Safety of medium- to long-term glucocorticoid therapy in rheumatoid arthritis: a meta-analysis

Vinod Ravindran¹, Satish Rachapalli¹ and Ernest H. Choy¹

Objective. Several randomized controlled trials (RCTs) and meta-analyses have confirmed clinical efficacy of glucocorticoids in RA. Concerns regarding safety associated with medium- to long-term use in RA have limited their use in clinical practice. In this meta-analysis, we assessed the toxicity related to medium- to long-term (defined as 1 year or longer) glucocorticoid therapy in RA.

Methods. MEDLINE, EMBASE and CINAHL databases were searched for RCTs of glucocorticoids in RA. RCTs fulfilling the following criteria were included: double-blinded, placebo-controlled, lasted 1 year or longer, used prednisolone (or equivalent) and in English. Toxicity was assessed by number of the patients withdrawn for adverse events (AEs), and the numbers of serious adverse events (SAEs) and AEs. RCTs were compared by meta-analysis using odd ratios (OR) with 95% CIs.

Results. Six RCTs with total of 689 patients met the inclusion criteria. All RCTs lasted ≥2 years. All studies allowed concomitant use of NSAIDs and DMARDs. Toxicity of glucocorticoid therapy based on number of patients withdrawn was limited (OR = 1.09; 95% CI 0.52, 2.25). Using number of AEs per patient-year (OR = 1.19; 95% CI 0.91, 1.57) and SAEs (OR = 1.06; 95% CI 0.67, 1.67) produced similar results. Efficacy/toxicity ratio was good for glucocorticoid treatment (number needed to harm/number needed to treat = 0.25).

Conclusion. Medium- to long-term glucocorticoid therapy in RA is associated with limited toxicity compared to placebo.

Key words: Rheumatoid arthritis, Treatment, Glucocorticoid, Meta-analysis.

Introduction
RA is a chronic inflammatory disease that leads to disability, impaired functioning and premature death. Though many patients now receive DMARDs and biologics, since 1950s glucocorticoids are commonly used in the treatment of RA. Whereas their clinical benefits and ability to inhibit the progression of radiological damage is generally accepted in RA [1–3], their clinical benefit/ risk associated with prolonged use is less certain because of concerns over toxicity.

Documentation of toxicity and adverse effects of therapy for RA, including glucocorticoids, in clinical trials lacks standardization [4]. Another potential problem in comparing studies done over past several decades is the use of different outcome measures. For example, modern randomized controlled trials (RCTs) have used summated indices like the ACR response criteria and disease activity scores (DASs) for assessing efficacy [5, 6]. However, such modern outcome assessments cannot be applied retrospectively to earlier RCTs.

We therefore based our meta-analysis on the simplest criterion of safety—whether treatment was stopped because of adverse effects. These outcome measures are routinely reported in clinical trials under the Consolidated Standards of Reporting Trials (CONSORT) guideline [7]. Validity of patient withdrawal as a marker for both efficacy and toxicity has been established in two large previous systematic reviews of treatments in RA and PsA [8, 9]. In this study, we have further validated this using the number of adverse events (AEs) and serious adverse events (SAEs).

Our primary aim in this meta-analysis was to assess the toxicity related to medium- to long-term (defined as 1 year or longer) glucocorticoid therapy in RA.

Methods
Search strategy
We searched the MEDLINE, EMBASE and CINAHL databases from their inception (starting in 1950) to December 2008. Medical subject headings (MeSH) terms used in the MEDLINE database search included ‘rheumatoid arthritis’, ‘corticosteroids’, ‘glucocorticoids’ (Supplementary Table 1, available as supplementary data at Rheumatology Online). Index terms were modified appropriately for the other databases. The Cochrane Library (the Cochrane Central Register of Controlled Trials and the Cochrane Database for Systematic Reviews) was also searched. This was supplemented by manually searching bibliographies of these articles and of previously published reviews.

