximum score 200

Notes Prednisolone equivalent dose 5840mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Suponitskaia 2004

Methods Randomised controlled trial

Participants Active RA (defined) < 2 years starting MTX

Effects of glucocorticoids on radiological progression in rheumatoid arthritis (Review)

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Suponitskaia 2004 (Continued)

Interventions	MTX & Prednisolone up to 10mg vs MTX for 1 year	
Outcomes	Larsen score for hands Max = 140	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Svensson 2005

Methods	Randomised controlled trial	
Participants	RA of less than 1 year and DAS28 >3.0	
Interventions	NSAID, DMARD, & Prednisolone 7.5mg daily vs NSAID & DMARD for 2 years	
Outcomes	Modified Sharp score hands and feet. Max erosion = 280, max JSN = 168 Erosions Maximum 280 (JSN maximum 168) Modified Sharp score hands and feet, Max erosion =280, max JSN = 168	
Notes	Mean prednisolone dose 5475 mg. Comparators: NSAID & fixed regimen DMARD; NSAID, fixed step up DMARD, possible prednisolone & posible infliximab; NSAID, MTX, & Infliximab	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

van Everdingen 2002

Methods	Double blind randomised placebo controlled trial	
Participants	Active RA (defined) < 1 year starting DMARD	
Interventions	NSAID, SZZ allowed after 6 months & Prednisolone 10mg daily vs NSAID, SZZ allowed after 6 months & Placebo for 2 years	
Outcomes	Modified Sharp score hands and feet. Max erosion = 280, max JSN = 168	
Notes	Prednisolone equivalent dose 7280mg	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

van Everdingen 2002 (Continued)

Allocation concealment?	Low risk	A - Adequate
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van Gestel 1995

Methods	Double blind randomised placebo controlled trial
Participants	Active RA (defined) starting IM Gold
Interventions	NSAID, IM gold & Placebo or Prednisolone 10mg then fixed reduction over treatment period of 18 weeks
Outcomes	Sharp score hands and feet. Max erosion = 280, max JSN = 168
Notes	Prednisolone equivalent dose 1050mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Wassenberg 2005

Methods	Double blind randomised placebo controlled trial
Participants	Active RA (defined) < 2 years starting DMARD
Interventions	NSAID, DMARD & prednisolone 5mg daily vs NSAID, DMARD & placebo for 2 years
Outcomes	Ratingen score for hand erosions, max 190
Notes	Prednisolone equivalent dose 365mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

DATA AND ANALYSES

Comparison 1. Glucocorticoids vs comparator

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	15	1421	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.52, -0.26]

Effects of glucocorticoids on radiological progression in rheumatoid arthritis (Review)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Erosions at 1 year data from 1&2 year studies	10	940	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.62, -0.23]
3 Erosions at 2 years at 2 years data from 1&2 year studies	10	967	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.56, -0.24]
4 Joint Space Narrowing at 1 year as a proportion of maximum score	6	711	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.50, -0.04]
5 Joint Space Narrowing at 2 years as a proportion of maximum score	4	512	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.51, -0.11]
6 Joint Space Narrowing at 1 year data from 1&2 year studies	4	473	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.51, 0.07]
7 Joint Space Narrowing at 2 years data from 1&2 year studies	3	345	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.57, 0.01]
8 Proportion of patients progressing at Year 1	4	261	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.48, 0.74]

Analysis 1.1. Comparison 1 Glucocorticoids vs comparator, Outcome 1 Erosions at 1 year as proportion of maximum score.

Analysis 1.2. Comparison 1 Glucocorticoids vs comparator, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 1.3. Comparison 1 Glucocorticoids vs comparator, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.

Analysis 1.4. Comparison 1 Glucocorticoids vs comparator, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.

Analysis 1.5. Comparison 1 Glucocorticoids vs comparator, Outcome 5 Joint Space Narrowing at 2 years as a proportion of maximum score.

Analysis 1.6. Comparison 1 Glucocorticoids vs comparator, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.

Analysis 1.7. Comparison 1 Glucocorticoids vs comparator, Outcome 7 Joint Space Narrowing at 2 years data from 1&2 year studies.

Analysis 1.8. Comparison 1 Glucocorticoids vs comparator, Outcome 8 Proportion of patients progressing at Year 1.

Comparison 2. Glucocorticoids + DMARD + NSAID vs DMARD+NSAID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	13	1279	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.51, -0.25]
2 Erosions at 1 year data from 1&2 year studies	7	748	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-0.64, -0.35]
3 Erosions at 2 years data from 1&2 year studies	8	889	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.54, -0.20]
4 Joint Space Narrowing at 1 year as a proportion of maximum score	6	711	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.50, -0.07]
5 Joint Space Narrowing at 2 years as a proportion of maximum score	4	512	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.51, -0.11]
6 Joint Space Narrowing at 1 year data from 1&2 year studies	4	473	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.51, 0.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Joint Space Narrowing at 2 years data from 1&2 year studies	3	345	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.57, 0.01]

Analysis 2.1. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD + NSAID, Outcome 1 Erosions at 1 year as proportion of maximum score.

Analysis 2.2. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD + NSAID, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 2.3. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 3 Erosions at 2 years data from 1&2 year studies.

Analysis 2.4. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.

Analysis 2.5. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 5 Joint Space Narrowing at 2 years as a proportion of maximum score.

Analysis 2.6. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.

Analysis 2.7. Comparison 2 Glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 7 Joint Space Narrowing at 2 years data from 1&2 year studies.

Comparison 3. Glucocorticoids vs NSAID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	2	142	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-0.89, -0.22]
2 Erosions at 1 year data from 1&2 year studies	2	78	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-1.16, -0.23]
3 Erosions at 2 years data from 1&2 year studies	2	78	Std. Mean Difference (IV, Random, 95% CI)	-0.65 [-1.11, -0.19]

Analysis 3.1. Comparison 3 Glucocorticoids vs NSAID, Outcome 1 Erosions at 1 year as proportion of maximum score.

Analysis 3.2. Comparison 3 Glucocorticoids vs NSAID, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 3.3. Comparison 3 Glucocorticoids vs NSAID, Outcome 3 Erosions at 2 years data from 1&2 year studies.

Comparison 4. Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	5	604	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.67, -0.08]
2 Erosions at 1 year data from 1&2 year studies	3	427	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-0.78, -0.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Erosions at 2 year data from 1&2 year studies	3	473	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.66, -0.30]
4 Joint Space Narrowing at 1 year as a proportion of maximum score	1	214	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.79, -0.24]
5 Joint Space Narrowing at 2 years as a proportion of maximum score	2	392	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.61, -0.13]
6 Joint Space Narrowing at 1 year data from 1&2 year studies	1	214	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.79, -0.24]
7 Joint Space Narrowing at 2 years data from 1&2 year studies	1	225	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.64, -0.12]

Analysis 4.1. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 1 Erosions at 1 year as proportion of maximum score.

Analysis 4.2. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 4.3. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 3 Erosions at 2 year data from 1&2 year studies.

Analysis 4.4. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.

Analysis 4.5. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 5 Joint Space Narrowing at 2 years as a proportion of maximum score.

Analysis 4.6. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.

Analysis 4.7. Comparison 4 Oral low dose glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 7 Joint Space Narrowing at 2 years data from 1&2 year studies.

Comparison 5. Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	6	539	Std. Mean Difference (IV, Random, 95% CI)	-0.37 [-0.54, -0.20]
2 Erosions at 1 year data from 1&2 year studies	2	184	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.74, 0.05]
3 Erosions at 2 years data from 1&2 year studies	2	170	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.63, 0.02]
4 Joint Space Narrowing at 1 year as a proportion of maximum score	3	187	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.32, 0.26]
5 Joint Space Narrowing at 2 years as a proportion of maximum score	1	49	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.41, 0.71]
6 Joint Space Narrowing at 1 year data from 1&2 year studies	2	185	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.32, 0.26]
7 Joint Space Narrowing at 2 years data from 1&2 year studies	1	49	Std. Mean Difference (IV, Random, 95% CI)	0.15 [-0.41, 0.71]

Analysis 5.1. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 1 Erosions at 1 year as proportion of maximum score.

Analysis 5.2. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 5.3. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD+NSAID, Outcome 3 Erosions at 2 years data from 1&2 year studies.

Analysis 5.4. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.

Analysis 5.5. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 5 Joint Space Narrowing at 2 years as a proportion of maximum score.

Analysis 5.6. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.

Analysis 5.7. Comparison 5 Step down glucocorticoids + DMARD + NSAID vs DMARD +NSAID, Outcome 7 Joint Space Narrowing at 2 years data from 1&2 year studies.