Criteria for considering studies for this review and data extraction
Using a pre-defined protocol, two reviewers (V.R. and S.R.) independently selected studies for evaluation when they met all of the following criteria: (i) RCTs, (ii) enrolled adult patients with RA, (iii) at least one of the treatment groups was placebo, (iv) had double-blinded assessment, (v) lasted 1 year or longer, (vi) prednisolone (or equivalent) was used and (vii) publication was in English. Quality assessments of the suitable RCTs and data extraction from them were done independently by two reviewers (V.R. and S.R.). In case of disagreement, consensus was aimed for and if it was not achieved, a third reviewer (E.H.C.) gave final judgement. It was pre-determined that the corresponding author of an included RCT would only be contacted if any data/information relevant to this meta-analysis was found missing in the published RCT.

Quality of trials
The Jadad score (range 1–5) was used to assess the quality of the included RCTs [10]. In addition, we also assessed whether RCTs used a standardized protocol to record AEs and whether studies pre-defined AEs.
**Primary outcome measure**

The primary outcome for toxicity was the number of patients withdrawn due to AEs. This was validated using number of AEs per patient-year and number of SAEs.

**AEs and SAEs**

Using the standard definition of AEs and SAEs [11], the numbers of AEs and SAEs from the included RCTs were extracted. To be able to apply these definitions uniformly, all SAEs were included even if the investigators of the RCTs did not ascribe them to glucocorticoid treatment.

**Data analysis**

We used Review Manager (RevMan version 4.2 for Windows, Oxford, UK: The Cochrane Collaboration, 2007) software to carry out meta-analysis. Results were expressed as odds ratios (OR) with 95% CIs for dichotomous outcomes. Homogeneity between trials was evaluated using both the $\chi^2$ and the $I^2$ test for heterogeneity, functions which are incorporated in the RevMan 4.2 software. Data were initially pooled using fixed effects models. However, a random effects model was planned to be used if there was evidence of significant heterogeneity between trials ($P < 0.05$ for the $\chi^2$ test).

Meta-analysis of AEs was done using number of AEs per patient-year and of SAEs using the number of SAEs, to validate the results of meta-analysis based on patient withdrawal.

Ratio of numbers needed to treat (NNT) to numbers needed to harm (NNH) was calculated to assess the benefit vs risk of glucocorticoid treatment.

**Sensitivity analysis**

Sensitivity analyses were pre-determined and included the following:

(i) including only studies where patients with early RA were recruited;
(ii) including only studies with good quality (Jadad score of 5);
(iii) including only studies where oral glucocorticoid was used and
(iv) including only studies where low-dose (<7.5 mg/day) glucocorticoid was used.

**Results**

**Identification and selection of RCTs**

We identified 261 potentially relevant studies and out of these 38 RCTs underwent detailed review [12–49]. Thirty-one RCTs were excluded for the following reason(s): open label (i.e. not double blind) studies [12–15]; studies with no placebo arm [12–25]; and studies with duration of trial less than a year [23, 24, 26–42]. One RCT of 1-year duration was excluded as in this trial intramuscular depot methylprednisolone (MPS) was given at 0, 4 and 12 weeks only and therefore it did not examine the efficacy/safety of medium- to long-term usage of glucocorticoids [43]. The remaining six RCTs fulfilled the criteria for inclusion in this review; they are listed in Table 1 [44–49]. Figure 1 shows the flow chart of this selection process.

One of the excluded RCTs was published in Russian [15]. It was an open-labelled RCT and had no placebo arm (it compared MTX and prednisolone with MTX alone). Three of the excluded RCTs used intramuscular MPS [38, 39, 43] and one study [41] used intravenous pulse MPS. All data/information relevant to the present meta-analysis were available from the published RCTs. Corresponding author of one included RCT [49] was contacted to obtain a list of SAEs; it confirmed that all SAEs were already included in the published RCT.

**Characteristics of included RCTs**

All six RCTs used parallel design and lasted for ≥2 years. A total of 348 patients were in the glucocorticoid group and 341 in the placebo group. One RCT [44] had three arms (one each with prednisolone 5 and 3 mg/day and one with placebo), and for this meta-analysis we have included the prednisolone 5 mg/day arm only because the prednisolone 3 mg/day dose is not routinely used in the management of RA. One RCT [48] used intramuscular depot MPS and the rest oral prednisolone (Table 1).