Study or subgroup	Treatment		Control		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI				
	N	Mean(SD)	N	Mean(SD)							
Heterogeneity: Not applicable											
Test for overall effect: Z=0.53(P=0.6)											
					-10	-5	0	5	10		
					Favours treatment				Favours control		

Comparison 6. Studies with less than 26 weeks of glucocorticoid treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	4	407	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.67, -0.27]
2 Erosions at 1 year data from 1&2 year studies	1	135	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-0.84, -0.16]
3 Erosions at 2 years data from 1&2 year studies	1	121	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.78, -0.06]
4 Joint Space Narrowing at 1 year as a proportion of maximum score	3	373	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.59, 0.01]
5 Joint Space Narrowing at 2 years as a proportion of maximum score	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Joint Space Narrowing at 1 year data from 1&2 year studies	1	135	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.45, 0.22]
7 Joint Space Narrowing at 2 years data from 1&2 year studies	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Studies with less than 26 weeks of glucocorticoid treatment, Outcome 1 Erosions at 1 year as proportion of maximum score.

Study or subgroup	Glucocorticoids		Comparator		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Boers 1997	70	1.6 (2.4)	65	2.9 (3)		33.21%	-0.5 [-0.84, -0.16]
Goekoop 2005	121	0.3 (0.7)	115	1.3 (2.9)		58.52%	-0.44 [-0.7, -0.18]
Harris 1983	18	1.9 (7.9)	16	8.3 (14.9)		8.27%	-0.54 [-1.23, 0.15]
van Gestel 1995	1	0 (0)	1	0 (0)			Not estimable
Total ***	210		197			100%	-0.47 [-0.67, -0.27]
Heterogeneity: Tau ² =0; Chi ² =0.12, df=2(P=0.94); I ² =0% Test for overall effect: Z=4.65(P<0.0001)							
					-1 -0.5 0 0.5 1		Favours treatment Favours control

Analysis 6.2. Comparison 6 Studies with less than 26 weeks of glucocorticoid treatment, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 6.3. Comparison 6 Studies with less than 26 weeks of glucocorticoid treatment, Outcome 3 Erosions at 2 years data from 1&2 year studies.

Analysis 6.4. Comparison 6 Studies with less than 26 weeks of glucocorticoid treatment, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.

Analysis 6.6. Comparison 6 Studies with less than 26 weeks of glucocorticoid treatment, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.

Study or subgroup	Treatment		Control		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI				
	N	Mean(SD)	N	Mean(SD)							
Test for overall effect: Z=0.67(P=0.5)											
					-10	-5	0	5	10		
					Favours treatment				Favours control		

Comparison 7. Studies with more than 26 weeks of glucocorticoid treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	11	966	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.55, -0.21]
2 Erosions at 1 year data from 1&2 year studies	9	757	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.68, -0.20]
3 Erosions at 2 years data from 1&2 year studies	9	853	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.58, -0.21]
4 Joint Space Narrowing at 1 year as a proportion of maximum score	2	288	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.69, -0.16]
5 Joint Space Narrowing at 2 years as a proportion of maximum score	3	463	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.59, -0.17]
6 Joint Space Narrowing at 1 year data from 1&2 year studies	2	288	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.69, -0.16]
7 Joint Space Narrowing at 2 years data from 1&2 year studies	2	296	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.62, -0.16]

Analysis 7.1. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 1 Erosions at 1 year as proportion of maximum score.

Study or subgroup	Glucocorticoids		Comparator		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Capell 2004	59	15.1 (15.1)	55	12.6 (13.5)		11.74%	0.17[-0.19,0.54]
Choy 2005	32	-0.4 (5.3)	30	2 (5.5)		7.92%	-0.44[-0.94,0.07]
Empire 1957	35	6 (8.3)	31	10 (11.7)		8.28%	-0.39[-0.88,0.09]
Hansen 1999	42	1.3 (3.9)	34	2.4 (7.3)		9.15%	-0.2[-0.65,0.25]
Joint 1960	41	4.9 (10)	35	14.3 (16.4)		8.84%	-0.7[-1.16,-0.23]
Kirwan 1995	49	0.9 (18.2)	54	8.8 (22.3)		10.99%	-0.38[-0.77,0.01]
Schaardenburg 1995	1	0 (0)	1	0 (0)			Not estimable
Suponitskaia 2004	20	3.4 (10.3)	20	4.9 (12)		5.84%	-0.13[-0.75,0.49]
Svensson 2005	101	0.3 (0.6)	112	0.9 (1.4)		15.57%	-0.51[-0.79,-0.24]
van Everdingen 2002	39	2.1 (3.5)	35	3.9 (3.9)		8.89%	-0.48[-0.94,-0.02]
Wassenberg 2005	68	0.4 (1.4)	72	1.7 (2.4)		12.77%	-0.63[-0.97,-0.29]
Total ***	487		479			100%	-0.38[-0.55,-0.21]
Heterogeneity: Tau ² =0.03; Chi ² =14.94, df=9(P=0.09); I ² =39.76%							
					-1 -0.5 0 0.5 1		
					Favours treatment Favours control		

Study or subgroup	Glucocorticoids		Comparator		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			

Test for overall effect: $Z=4.38(P<0.0001)$

Favours treatment -1 -0.5 0 0.5 1 Favours control

Analysis 7.2. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Study or subgroup	Treatment		Control		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			

Capell 2004	59	15.1 (15.1)	55	12.6 (13.5)		15.37%	0.17[-0.19,0.54]
Choy 2005	32	-0.4 (5.3)	30	2 (5.5)		11.72%	-0.44[-0.94,0.07]
Empire 1957	1	0 (0)	1	0 (0)			Not estimable
Joint 1960	41	4.9 (10)	35	14.3 (16.5)		12.68%	-0.7[-1.16,-0.23]
Kirwan 1995	49	0.9 (18.2)	54	8.8 (22.3)		14.71%	-0.38[-0.77,0.01]
Schaardenburg 1995	1	0 (0)	1	0 (0)			Not estimable
Svensson 2005	101	0.3 (0.6)	112	0.9 (1.4)		18.27%	-0.51[-0.79,-0.24]
van Everdingen 2002	39	2.1 (3.5)	35	3.9 (3.9)		12.73%	-0.48[-0.94,-0.02]
Wassenberg 2005	68	0.4 (1.4)	43	1.9 (2.4)		14.52%	-0.81[-1.21,-0.41]
Total ***	391		366			100%	-0.44[-0.68,-0.2]

Heterogeneity: $\tau^2=0.06$; $\chi^2=15.58$, $df=6(P=0.02)$; $I^2=61.48\%$
Test for overall effect: $Z=3.58(P=0)$

Favours treatment -1 -0.5 0 0.5 1 Favours control

Analysis 7.3. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 3 Erosions at 2 years data from 1&2 year studies.

Study or subgroup	Treatment		Control		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			

Capell 2004	58	18.3 (16.9)	55	16.7 (14.6)		13.85%	0.1[-0.27,0.47]
Choy 2005	32	0.2 (6.7)	30	4.5 (12.6)		9.31%	-0.42[-0.93,0.08]
Empire 1957	1	0 (0)	1	0 (0)			Not estimable
Joint 1960	41	10 (20.6)	35	27 (30.9)		10.45%	-0.65[-1.11,-0.19]
Kirwan 1995	49	0.9 (20.1)	57	14 (24.2)		13%	-0.58[-0.97,-0.19]
Schaardenburg 1995	28	0.2 (3.3)	28	0.5 (2.8)		8.8%	-0.1[-0.62,0.43]
Svensson 2005	107	0.7 (1.3)	118	1.4 (2.4)		19.14%	-0.38[-0.64,-0.12]
van Everdingen 2002	36	3.9 (5.6)	35	7.5 (6.7)		10.1%	-0.57[-1.05,-0.09]
Wassenberg 2005	70	0.6 (1.8)	72	2.3 (3.6)		15.35%	-0.57[-0.9,-0.23]
Total ***	422		431			100%	-0.39[-0.58,-0.21]

Heterogeneity: $\tau^2=0.03$; $\chi^2=11.75$, $df=7(P=0.11)$; $I^2=40.44\%$
Test for overall effect: $Z=4.23(P<0.0001)$

Favours treatment -1 -0.5 0 0.5 1 Favours control

Analysis 7.4. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 4 Joint Space Narrowing at 1 year as a proportion of maximum score.

Analysis 7.5. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 5 Joint Space Narrowing at 2 years as a proportion of maximum score.

Analysis 7.6. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 6 Joint Space Narrowing at 1 year data from 1&2 year studies.