**Retrobulbar vs Intraocular**

- **Table 1. Characteristics of RCTs included in the meta-analysis**

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>Trial duration, years</th>
<th>Numbers</th>
<th>Disease duration, years</th>
<th>Jadad score</th>
<th>Treatment</th>
<th>Prednisolone dose, mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamberlain and Keenan [44]</td>
<td>3.5</td>
<td>30</td>
<td>3–15</td>
<td>3</td>
<td>Pred + IM gold vs placebo + IM gold</td>
<td>5</td>
</tr>
<tr>
<td>Kirwan et al. [45]</td>
<td>2</td>
<td>128</td>
<td>&lt;2</td>
<td>5</td>
<td>DMARD + Pred vs DMARD + placebo</td>
<td>7.5</td>
</tr>
<tr>
<td>van Everdingen et al. [46]</td>
<td>2</td>
<td>81</td>
<td>&lt;2</td>
<td>5</td>
<td>Pred + SSZ vs placebo + SSZ</td>
<td>10</td>
</tr>
<tr>
<td>Capell et al. [47]</td>
<td>2</td>
<td>167</td>
<td>&lt;3</td>
<td>5</td>
<td>SSZ + Pred vs SSZ + placebo</td>
<td>7</td>
</tr>
<tr>
<td>Choy et al. [48]</td>
<td>2</td>
<td>91</td>
<td>2–10</td>
<td>3</td>
<td>IM depomedrone + DMARD vs placebo + DMARD</td>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Wassenberg et al. [49]</td>
<td>2</td>
<td>192</td>
<td>&lt;2</td>
<td>5</td>
<td>DMARD + Pred vs DMARD + placebo</td>
<td>5</td>
</tr>
</tbody>
</table>

IM gold: intramuscular gold (gold sodium thiomalate); Pred: prednisolone. *Not in first 6 months. **Equivalent dose.
All RCTs used low-dose (mean dose 6.5 ± 2 mg/day) prednisolone (or equivalent), one RCT [46] used 10 mg/day and the rest a dose of ≤7.5 mg/day. All RCTs allowed concomitant use of NSAIDs and DMARDs; however, in one RCT [46] no DMARDs were allowed in the first 6 months. Three of the RCTs included patients with early RA (disease duration <2 years) [42, 43, 46] and in one [47] median disease duration was 1 year.

Quality assessment

All RCTs were of good quality and four had Jadad score of 5. All but one [45] RCT used a standardized protocol to record AEs and all but two [44, 45] pre-defined AEs.

Toxicity

Toxicity based on the number of patients withdrawn due to AE was limited (OR = 1.09; 95% CI 0.52, 2.25; P = 0.82) (Fig. 2). The RCTs did not show significant heterogeneity ($\chi^2 = 2.22; P = 0.53$).

Sensitivity analysis

Sensitivity analyses were carried out based on type of glucocorticoid used, disease duration, daily dose of glucocorticoid and quality of studies (Table 2) and it showed lack of statistical difference in the ORs.

**AEs**

The total numbers of AEs were 237 in 726 patient-years and 211 in 697 patient-years in the glucocorticoid group and placebo group, respectively (Fig. 3). This difference was not statistically significant (OR = 1.19; 95% CI 0.91, 1.57; P = 0.21).

**SAEs**

Numbers of SAEs were 60 and 58 in the glucocorticoid group and placebo group, respectively (Fig. 4). This difference was not statistically significant (OR = 1.06; 95% CI 0.67, 1.67; P = 0.80).

**Benefit vs risk**

Ratio of NNT to NNH for glucocorticoid therapy was 0.25. To calculate this, the number of patients withdrawn because of lack of efficacy was also extracted (in the glucocorticoid group 11/348 patients and in the placebo group 21/341 patients).

**Discussion**

Few treatment strategies incite such diversity of opinion amongst rheumatologists as the medium- to long-term use of glucocorticoids in the treatment of RA. We carried out a meta-analysis of double-blind, placebo controlled, randomized trials of medium- to long-term glucocorticoid therapy in RA to assess the evidence for their safety.