Analysis 7.7. Comparison 7 Studies with more than 26 weeks of glucocorticoid treatment, Outcome 7 Joint Space Narrowing at 2 years data from 1&2 year studies.

Comparison 8. Glucocorticoids vs comparator using modelled SDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	15	1459	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.54, -0.29]
2 Erosions at 1 year data from 1&2 year studies	10	940	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.62, -0.23]
3 Erosions at 2 years data from 1&2 year studies	10	967	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.54, -0.23]

Analysis 8.1. Comparison 8 Glucocorticoids vs comparator using modelled SDs, Outcome 1 Erosions at 1 year as proportion of maximum score.

Analysis 8.2. Comparison 8 Glucocorticoids vs comparator using modelled SDs, Outcome 2 Erosions at 1 year data from 1&2 year studies. **Analysis 8.3. Comparison 8 Glucocorticoids vs comparator using modelled SDs, Outcome 3 Erosions at 2 years data from 1&2 year studies.** **Comparison 9. Glucocorticoids vs comparator using only studies with modelled SDs**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	3	251	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.73, -0.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Erosions at 1 year data from 1&2 year studies	2	211	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.84, -0.29]
3 Erosions at 2 years data from 1&2 year studies	2	197	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.74, -0.17]

Analysis 9.1. Comparison 9 Glucocorticoids vs comparator using only studies with modelled SDs, Outcome 1 Erosions at 1 year as proportion of maximum score.

Analysis 9.2. Comparison 9 Glucocorticoids vs comparator using only studies with modelled SDs, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 9.3. Comparison 9 Glucocorticoids vs comparator using only studies with modelled SDs, Outcome 3 Erosions at 2 years data from 1&2 year studies.

Comparison 10. Glucocorticoids vs comparator using original SDs in studies with modelled SDs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	3	251	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.60, -0.10]
2 Erosions at 1 year data from 1&2 year studies	2	211	Std. Mean Difference (IV, Random, 95% CI)	-0.57 [-0.84, -0.29]
3 Erosions at 2 years at 2 years data from 1&2 year studies	2	197	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-0.79, -0.22]

Analysis 10.1. Comparison 10 Glucocorticoids vs comparator using original SDs in studies with modelled SDs, Outcome 1 Erosions at 1 year as proportion of maximum score.

Analysis 10.2. Comparison 10 Glucocorticoids vs comparator using original SDs in studies with modelled SDs, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 10.3. Comparison 10 Glucocorticoids vs comparator using original SDs in studies with modelled SDs, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.

Comparison 11. Glucocorticoids vs comparator sensitivity analyses by quality standards - Concealed Treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	6	648	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.60, -0.29]
2 Erosions at 1 year data from 1&2 year studies	4	314	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.68, -0.23]
3 Erosions at 2 years at 2 years data from 1&2 year studies	4	300	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-0.74, -0.28]

Analysis 11.1. Comparison 11 Glucocorticoids vs comparator sensitivity analyses by quality standards - Concealed Treatment, Outcome 1 Erosions at 1 year as proportion of maximum score.

Analysis 11.2. Comparison 11 Glucocorticoids vs comparator sensitivity analyses by quality standards - Concealed Treatment, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 11.3. Comparison 11 Glucocorticoids vs comparator sensitivity analyses by quality standards - Concealed Treatment, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.

Comparison 12. Glucocorticoids vs comparator sensitivity analyses by quality standards - Blinding of Patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	7	524	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.59, -0.06]
2 Erosions at 1 year data from 1&2 year studies	5	488	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.58, -0.05]
3 Erosions at 2 years at 2 years data from 1&2 year studies	5	473	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.63, -0.10]

Analysis 12.1. Comparison 12 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blinding of Patients, Outcome 1 Erosions at 1 year as proportion of maximum score.

Analysis 12.2. Comparison 12 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blinding of Patients, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 12.3. Comparison 12 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blinding of Patients, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.

Comparison 13. Glucocorticoids vs comparator sensitivity analyses by quality standards - Intention to Treat

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	9	1003	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.51, -0.15]
2 Erosions at 1 year data from 1&2 year studies	6	689	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.55, -0.10]
3 Erosions at 2 years at 2 years data from 1&2 year studies	6	685	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.54, -0.11]

Analysis 13.1. Comparison 13 Glucocorticoids vs comparator sensitivity analyses by quality standards - Intention to Treat, Outcome 1 Erosions at 1 year as proportion of maximum score. **Analysis 13.2. Comparison 13 Glucocorticoids vs comparator sensitivity analyses by quality standards - Intention to Treat, Outcome 2 Erosions at 1 year data from 1&2 year studies.**

Study or subgroup	Treatment		Control		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Test for overall effect: Z=2.78(P=0.01)							
					-1-0.500.51		
					Favours treatment	Favours control	

Analysis 13.3. Comparison 13 Glucocorticoids vs comparator sensitivity analyses by quality standards - Intention to Treat, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.

Study or subgroup	Treatment		Control		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Boers 1997	65	2.4 (3.4)	56	4 (3.9)		18.11%	-0.42[-0.78,-0.06]
Capell 2004	58	18.3 (16.9)	55	16.7 (14.6)		17.71%	0.1[-0.27,0.47]
Kirwan 1995	49	0.9 (20.1)	57	14 (24.2)		16.67%	-0.58[-0.97,-0.19]
Schaardenburg 1995	25	2.6 (2.7)	24	2.8 (4)		10.41%	-0.06[-0.62,0.5]
Svensson 2005	107	0.7 (1.3)	118	1.4 (2.4)		24.02%	-0.38[-0.64,-0.12]
van Everdingen 2002	36	3.9 (5.6)	35	7.5 (6.7)		13.08%	-0.57[-1.05,-0.09]
Total ***	340		345			100%	-0.33[-0.54,-0.11]
Heterogeneity: Tau ² =0.03; Chi ² =9.04, df=5(P=0.11); I ² =44.69%							
Test for overall effect: Z=3.02(P=0)							
					Favours treatment -1 -0.5 0 0.5 1 Favours control		

Comparison 14. Glucocorticoids vs comparator sensitivity analyses by quality standards - Blind Assessors

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Erosions at 1 year as proportion of maximum score	12	1239	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.57, -0.27]
2 Erosions at 1 year data from 1&2 year studies	9	938	Std. Mean Difference (IV, Random, 95% CI)	-0.43 [-0.62, -0.23]
3 Erosions at 2 years at 2 years data from 1&2 year studies	9	965	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.56, -0.24]

Analysis 14.1. Comparison 14 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blind Assessors, Outcome 1 Erosions at 1 year as proportion of maximum score.

Study or subgroup	Glucocorticoids		Comparator		Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)			
Boers 1997	70	1.6 (2.4)	65	2.9 (3)		10.83%	-0.5[-0.84,-0.16]
Capell 2004	59	15.1 (15.1)	55	12.6 (1.5)		9.97%	0.23[-0.14,0.6]
Choy 2005	32	-0.4 (5.3)	30	2 (5.5)		6.57%	-0.44[-0.94,0.07]
Goekoop 2005	121	0.3 (0.7)	115	1.3 (2.9)		14.27%	-0.44[-0.7,-0.18]
Harris 1983	18	1.9 (7.9)	16	8.3 (14.9)		4.04%	-0.54[-1.23,0.15]
Joint 1960	41	4.9 (10)	35	14.3 (16.4)		7.38%	-0.7[-1.16,-0.23]
					Favours treatment -1 -0.5 0 0.5 1 Favours control

Analysis 14.2. Comparison 14 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blind Assessors, Outcome 2 Erosions at 1 year data from 1&2 year studies.

Analysis 14.3. Comparison 14 Glucocorticoids vs comparator sensitivity analyses by quality standards - Blind Assessors, Outcome 3 Erosions at 2 years at 2 years data from 1&2 year studies.

ADDITIONAL TABLES

Table 1. Methodological Quality of Included Studies

Study Name	Ran- domised	Concealed treatment	Similar prognosis	Entry crite- ria	Blind asses- sors	Blind pa- tients	Outcome estimates	Intention to treat
Kirwan 1995	Y	Y	Y	Y	Y	Y	Y	Y
Svensson 2005	Y	?	Y	Y	Y	N	Y	Y
Goekoop-Ruiterman 2005	Y	Y	Y	Y	Y	?	Y	Y
Choy 2005	Y	?	Y	Y	Y	Y	Y	?
Boers 1997	Y	Y	Y	Y	Y	Y	Y	Y
Schaardenburg 1995	Y	N	Y	Y	Y	?	Y	Y
Empire 1955	Y	Y	Y	Y	?	?	Y	N
Hansen 1999	Y	N	Y	Y	N	N	Y	Y
Harris 1983	?	Y	Y	Y	Y	Y	Y	N
Joint Pred 1960	?	?	?	N	Y	N	N	?
Wassenberg 2005	Y	?	Y	Y	Y	?	Y	?
Suponitskaia 2004	Y	N	Y	Y	N	N	Y	N
van Gestel 1995	Y	?	Y	Y	Y	Y	Y	Y
van Everdingen 2002	Y	Y	Y	Y	Y	Y	Y	Y
Capell 2004	Y	?	Y	Y	Y	Y	Y	Y