Documentation of toxicity and adverse effects of therapy for RA in clinical trials lacks standardization, whereas for evaluating therapeutic effects in RA, such criteria have been extensively developed, enabling meta-analyses [4]. The present meta-analysis using patient withdrawal as a marker for toxicity and adverse effects overcomes such limitation and has shown that the toxicity of glucocorticoid therapy in trials lasting ≥2 years is low. This was further supported by the lack of difference in both AEs and SAEs associated with glucocorticoid therapy compared with placebo in the present meta-analysis.

Results of our meta-analysis support the conclusion of a recent comprehensive review [50] of the safety of low-dose glucocorticoid therapy in four prospective trials [45–47, 49] (included in the present meta-analysis) and of the Combinatietherapie Bij Reumatoide Artritis (COBRA) study [23] that the evidence on which to support clear recommendations about toxicity of low-dose glucocorticoids is surprisingly weak. In the present meta-analysis of studies using lower dose of prednisolone (mean dose 6.5 mg/day), the ratio of NNT:NNH was 0.25, implying good tolerability. These findings raise the possibility that the balance of risks/benefits of low-dose treatment might be different from that of medium- and high-dose treatment, for which the mechanisms of action of glucocorticoids may be different [51].

Patient withdrawal is complex and may be the result of a combination of both AEs and poor efficacy. The reason for withdrawal, which is determined arbitrarily by the investigator, is a potential limitation. Lack of significant difference in both AEs and SAEs determined by meta-analysis confirms the validity of patient withdrawal as a marker of toxicity in the present meta-analysis.

![Fig. 2. Overall toxicity based on withdrawals due to AEs. M-H: Mantel-Haenszel method; fixed: fixed effects model.](https://academic.oup.com/rheumatology/article-abstract/48/7/807/1790043/809)
Six RCTs with a total of 689 patients met the inclusion criteria. Methodologically, small number of studies may reduce the power of this study to detect rare uncommon AEs although the results of all the trials appear consistent (chi-square for heterogeneity, $\chi^2 = 2.22; P = 0.53$; Fig. 2). Moreover, sensitivity analyses of the studies (based on type of glucocorticoid used, disease duration, daily dose of glucocorticoid and quality of studies; Table 2) showed similar results.

Meta-analysis is not a substitute for well designed, large, controlled trials [52]. Several areas of glucocorticoid therapy such as patient selection, duration, dose, timing and measures to prevent side effects are a part of the currently agreed research agenda at international level [4]. Standardization of assessment of AEs may enable aetiological and causal inferences [53]. Recently, evidence-based recommendations for the safer use of systemic glucocorticoid therapy in rheumatic diseases have been published [4]. These include patient education, monitoring for AEs and use of concomitant therapy to reduce unwanted side effects and special safety advice. Adherence to these guidelines might reduce the AEs in patients on glucocorticoids.

Our meta-analysis of randomized, double-blind and placebo controlled trials has shown that glucocorticoid therapy in medium to long term has limited toxicity compared to placebo. Currently, because of lack of consensus regarding factors such as duration, dose and timing of glucocorticoid therapy and due to availability of more efficacious therapies for RA, long-term therapy with glucocorticoids is not thought to be justified [54]. On the other hand, use of high-dose prednisolone for shorter duration with DMARDs in early RA [23, 25] is a widely accepted strategy as is the targeted use of glucocorticoids to treat flares in RA [1]. Results of our meta-analysis highlight the need for research in several areas of glucocorticoid therapy in RA.

**Rheumatology key messages**

- Medium- to long-term glucocorticoid therapy in RA is associated with limited toxicity compared to placebo.
- Long-term, low-dose glucocorticoid therapy is not considered a substitute for aggressive therapy for early RA.
- Further research employing standardized assessments of AEs of glucocorticoid therapy in RA is required.

**Acknowledgements**

We thank Dr S. Wassenberg for providing details of serious adverse events in the low dose prednisolone therapy study [49].

**Funding:** Sir Alfred Baring Garrod Clinical Trials Unit is supported by an ARC (Arthritis Research Campaign, UK)-integrated clinical academic centre grant.

**Disclosure statement:** The authors have declared no conflicts of interest.

**Supplementary data**

Supplementary data are available at *Rheumatology* Online.

**References**


Safety of glucocorticoid therapy in RA