Table 2. Mean, proportion change and benefit in original erosion scores

Trial	Baseline Mean	1 Year Mean	2 Year Mean	1 Year In- crease (%)	2 Year In- crease (%)	1 Yr Ab- solute Benefi	2 Yr Ab- solute Benefi	1 Yr Bene- fit (%)	2 Yr Bene- fit (%)

Table 2. Mean, proportion change and benefit in original erosion scores *(Continued)*

Kirwan 1995 Treatment Group	4.0	5.3	5.9	34.3	50.3	2.3	3.4	62.6	62.9
Comparator Group	6.2	9.9	11.6	58.2	86.2				
Svensson 2005 Treatment Group	4.1	6.5	9.3	58.5	126.8	2.9	3.9	54.7	42.9
Comparator Group	4.8	10.1	13.9	110.4	189.6				
Goekoop-Ruiterman 2005 Treatment Group	1.18	1.5		27.1		0.9		74.4	
Comparator Group	1.46	2.71		85.6					
Choy 2005 Treatment Group	46.6	46.0	46.9	7.5	0.6	4.1	6.0	117.1	95.5
Comparator Group	37.1	40.6	43.4	9.4	16.9				
Boers 1997 Treatment Group	8.9	13.3	15.7	49.4	76.4	3.8	4.3	46.3	38.7
Comparator Group	11.4	19.6	22.5	71.9	97.4				
Schyaardenburg 1995 Treatment Group	4.8		5.1		6.3		0.6		66.7
Comparator Group	4.6		5.5		19.6				
Empire 1955 (no absolute values available)									
Hansen 1999 Treatment Group	29.4	31.2		6.1		1.6		47.1	
Comparator Group	34.3	37.7		9.9					
Harris 1983 (6 months data only)									
Joint Pred 1960 Treatment Group	1.41	1.55	1.69	9.9	19.9	0.3	0.6	68.9	69.6
Comparator Group	1.42	1.87	2.34	31.7	64.8				
Wassenberg 2005 Treatment Group	3.3	4.1	4.5	22.4	36.4	2.4	3.1	75.0	72.1
Comparator Group	2.1	5.3	6.4	152.4	204.8				
Suponitskaia 2004 Treatment Group	16.4	21.2		29.3		2.1		30.4

Table 2. Mean, proportion change and benefit in original erosion scores (Continued)

Comparator Group	14.4	21.3	47.9						
van Gestel 1995 (1 yr = 44wks) Treatment Group	17.0	24.0	41.2	2.5				35.7	
Comparator Group	11	15.5	40.9						
van Everdingen 2002 Treatment Group	5	11	16	120.0	220.0	5.0	10.0	45.5	47.6
Comparator Group	8	19	29	137.5	262.5				
Capell 2004 Treatment Group				97.7	146.6				
Comparator Group				75.5	118.2				

WHAT'S NEW

Date	Event	Description
17 September 2008	Amended	Converted to new review format. C099-R

HISTORY

Review first published: Issue 1, 2007

Date	Event	Description
22 February 2007	Feedback has been incorporated	Minor update - see published notes

CONTRIBUTIONS OF AUTHORS

All reviewers contributed to the design of the study, interpretation of the results and writing the text of the review. JRK, MB and BS undertook data extraction and verification. BS directed the quality assessment. MB undertook additional statistical analyses. JRK undertook data entry. The review was coordinated by JRK who is the guarantor.

DECLARATIONS OF INTEREST

No known conflict of interest.

NOTES

This version includes changes in response to Referees' comments. The reference to a sensitivity analysis of high quality based on quality scores was removed.

INDEX TERMS

Medical Subject Headings (MeSH)

Antirheumatic Agents [therapeutic use]; Arthritis, Rheumatoid [*diagnostic imaging] [*drug therapy]; Disease Progression; Glucocorticoids [*therapeutic use]; Radiography; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans