Systematic review and meta analysis

The efficacy of systemic glucocorticosteroids for pain in rheumatoid arthritis: a systematic literature review and meta-analysis

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Abstract

Objectives. Glucocorticosteroids (GCs) are recommended to suppress inflammation in people with active RA. This systematic review and meta-analysis aimed to quantify the effects of systemic GCs on RA pain.

Methods. A systematic literature review of randomized controlled trials (RCTs) in RA comparing systemic GCs to inactive treatment. Three databases were and spontaneous pain and evoked pain outcomes were extracted. Standardized mean differences (SMDs) and mean differences were meta-analysed. Heterogeneity (I², tau statistics) and bias (funnel plot, Egger’s test) were assessed. Subgroup analyses investigated sources of variation. This study was pre-registered (PROSPERO CRD42019111562).

Results. A total of 18 903 titles, 880 abstracts and 226 full texts were assessed. Thirty-three RCTs suitable for the meta-analysis included 3123 participants. Pain scores (spontaneous pain) decreased in participants treated with oral GCs; SMD = 0.65 (15 studies, 95% CI 0.82, 0.49, P < 0.001) with significant heterogeneity (I² = 56%, P = 0.0002). Efficacy displayed time-related decreases after GC initiation. Mean difference visual analogue scale pain was –15 mm (95% CI –20, –9) greater improvement in GC than control at ≤3 months, –8 mm (95% CI –12, –3) at >3–6 months and –7 mm (95% CI –13, 0) at >6 months. Similar findings were obtained when evoked pain outcomes were examined. Data from five RCTs suggested improvement also in fatigue during GC treatment.

Conclusion. Oral GCs are analgesic in RA. The benefit is greatest shortly after initiation and GCs might not achieve clinically important pain relief beyond 3 months. Treatments other than anti-inflammatory GCs should be considered to reduce the long-term burden of pain in RA.

Key words: RA, glucocorticoids, pain, tender joint, meta-analysis

Rheumatology key messages

- The magnitude and duration of the effects of systemic glucocorticosteroids on pain in RA are not well-described.
- Systemic glucocorticosteroids were effective for pain for ≤3 months and appeared less effective ≥6 months.
- Systemic glucocorticosteroid treatments should be time-limited and new treatments are required for RA pain.

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**Introduction**

Pain is the most troublesome symptom of RA [1]. Glucocorticosteroids (GCs) are used to provide rapid relief of symptoms in people with active RA, as part of disease-modifying combination treatments [2,3]. Current clinical practice uses GCs with a range of doses, treatment durations and routes of administration. Short-term, low dose oral GCs are effective in reducing pain [4,5], but the magnitude and duration of benefit over placebo are uncertain for the range of regimens in current clinical practice. Long-term GC use is associated with significant health problems, such as total joint replacement, osteoporosis, diabetes mellitus and cardiovascular risk [6,7]. A precise understanding of benefit is required to inform decisions about their use to relieve pain.

Persistent pain remains a problem in RA. DMARDs, including biologics, reduce pain from the high levels associated with high disease activity. However, complete pain resolution is not common and there may be multiple mechanisms acting on the pain experience. Many people report persistent pain despite inflammation responding well to biologic treatment [8]. People with RA experience pain at rest and during normal activities. They also display increased sensitivity to evoked pain in response to stimuli such as normal movement or gentle pressure on the joints. This pain sensitivity may indicate sensitization of peripheral or central nociceptive pathways and contributes to the clinical pain reported by people with RA [9]. Peripheral sensitization may be due to articular inflammation. In addition, widespread pain and other evidence of central sensitization are common and contribute to pain in people with RA [10]. Chronic pain is strongly associated with fatigue, which may itself be an indication of central sensitization [11,12]. Chronic joint pain in longstanding, inadequately controlled disease might in addition be influenced by common secondary OA [13]. Systemic GCs and DMARDs might therefore not be sufficient to adequately relieve pain in people with RA.

To inform the optimal use of systemic GCs, this study aimed to quantify the specific effects of systemic GCs for pain in people with RA, including both clinical and evoked pain (joint tenderness), across treatment durations, routes of administration and doses. This study was pre-registered with PROSPERO (CRD42019111562).

**Methods**

**Search methods**

OVID Medline, OVID Embase and Cochrane CENTRAL databases were searched for studies until 22 October 2020. Reference lists of publications were also searched. Search terms are presented in Supplementary Data S1, available at Rheumatology online. Reviewers independently assessed titles, abstracts and full texts in duplicate (D.F.M. with J.J.-D., D.T., R.M. and O.S.I.). No language restrictions were placed on searching, but only data that were reported in English language were extracted. Study selection is summarized in Fig. 1. Data extraction was performed in duplicate using a predefined form (D.F.M., J.J.-D., D.T. and O.S.I.). Any disagreements were resolved through discussion and if necessary, the involvement of another author (D.A.W.).

The following study characteristics were extracted. Descriptives: first author, year of publication, name of trial, registration number of trial. Participants and clinical details at baseline: number, age data, sex data, DAS, 28-joint DAS (DAS28), HAQ and other indicators of RA activity/severity. Interventions: GC and DMARD name(s), GC dose(s), sample size (n) per trial arm, route of GC administration, duration of GC administration, duration of follow-up assessments. Outcomes: all pain-related outcomes including fatigue outcomes at all time points reported. Data were extracted from published graphs using manual measurement. Crossover trial data from all phases of the study were used [14]. Trial quality and risk of bias indicators were recorded as high/low risk of bias or unclear [14]. Random sequence generation, allocation concealment, blinding of participants, blinding of trial physicians, blinding of outcome observers, study attrition rate (>5% threshold used), intention to treat analysis, outcome reporting were all assessed. Trial reports that scored ≥4 low risk items were classified as high quality for the purposes of this study.

**Types of studies and participants**

Randomized controlled trials published in the peer-reviewed literature were included. Studies were in adults (≥18 years) diagnosed with RA by a physician or formally classified according to published criteria (e.g. [15]).

**Types of interventions**

Studies were included if they allowed systemic GCs to be compared with an inactive treatment (with other DMARDs kept equal or stable across the study arms), or comparisons between different GC treatments or regimens (e.g. dosages or routes of administration). Studies were included when participants received other DMARD treatments, as long as a specific treatment effect could be assigned to systemic GCs. One synthetic agonist of the GC receptor was also identified during the searches and was included. Studies of IA GC administration were excluded.

**Types of outcome measures**

Pain outcomes were classified as ‘spontaneous’ or ‘evoked’. Spontaneous pain included bodily pain, joint pain or morning/evening pain. Evoked pain included observer-induced pain measured by Ritchie Articular Index (RAI), tender joint counts (TJC) and quantitative sensory testing/measures of pain sensitivity, and also pain reported upon movement. All pain outcomes from all time points were recorded. Additional to the published protocol, a parallel synthesis of fatigue, as a pain-related outcome measure, was performed and all fatigue
measures were extracted. Painful adverse effects/events were not extracted or analysed.

**Measures of treatment effect**

The average outcome measure and an estimate of its spread/variation were extracted. If no other data were available, then published median and interquartile range were used to estimate the mean and s.d. \((1.35 \times \text{interquartile range})\). Each study’s own published data were used to extrapolate missing s.d. and other values (using RevMan5 software calculator, Cochrane collaboration). Mean (s.d.) values were calculated for short ordinal scales, such as pain score from 0–3, by treating the scales like continuous data. Unless stated otherwise, the first reported follow-up time point per study was used for analysis.

**Statistical analysis and meta-analysis**

Meta-analyses of pain, evoked pain and fatigue were performed in parallel. Standardized mean differences (SMDs) were calculated for follow-up time points (the primary dependent variable for this study) and for change scores from baseline (mean and s.d. of change from baseline). Mean differences (MDs) of each measure were also calculated, allowing estimation of the absolute patient-reported levels of improvement, rather than standardized measures of relative effects. As TJC and RAI are both indices of tender joints, their scores were normalized (range 0–1), allowing for MD to be calculated for studies using either score. Meta-analyses were performed using the Meta [16, 17] and Metafor [18] packages in R, weighted by standard inverse-variance methods [14]. Heterogeneity was quantified using \(I^2\) and tau statistics [19] and the \(P\)-value of the Q statistic, \(p(Q)\) [19]. Bias was assessed with a funnel plot and Egger’s test [20]. Subgroup analyses were performed to investigate potential sources of variation: administration route, duration of treatment and risk of bias.

Meta-regression analysis for pain data from all time points of each study was used to look for the association between duration of follow-up (or improvement in inflammation), and the SMD was adjusted for multiple observations within studies. Meta-regressions were performed using multilevel analyses with level 3 = study, level 2 = participant, level 1 = outcome data from all reported time points [21].

**Results**

**Study selection and systematic review**

A total of 18 903 papers were identified, 880 abstracts were selected for review and 226 full texts were assessed. A total of 70 full texts were retrieved, of which 33 reported GC efficacy for spontaneous pain, 38 for evoked pain and 26 additional texts reported other comparisons related to pain (some recorded multiple outcomes; Table 1). The study selection process is summarized in Fig. 1. The systematic review of GC efficacy for pain in RA is summarized in the harvest plot in Fig. 2. None of the studies reported increased pain outcomes in response to systemic GC treatment, and most studies reported a significant improvement during follow-up (Fig. 2A, D and G). Details of the studies comparing GC with inactive comparator are shown in Table 1 (for those included in meta-analysis [22–61]) and supplementary Table S1, available at *Rheumatology* online (all studies [22–91]).

A total of 33 studies (26 for spontaneous pain and 25 for evoked pain measures) were included for the meta-analyses. Most of these studies reported oral GC dosing \((n = 22)\), whereas four studies used i.m., six studies used i.v. and one study used iontophoresis routes of administration. The most common measures reported were the 100 mm pain visual analogue scale (VAS; \(n = 26\)), 28-joint TJC \((n = 22)\) and RAI \((n = 13)\). A total of 3123 participants (70% female) were enrolled in the 33 studies. The
| First author | Year | Country     | Female (%) | Average age (years) | Total N | GC Administration | Dose | Freq. | GC duration | Study duration | Ran domisation | Attrition |Participants blinded | Physic ians blinded | Assess or s blinded | Attr i on | Spec i fied analysis | ITT Reporting |
|--------------|------|-------------|------------|--------------------|---------|--------------------|------|------|-------------|----------------|----------------|-----------|----------------------|-------------------|---------------------|-----------|---------------------|--------------|
| Bakker [22]  | 2012 | Netherlands | 71         | 54                 | 236     | Prednisolone Oral  | 10 mg| Daily | 2 y         | 8 d            | Yes           | No        | Yes                  | No                | Yes                 | Yes        | Yes                 | Yes          |
| Bohm [23, 24]| 1967 | Germany     | 75         | 49                 | 40      | Prednisolone Oral  | 2.5 mg| Un known | 8 d         | 24 w           | Yes           | No        | Yes                  | Yes               | Yes                 | Yes        | Yes                 | Yes          |
| Corkill [25] | 1990 | UK          | 64         | 54                 | 59      | Depot methyl prednisolone I.m. | 120 mg| 8 w    | 24 w        | Yes            | Yes           | Yes       | No                  | No                | Yes                 | Yes        | Yes                 | Yes          |
| Kirwan [26]  | 1995 | UK          | 64         | 49                 | 128     | Prednisolone Oral  | 7.5 mg| Daily | 2 y         | 2 w            | Yes           | Yes       | Yes                  | Yes               | Yes                 | Yes        | Yes                 | Yes          |
| Lee [45]     | 1973 | Unknown     | Unknown     | 141                |         | Prednisolone Oral  | 15 mg| Daily | 2 w         | 32 w           | Yes           | No        | Yes                  | No                | Yes                 | Yes        | Yes                 | Yes          |
| Scott [28–30]| 2016 | UK          | 76         | 54                 | 467     | Prednisolone Oral  | 60 mg, tapered to 7.5 mg at 6 w, continued to 28 w | Daily | 28 w (up to 34 w) | Yes           | Yes       | Yes                  | Yes               | Yes                 | Yes        | Yes                 | Yes          |
| Sheldon [31] | 2003 | UK          | 62         | 56                 | 26      | Budesonide Oral    | 9 mg  | Daily | 4 w         | 4 w            | Yes           | Yes       | Yes                  | No                | Yes                 | Yes        | Yes                 | Yes          |
| van Gestel [33]| 1995 | Netherlands | 70         | 57                 | 40      | Prednisolone Oral  | 10 mg, tapering Daily | 18 w  | 18 w        | Yes           | Yes       | Yes                  | Yes               | Yes                 | Yes        | Yes                 | Yes          |
| Alten [34, 35]| 2015 | Germany     | 84         | 57                 | 350     | Prednisolone Oral  | 5 mg  | Daily | 12 w        | 3 w            | Yes           | Yes       | Yes                  | No                | Yes                 | Yes        | Yes                 | Yes          |
| Berry [36]   | 1974 | UK          | 50         | 58                 | 12      | Prednisolone Oral  | 15 mg| Daily | 1 w         | 3 w            | Yes           | Yes       | Yes                  | Yes               | Yes                 | Yes        | Yes                 | Yes          |
| Buttgeriet [37]| 2019| Germany     | 69         | 55                 | 323     | Fosdagrocort (F)/prednisolone (P) I.m. | 120 mg| Not sure | 2 y         | 2 y            | Yes           | Yes       | Yes                  | Yes               | Yes                 | Yes        | No                  | Yes          |
| Choy [38]    | 2005 | UK          | 78         | 57                 | 91      | Depomedrone (methylpred) I.m. | 120 mg| Not sure | 2 y         | 2 y            | Yes           | Yes       | Yes                  | Yes               | Yes                 | Yes        | Yes                 | Yes          |
| Harris [39]  | 1983 | USA         | 68         | 55                 | 34      | Prednisolone Oral  | 5 mg  | Daily | 24 w        | 32 w           | Yes           | Yes       | Yes                  | Yes               | Yes                 | Yes        | Yes                 | Yes          |
| Hua [40]     | 2020 | China       | 78         | 47                 | 59      | Prednisone Oral    | 10 mg dally daily for 12 w, 5 mg daily for next 8 w | Daily | 6 m           | 6 m           | Yes           | Yes       | Yes                  | Yes               | Yes                 | Yes        | Yes                 | Yes          |
| Jasani [41]  | 1968 | UK          | 78         | 50                 | 9       | Prednisolone Oral  | 15 mg| Daily | 1 w         | 4 w            | Yes           | Yes       | Yes                  | Yes               | No                  | Yes        | No                  | Yes          |
| Jelinek [42] | 1991 | Australia   | 59         | 22–77 y range      | 22      | Methyl prednisolone I.v. | 40 mg| Once | 8 w         | Yes            | Yes           | Yes       | Yes                  | Yes               | No                  | Yes        | No                  | Yes          |
| Kennedy [43] | 1973 | UK          | 83         | 50                 | 24      | Triamcinolone acetoniode (Kenalog) I.m. | 80 mg| Once | 4 w         | Yes            | Yes           | Yes       | Yes                  | Yes               | No                  | Yes        | Yes                 | Yes          |
| Kirwan [44]  | 2004 | UK, Belgium, Sweden | 71          | 55                 | 143     | Budesonide (B) and prednisolone (P) Oral | B 9 mg, B 3 mg, P 7.5 mg | Daily | 12 w        | 16 w           | Yes           | Yes       | Yes                  | Yes               | Yes                 | Yes        | Yes                 | Yes          |
| Li [46]      | 1996 | Canada      | 80         | 57                 | 10      | 4 mg/ml 2 d      | 5 d  | 20 d        | Yes           | Yes           | Yes       | Yes                  | Yes               | Yes                 | Yes        | Yes                 | Yes          |

(continued)
| First author | Year | Country            | Female (%) | Average age (years) | Total N | GC Administration | Dose               | GC duration | Study duration | Ran domization | Alloca tion conceal ment | Participants blinded | Physici ans blinded | Assess blinded | Attrition | Speci fied analysis | ITT Reporting |
|--------------|------|--------------------|------------|---------------------|---------|-------------------|--------------------|--------------|----------------|-----------------|--------------------------|----------------------|---------------------|---------------|------------|----------------------|---------------------|
| Montecucco   | 2012 | Italy              | 64         | 60                  | 220     | Dexamethasone     | Prednisolone       | Oral         | 12.5 mg to 6.25 mg after 2 w | Daily          | 52 w         | 1 y                | No                  | Yes               | No               | No           | Yes                   | Yes               |
| Pavelka      | 1992 | Czech Republic     | Unknown    | Unknown             | 34      | Methylprednisolone| I.v. 1 g           | 3×           | 8 w              | Un clear       | Un clear         | Yes               | Un clear           | Yes               | Un clear     | Yes                   | Yes               |
| Stenberg     | 1992 | USA                | 61         | 61                  | 36      | Prednisolone      | Oral 5 mg          | Daily         | 6 m             | 1 y             | Un clear         | Yes               | Un clear           | Yes               | Yes                   | Yes               |
| Stock        | 2017 | USA                | 59         | 56                  | 86      | Fosdagrocorat (F), prednisolone (P) | Oral 10 mg, F 25 mg, P 5 mg | Daily       | 2 w             | 2 w             | Yes             | Yes               | Yes               | Yes                   | Yes               |
| Taylor       | 1999 | New Zealand        | 75         | 55                  | 36      | Syncathen depot  | Prednisolone       | Oral         | 10 mg           | Daily          | 2 d            | 6 m             | Yes               | Un clear         | Yes               | Yes                   | Yes               |
| van Everdingen | 2002 | Netherlands        | 64         | 62                  | 81      | Prednisolone      | Oral 10 mg         | Daily         | 2 y             | 2 y             | Yes             | Yes               | Yes               | Yes                   | Yes               |
| Williams     | 1982 | UK                 | 90         | 56                  | 20      | Methylprednisolone| I.v. 1 g           | Once         | 1 d             | 6 w             | Un clear        | Yes               | Yes               | Yes                   | Yes               |
| Evoked pain  |      |                    |            |                     |         |                   |                   |             |                 |                 |                |                   |                   |                       |                   |
| Dick         | 1970 | UK                 | 46         | 48                  | 24      | Prednisolone      | Oral 10 mg         | Daily        | 1 w             | 1 w             | Un clear        | Yes               | Un clear          | Yes               | Yes                   | Yes               |
| Hansen [61]  | 1990 | Denmark             | 73         | 60                  | 97      | methylprednisolone| l.v. 15 mg/kg      | 4 weeks     | 6 m             | 1 y             | Yes             | Yes               | Yes               | Yes                   | Yes               |
| Kuzkaz [56]  | 1990 | Syria              | 80         | 49                  | 41      | Methylprednisolone| l.v. 1 g           | Once        | 1 day           | 8 w             | Yes             | Yes               | Yes               | Yes                   | Yes               |
| Lee          | 1974 | UK                 | Unknown    | Unknown             | 21      | Prednisolone      | Oral 2.5 mg        | Daily       | 4× daily        | 1 w             | Un clear        | Yes               | Un clear          | Yes               | Yes                   | Yes               |
| Liebling     | 1981 | USA                | 70         | 55                  | 10      | Methylprednisolone| l.v. 1 g           | Monthly     | 6 m             | 12 m            | Yes             | Yes               | Yes               | Yes                   | Yes               |
| Vershueren   | 2017 | Belgium            | 79         | 51                  | 91      | Prednisone        | Oral 30–20–12.5–10–7.5–5 mg tapering | Daily       | 2 y             | 2 y             | Yes             | Yes               | Yes               | Yes                   | Yes               |
| van der Elst | 2017 | Belgium            | 79         | 51                  | 91      | Prednisone        | Oral 30–20–12.5–10–7.5–5 mg tapering | Daily       | 2 y             | 2 y             | Yes             | Yes               | Yes               | Yes                   | Yes               |
| Wang [60]     | 2017 | China              | 112        |                     |         | Prednisone        | Oral 30–20–12.5–10–7.5–5 mg tapering | Daily       | 2 y             | 2 y             | Yes             | Yes               | Yes               | Yes                   | Yes               |

ITT: intention to treat; d: days; m: months; w: weeks; y: years.
mean age of participants was 55 years. Baseline disease activity characteristics indicated active RA (supplementary Table S1, available at Rheumatology online).

Spontaneous pain

Meta-analysis of spontaneous pain data from all studies at the single earliest available time point showed SMD (95% CI) for GCs on spontaneous pain of −0.67 (−0.84, −0.50) with significant heterogeneity measured by $I^2 = 62\%$, tau = 0.28, p(Q) < 0.01 (Egger’s P-value for asymmetry <0.0001). Oral GCs were examined alone (n = 15 studies) and showed a statistically significant reduction in spontaneous pain (Fig. 3A for forest plot and Fig. 3B for funnel plot) with SMD $I^2 = 56\%$, tau = 0.21, p(Q) = 0.0045]. The funnel plot indicated statistically significant asymmetry for the analyses of oral GCs (Egger’s P < 0.0001; Fig. 3B). MDs in 100 mm VAS pain showed improvements of $15\text{mm}$ with significant heterogeneity $I^2 = 62\%$, tau = 4.7, p(Q) = 0.0024. Egger’s test for funnel plot asymmetry yielded $P = 0.052$.

Further subgroup analyses investigated the time course of oral GCs effects on spontaneous pain. Efficacy displayed time-related decreases across three subgroups of increasing duration (Fig. 4A). For these studies, the MDs in 100 mm VAS pain showed the greatest improvement (−15 mm) in the 0–3 month period (Fig. 4B), with MDs of −8 mm and −7 mm for longer durations of treatment (>3–6 months and >6 months, respectively). These findings were supported by the SMD and MD for change in spontaneous pain (supplementary Fig. S1, available at Rheumatology online) and by meta-regression (supplementary Fig. S2, available at Rheumatology online).

Trials classified as high quality retained similar findings to those from all studies. The earliest time point for all high-quality trials showed 14 studies with SMD $I^2 = 56\%$, tau = 0.73, −0.42. Time-related changes in efficacy of oral GCs in high quality studies are shown in supplementary Fig. S3A, available at Rheumatology online.

No association was detected between routes of administration and analgesic effect (supplementary Fig. S4, available at Rheumatology online). Meta-regression analysis indicated that improvements in ESR were associated with improvements in spontaneous pain (Supplementary Data S2, available at Rheumatology online).

Evoked pain

A meta-analysis of evoked pain from all studies at the single earliest available time point showed SMD (95% CI) for GCs of −0.57 (−0.73, −0.42) with significant heterogeneity $I^2 = 72\%$, tau = 0.42, p(Q) < 0.001 (Egger’s P = 0.0041). Oral GCs (n = 15 studies) showed a statistically significant reduction in evoked pain of −0.71 (−0.97, −0.45) with heterogeneity $I^2 = 78\%$, tau = 0.43, p(Q) < 0.001 (Egger’s P = 0.0003). In oral GCs, the MD for a harmonized TJC and RAI joint scores showed improvements equivalent to 2.5 tender joints or 9.7 points of the RAI [normalized MD = −0.12 (−0.18, −0.07), with $I^2 = 79\%$, tau = 0.09, p(Q) < 0.001 (Egger’s P = 0.0008)].

Subgroup analysis was used to investigate the time course of oral GCs on evoked pain. A pattern of decreasing efficacy at the >6 months subgroup was observed (Fig. 5). The MDs for a normalized TJC and RAI joint score showed improvements that decreased as follow-up time progressed, equivalent to 3.6 tender joints or 10 points on the RAI for the first 3 months and decreasing to 0.8 joints or 2.3 points on the RAI in the >6 month treatment duration category (supplementary Fig. S5, available at Rheumatology online).

Trials classified as high quality retained similar findings to the overall comparisons. The earliest time point for all higher quality GC reports showed n = 16 studies with SMD $I^2 = 56\%$, tau = 0.73, −0.67 $I^2 = 79\%$, tau = 0.82, $I^2 = 73\%$, tau = 0.97. The funnel plot (supplementary Fig. S6, available at Rheumatology online) yielded $P < 0.0001$ (Egger’s $I^2 = 79\%$, tau = 0.08, $P = 0.01$ (Egger’s $I^2 = 79\%$, tau = 0.07), with $I^2 = 79\%$, tau = 0.09, p(Q) < 0.001 (Egger’s $I^2 = 79\%$, tau = 0.07)]

GC withdrawal studies and head-to-head comparisons between GCs or treatment regimens

The studies related to GC withdrawal and head-to-head comparisons of GCs are shown in supplementary Table S2, available at Rheumatology online. Both spontaneous and evoked pain worsened with GC withdrawal in most studies (Fig. 2). Higher doses of GC were generally not associated with greater pain improvement (Fig. 2). Head-to-head comparisons of different oral GCs found that 1 mg betamethasone and 8 mg prednisolone daily gave similar outcomes [73], as did budesonide at 9 mg and 3 mg daily [44]. One trial of the GC receptor partial agonist fosdagrocorat daily at 15 mg gave similar outcomes to 10 mg prednisolone but stronger response for spontaneous pain than 5 mg prednisolone after 8 weeks [37]. Another study of fosdagrocorat found similar responses for 25 mg and 10 mg of the agonist compared with 7.5 mg and 5 mg prednisolone [49].

Aqueous drops and tablets of deflazacort were found to give similar outcomes over 3 weeks [83]. I.m. methylprednisolone (120 mg every 4 weeks) improved spontaneous pain more than 500 mg tablets (every 4 weeks), but evoked pain changes were similar between groups [82]. I.v. methylprednisolone (1000 mg for 3 days) and oral tablets (1000 mg for 3 days) gave similar levels of pain improvement [88].

Delayed release prednisolone gave similar pain improvement to standard release after 12 weeks of nighttime dosing in the CAPRA-1 study [75]. Six weeks of ultradian dosing gave similar results to circadian dosing of prednisolone in one trial [80]. Additionally, dosing at 2 a.m. with 7.5 mg prednisolone yielded greater pain improvements than 7.30 a.m. doses (25 mm difference on 100 mm VAS) in one study [81].
Fatigue
Five studies reported fatigue outcomes in response to systemic GCs [28, 32, 34, 35, 89, 92]. Fatigue was reported to improve with GC use in three trials verses placebo (two high-quality double-blind studies [28, 35] and one open-label [32]), using fatigue scales of functional assessment of chronic illness therapy – fatigue (FACIT-F), VAS and Short Form 36-Vitality. These studies contained a total of 907 people that used oral GCs between 12 and 28 weeks. A meta-analysis of fatigue suggested that GC was associated with an SMD (95% CI) of −0.24 (−0.47, 0.00, n = 3 studies) when compared with placebo [28, 32, 35]. Withdrawal of oral GCs (and replacement with placebo) was reported to increase fatigue in two trials [89, 92].

Discussion
The data suggest that systemic GCs reduce pain outcomes in people with active RA. Heterogeneity between studies was partly explained by duration of GC treatment, but not by route of administration or study quality. Systemic GCs may also improve fatigue in people with active RA. Pain improvement with systemic GCs was most pronounced within 3 months of starting treatment, and might be substantially less beyond 6 months. Systemic GCs are often administered to provide symptomatic relief for people with active RA. Current UK treatment guidelines recommend GC use in early RA, for bridging and for flares [2], and examples of all these were included in our meta-analysis. Long-term GC use is recommended if other DMARDs have been unsuccessful [2]. At an individual level, improvements of 10–20 mm on a 100 mm VAS pain scale may be considered clinically important [93]. Mean effects beyond the first 6 months of treatment might not be clinically important, suggesting that fewer than half of participants on long-term GC treatment gain a clinically important improvement above placebo responses. Systemic GCs also reduced fatigue, but again improvements were small by comparison with placebo. Lack of analgesic dose-response for oral GCs, or between oral and parenteral treatment, but not by route of administration or study quality. Systemic GCs may also improve fatigue in people with active RA. Pain improvement with systemic GCs was most pronounced within 3 months of starting treatment, and might be substantially less beyond 6 months. Systemic GCs are often administered to provide symptomatic relief for people with active RA. Current UK treatment guidelines recommend GC use in early RA, for bridging and for flares [2], and examples of all these were included in our meta-analysis. Long-term GC use is recommended if other DMARDs have been unsuccessful [2]. At an individual level, improvements of 10–20 mm on a 100 mm VAS pain scale may be considered clinically important [93]. Mean effects beyond the first 6 months of treatment might not be clinically important, suggesting that fewer than half of participants on long-term GC treatment gain a clinically important improvement above placebo responses. Systemic GCs also reduced fatigue, but again improvements were small by comparison with placebo. Lack of analgesic dose-response for oral GCs, or between oral and parenteral

This harvest plot summarizes all of the different types of evidence for the primary hypothesis in the systematic review of GC efficacy for pain outcomes. Each study can provide spontaneous and evoked pain data, which are represented as single bars [each study can contribute a spontaneous and an evoked pain outcome to each row of three panels, e.g. (A–C)]. The height of each bar is the study quality (range 0–9). Study results that showed statistically significant evidence for GCs improving pain are shown in the left-hand panels (A, D, G, J, M); studies that only found non-significant differences are shown in the middle panels (B, E, H, K, N). No studies reported that GCs increased pain (right-hand panels C, F, I, L, O). Panels (A–C) summarize all trials of GC vs inactive comparator (all analysis methodologies). Panels (D–F) summarize all data comparing GC vs inactive comparator [the primary method for calculating SMDs and MD in this review; these are subsets of panels (A–C)]. Panels (G–I) summarize all data comparing change scores for pain between GC and inactive comparator [the secondary method of calculating SMDs in this review; these are subsets of panels (A–C)]. Panels (J–L) summarize data from trials that withdrew GCs and replaced them with placebo (increased pain implied that GCs were effective at reducing pain prior to withdrawal). Panels (M–O) summarize dose-response studies (higher doses of GCs reduce pain more than lower doses). If any reported significant difference in pain was reported, the study is presented as showing a significant difference. GCs: glucocorticosteroids; MD: mean difference; SMD: standardized mean difference.
GCs, might suggest that maximum analgesic effect is achieved with low doses of oral prednisolone (possibly ≤15 mg daily). Long-term GC use, particularly at high doses, is associated with risk of adverse events, including total joint replacement, fracture risk, diabetes mellitus and cardiovascular disease [7, 94]. Systemic GCs are effective for reducing pain in people with active RA, but benefits might not outweigh risks with long-term treatment.

We categorized pain outcomes as spontaneous or evoked. We found similar magnitudes of reductions in both spontaneous and evoked pain outcomes with systemic GCs, supporting the relevance of evoked pain to clinically important pain for the person with RA. Fatigue reflects mechanisms within the CNS closely associated with central sensitization and pain, and is also an important outcome for people with RA [12, 95]. Systemically administered GCs cross the blood–brain barrier and may have psychoactive effects (some of which may be undesirable) [96]. However, the analgesic response to GCs is more likely to be due to anti-inflammatory effects within joints, rather than actions on the CNS. The relatively weak response of fatigue to GC treatment also implies that central mechanisms might not be much altered. Long-term analgesic benefit from systemic GCs might be suggested by increased pain during withdrawal, but it is possible that steroid-responsive individuals are enriched in these trials. Pain is exacerbated by stress [97], and steroid withdrawal might be associated with physiological changes that could increase pain, particularly in long-term users.

This study has several limitations. Not all studies reported pain outcomes, despite pain being common and a VAS being part of the ACR20 [98], and not all reported data were amenable to meta-analysis. However, the findings from meta-analysis were corroborated by the other studies that were included in our systematic review. Different treatment regimens, such as bridging and combination therapies, were used in different studies, although all studies allowed for specific GC effects to be assigned. Studies using GCs as part of a combination, but without suitable controls for our study, were not included. Aspects of quality of life other than pain and fatigue are important to patients, but were not addressed by our study. Systemic GCs may be used as a disease-modifying agent [3, 4]. Effects on pain may differ according to whether pain was the primary indication for GC use. The reliance upon self-report is a necessary limitation in studies of pain, which is, by definition, a subjective experience. Although most included studies measured contemporaneous reporting of pain, there may be heterogeneity in self-reporting across time, for multiple reasons such as memories or previous experiences of pain influencing future reporting, or variability of the metric. Many trials were small and focused on short treatment durations. Additional studies, beyond 6 months, could provide more accurate estimates of analgesic efficacy.

The current use of GCs to treat RA pain appears to be largely guided by clinical experience rather than robust evidence from randomized controlled trials. Many patients receive GCs, often at a high dose, when DMARDs have not controlled pain, and estimates from the USA suggested that up to one-third of people with RA might be using regular systemic GCs [6]. The benefit from systemic GCs appears to diminish with time, while the risks of adverse events may increase. The studies we retrieved of head-to-head GC comparisons did not provide a consensus regarding the effects of different regimens [99], as the different studies were heterogeneous and might not reflect current clinical practice. Further research is needed to determine who could benefit most from systemic GCs to inform personalized treatment. More research is also required to determine the potential benefits and risks of withdrawal in people who are already using long-term systemic GCs. The evidence from this review suggests systemic GCs are not a FIG. 3 Earliest time point and pain in response to oral GCs

(A) SMDs of pain in trials of oral GCs. Forest plot showing results of random effects meta-analysis. Negative values favour GC over comparator. (B) Funnel plot of effect sizes. Egger’s test P < 0.0001. GCs: glucocorticosteroids; SMD: standardized mean difference.
Fig. 4 Forest plot for subgroup analysis of pain stratified by duration of treatment with oral GCs

(A) SMDs of pain in trials of oral GCs, and (B) MDs of 100 mm VAS pain stratified by duration of follow-up. Forest plot showing results of random effects meta-analysis. Negative values favour GC over comparator. Each trial may contribute data to each of the three follow-up time periods. GCs: glucocorticosteroids; MD: mean difference; SMD: standardized mean difference; VAS: visual analogue scale.

complete solution to RA pain, and additional analgesic strategies are urgently needed.
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Data availability statement

Data are available upon reasonable request from the corresponding author (D.F.M.).

Supplementary data

Supplementary data are available at Rheumatology online.

References

1 Taylor P, Manger B, Alvaro-Gracia J et al. Patient perceptions concerning pain management in the treatment of rheumatoid arthritis. J Int Med Res 2010;38: 1213–24.

2 NICE. NG100: Rheumatoid arthritis in adults: management, 2020. https://www.nice.org.uk/guidance/NG100 (21 September 2021, date last accessed).

3 Kirwan J, Bijlsma JWJ, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007;1:CD006356.

4 Kirwan J. The origins, results and consequences of the 1995 Arthritis Research Campaign Low-Dose Glucocorticoid Study. Clin Exp Rheumatol 2011;29(5 Suppl 68):S52–8.

5 Gotzsche PC, Johansen HK, Group CM. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. Cochrane Database Syst Rev 2005;1:CD000189.
6 Caplan L, Wolfe F, Russell AS, Michaud K. Corticosteroid use in rheumatoid arthritis: prevalence, predictors, correlates, and outcomes. J Rheumatol 2007;34:696–705.

7 Hua C, Buttgereit F, Combe B. Glucocorticoids in rheumatoid arthritis: current status and future studies. RMD Open 2020;6:e000536.

8 McWilliams DF, Walsh DA. Factors predicting pain and early discontinuation of tumour necrosis factor-α-inhibitors in people with rheumatoid arthritis: results from the British society for rheumatology biologics register. BMC Musculoskelet Disord 2016;17:337.

9 Joharatnam N, McWilliams DF, Wilson D et al. A cross-sectional study of pain sensitivity, disease-activity assessment, mental health, and fibromyalgia status in rheumatoid arthritis. Arthritis Res Ther 2015;17:11.

10 Heisler AC, Song J, Dunlop DD et al. Association of pain centralization and patient-reported pain in active rheumatoid arthritis. Arthritis Care Res (Hoboken) 2020;72:1122–9.

11 Strand V, Kaine J, Alten R et al. Associations between patient global assessment scores and pain, physical function, and fatigue in rheumatoid arthritis: a post hoc analysis of data from phase 3 trials of tofacitinib. Arthritis Res Ther 2020;22:243.

12 Druce KL, McBeth J. Central sensitization predicts greater fatigue independently of musculoskeletal pain. Rheumatology (Oxford) 2019;58:1923–7.

13 McWilliams DF, Marshall M, Jayakumar K et al. Erosive and osteoarthritis structural progression in early rheumatoid arthritis. Rheumatology (Oxford) 2016;55:1477–88.

14 Higgins JPT, Thomas J, Chandler J et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.1. 2020. www.training.cochrane.org/handbook (21 September 2021, date last accessed).

15 Aletaha D, Neogi T, Silman AJ et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8.

16 Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Ment Health 2019;22:153–60.

17 Schwarzer G. meta: an R package for meta-analysis. R News 2007;7:40–5.

18 Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.

19 Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

20 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

21 Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing Meta-Analysis in R: A Hands-on Guide: bookdown.org/. 2019. https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/ (21 September 2021, date last accessed).

22 Bakker M, Jacobs J, Welsing P et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Ann Intern Med 2012;156:329–39.

23 Böhm C. On long term drug therapy of primary chronic polyarthritis. Die Medizinische Welt 1967;35:2047–50.

24 Schoger G. On the evaluation of the effect of a combination of salicylates and prednisolone in rheumatic diseases. Arzneimittel-forschung 1968;18:758–60.

25 Corkill M, Kirkham B, Chikanza I, Gibson T, Panayi G. Intra muscular depot methylprednisolone induction of chrysotherapy in rheumatoid arthritis: a 24-week randomized controlled trial. Br J Rheumatol 1990;29:274–9.

26 Kirwan J. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med 1995;333:142–6.

27 Montecucco C, Todoerti M, Sakellarious G, Scirè CA, Caporali R. Low-dose oral prednisone improves clinical and ultrasonographic remission rates in early rheumatoid arthritis: results of a 12-month open-label randomised study. Arthritis Res Ther 2012;14:R112.

28 Scott IC, Ibrahim F, Lewis CM, Scott DL, Strand V. Impact of intensive treatment and remission on health-related quality of life in early and established rheumatoid arthritis. RMD Open 2016;2:e000270.

29 Matcham F, Norton S, Scott DL, Steer S, Hotopf M. Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: secondary analysis of a randomized controlled trial. Rheumatology (Oxford) 2016;55:268–78.

30 Choy EHS, Smith CM, Farewell V et al.: CARDERA (Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis) Trial Group. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Ann Rheum Dis 2008;67:656–63.

31 Sheldon P. Ileum-targeted steroid therapy in rheumatoid arthritis: double-blind, placebo-controlled trial of controlled-release budesonide. Rheumatol Int 2003;23:154–8.

32 Van der Elst K, Verschuuren P, Stouwen V et al. Patient-reported outcome data from an early rheumatoid arthritis trial: opportunities for broadening the scope of treating to target. Arthritis Care Res (Hoboken) 2019;71:1566–75.

33 van Gestel A, Laan R, Haagsma C, van de Putte L, van Riel P. Oral steroids as bridge therapy in rheumatoid arthritis patients starting with parenteral gold. A randomized double-blind placebo-controlled trial. Br J Rheumatol 1995;34:268–78.

34 Buttgerit F, Mehta D, Kirwan J et al. Low-dose prednisone chronic therapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). Ann Rheum Dis 2013;72:204–10.

35 Alten R, Grahn A, Holt RJ, Rice P, Buttgerit F. Delayed-release prednisone improves fatigue and health-related quality of life: findings from the CAPRA-2 double-blind randomised study in rheumatoid arthritis. RMD Open 2015;1:e000134.
36 Berry H, Huskisson EC. Isotopic indices as a measure of inflammation in rheumatoid arthritis. Ann Rheum Dis 1974;33:523–5.
37 Buttgereit F, Strand V, Lee EB et al. Fosdagrocorat (PF-04171327) versus prednisone or placebo in rheumatoid arthritis: a randomised, double-blind, multicentre, phase IIb study. RMD Open 2019;5:e000869.
38 Choy E, Kingsley G, Khoshaba B, Pipitone N, Scott D; Intramuscular Methylprednisolone Study Group. A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. Ann Rheum Dis 2005;64:1288–93.
39 Harris ED Jr, Emkey RD, Nichols JE, Newberg A. Low dose prednisone therapy in rheumatoid arthritis: a double blind study. J Rheumatol 1983;10:713–21.
40 Hua L, Du H, Ying M et al. Efficacy and safety of low-dose glucocorticoids combined with methotrexate and hydroxychloroquine in the treatment of early rheumatoid arthritis: a single-center, randomized, double-blind clinical trial. Medicine 2020;99:e20824.
41 Jasani MK, Downie WW, Samuels BM, Buchanan WW. Ibuprofen in rheumatoid arthritis. Clinical study of analgesic and anti-inflammatory activity. Ann Rheum Dis 1968;27:457–62.
42 Jelinek G, Will R, Dusci L, Potter J, Black K. Intravenous regional administration of methylprednisolone in rheumatoid arthritis. Rheumatol Int 1991;11:147–50.
43 Kennedy A, Lee P, Webb J, Deodhar S. Evaluation of the effect and duration of triamcinolone acetonide in the treatment of rheumatoid arthritis. Curr Med Res Opin 1973;1:212–8.
44 Kirwan J, Hällgren R, Mielants H et al. A randomised placebo controlled 12 week trial of budesonide and prednisolone in rheumatoid arthritis. Ann Rheum Dis 2004;63:688–95.
45 Lee P, Jasani MK, Dick WC, Buchanan WW. Evaluation of a functional index in rheumatoid arthritis. Scand J Rheumatol 1973;2:71–7.
46 Li L, Scudds R, Heck C, Harth M. The efficacy of dexamethasone iontophoresis for the treatment of rheumatoid arthritic knees: a pilot study. Arthritis Care Res 1996;9:126–32.
47 Pavelka K Jr, Honzlova M, Vencovsky J. [Use of pulsed steroid therapy in active rheumatoid arthritis]. Cas Lek Cesk 1992;131:583–9.
48 Stenberg V, Flechtnier J, Rice J, Miller D, Johnson L. Endocrine control of inflammation: rheumatoid arthritis double-blind, crossover clinical trial. Int J Clin Pharmacol Res 1992;12:11–8.
49 Stock T, Fleishaker D, Wang X, Mukherjee A, Mecbus C. Improved disease activity with fosdagrocorat (PF-04171327), a partial agonist of the glucocorticoid receptor, in patients with rheumatoid arthritis: a Phase 2 randomized study. Int J Rheum Dis 2017;20:960–70.
50 Taylor W, Rajapakse C, Harris K, Harrison A, Corkill M. Inpatient treatment of rheumatoid arthritis with synachten depot: a double blind placebo controlled trial with 6 month followup. J Rheumatol 1999;26:2544–50.
51 van Everdingen A, van Reesema S, Jacobs J, Bijlsma J. Low-dose glucocorticoids in early rheumatoid arthritis: discordant effects on bone mineral density and fractures? Clin Exp Rheumatol 2003;21:155–60.
52 van Everdingen A, van Reesema S, Jacobs J, Bijlsma J. The clinical effect of glucocorticoids in patients with rheumatoid arthritis may be masked by decreased use of additional therapies. Arthritis Rheum 2004;51:233–8.
53 van Everdingen A, Jacobs J, Van Reesema S, Bijlsma J. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med 2002;136:1–12.
54 Williams IA, Baylis EM, Shipley ME. A double-blind placebo-controlled trial of methylprednisolone pulse therapy in active rheumatoid disease. Lancet 1982;2:237–40.
55 Dick WC, Nuki G, Whaley K, Deodhar S, Buchanan WW. Some aspects in the quantitation of inflammation in joints of patients suffering from rheumatoid arthritis. Rheumatol Phys Med 1970;10(Suppl 10):40–7.
56 Kazkaz L. Methylprednisolone pulse therapy in the symptomatic relief of rheumatoid disease. Acta Ther 1990;16:329–35.
57 Lee P, Baxter A, Dick W, Webb J. An assessment of grip strength measurement in rheumatoid arthritis. Scand J Rheumatol 1974;3:17–23.
58 Liebling MR, Leib E, McLaughlin K et al. Pulse methylprednisolone in rheumatoid arthritis. A double-blind cross-over trial. Ann Intern Med 1981;94:21–6.
59 Verschueren P, De Cock D, Corluy L et al. Effectiveness of methotrexate with step-down glucocorticoid remission induction (COBRA Slim) versus other intensive treatment strategies for early rheumatoid arthritis in a treat-to-target approach: 1-year results of CareRA, a randomised pragmatic open-label superiority trial. Ann Rheum Dis 2017;76:511–20.
60 Wang Y-Y, Ling B, Guilxian-Aierken JP, Luo L. Observation on the effect of MTX or LEF combined with glucocorticoid in the treatment of elderly patients with rheumatoid arthritis. Prog Modern Biomed 2017;17:2903–6.
61 Hansen T, Kryger P, Elling H et al. Double blind placebo controlled trial of pulse treatment with methylprednisolone combined with disease modifying drugs in rheumatoid arthritis. BMJ 1990;301:268–70.
62 Boers M, Buttgereit F, Saag K, Alten R, Grahn A, Storey D et al. What is the Relationship Between Morning Symptoms and Measures of Disease Activity in Patients With Rheumatoid Arthritis? Arthritis Care Res 2015;67:1202–9.
63 Bengtsson A, Bengtsson M, Nilsson I, Sörensen J. Effects of intravenous regional administration of methylprednisolone plus mepivacaine in rheumatoid arthritis. Scand J Rheumatol 1998;27:277–80.
64 Iglehart I, Sutton J, Bender J et al. Intravenous pulsed steroids in rheumatoid arthritis: a comparative dose study, J Rheumatol 1990;17:159–62.
65 Capell H, Madhok R, Hunter J et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Ann Rheum Dis 2004;63:797–803.

66 Ciconelli R, Ferraz M, Visioni R, Oliveira L, Atra E. A randomized double-blind controlled trial of sulphasalazine combined with pulses of methylprednisolone or placebo in the treatment of rheumatoid arthritis. J Rheumatol 1996;35:150–4.

67 Fan PT, Yu DT, Clements PJ, Fowlston S, Eisman J, Bluestone R. Effect of corticosteroids on the human immune response: comparison of one and three daily 1 gm intravenous pulses of methylprednisolone. J Lab Clin Med 1978;91:625–34.

68 Ferraz M, Visioni R, Oliveira L, Ciconelli R, Atra E. Intravenous methylprednisolone therapy in rheumatoid arthritis: a comparative dose study. Scand J Rheumatol 1992;21:260–1.

69 Gjeddebaek N, Graudal H. [Rheumatoid Arthritis Treatment with Betamethasone (Celestone). A Clinical Trial of Shorter Duration]. Ugeskr Laeger 1964;126:7–14.

70 Gough A, Sheeran T, Arthur V, Panayi G, Emery P. Adverse interaction between intramuscular methylprednisolone and sulphasalazine in patients with early rheumatoid arthritis. A pilot study. Scand J Rheumatol 1994;23:46–8.

71 Hansen TM, Dickmeiss E, Jans H, Ingemann Hansen T, Ingeman-Nielsen M, Lorenzen I. Combination of methylprednisolone pulse therapy and remission inducing drugs in rheumatoid arthritis. Ann Rheum Dis 1987;46:290-5.

72 Laan RF, van Riel PL, van de Putte LB, van Erning LJ, van’t Hof MA, Lemmens JA. Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study. Ann Intern Med 1993;119:963–8.

73 Marwah RJ, Pickup ME, Al-Shakarchi H et al. A pharmacological and clinical comparison of prednisolone and betamethasone in rheumatoid arthritis. Eur J Clin Pharmacol 1982;23:321–5.

74 Pincus T. The clinical efficacy of 3 mg/day prednisone in patients with rheumatoid arthritis: evidence from a randomised, double-blind, placebo-controlled withdrawal clinical trial. Clin Exp Rheumatol 2011;29(5 suppl. 68):S73–S6.

75 Buttgerit F, Doering G, Schaaffler A et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. Lancet 2008;371:205–14.

76 Buttgerit F, Doering G, Schaaffler A et al. Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. Ann Rheum Dis 2010;69:1275–80.

77 van der Veen MJ, Blijstma JW. The effect of methylprednisolone pulse therapy on methotrexate treatment of rheumatoid arthritis. Clin Rheumatol 1993;12:500–5.

78 Vischer T, Sinniger M, Ott H, Gerster J. A randomized, double-blind trial comparing a pulse of 1000 with 250 mg methylprednisolone in rheumatoid arthritis. Clin Rheumatol 1986;5:325–6.

79 Kaminska-Tchorzewska E, Sliwinska-Stanczyk P, Kubasiewicz E, Baryika-Morawska I, Jaworski J, Pazdur J. The evaluation of aggressive treatment (methotrexate + methylprednisolone) in patients with early rheumatoid arthritis. Rheumatologia 2001;39:326–34.

80 Alten R, Nolte M, Doring G, Werder K. Circadian versus ultradian glucocorticoid regimen in the treatment of rheumatoid arthritis. Aktuelle rheumatologie 2009;34:363–9.

81 Arvidson N, Gudbjörnsson B, Larsson A, Hällgren R. The timing of glucocorticoid administration in rheumatoid arthritis. Ann Rheum Dis 1997;56:27–31.

82 Choy E, Kingsley G, Corkill M, Panayi G. Intramuscular methylprednisolone is superior to pulse oral methylprednisolone during the induction phase of chryotherapy. Br J Rheumatol 1993;32:734–9.

83 Di Munno O, Mazzantini M, Milani S, Pasero G. Clinical equivalence between deflazacort oral drops and tablets in active rheumatoid arthritis. Clin Rheumatol 1999;18:140–4.

84 Kowanko IC, Pownall R, Knapp MS, Swannell AJ, Mahoney PG. Time of day of prednisolone administration in rheumatoid arthritis. Ann Rheum Dis 1982;41:447–52.

85 Hayball PJ, Cosh DG, Ahern MJ, Schultz DW, Roberts-Thomson PJ. High dose oral methylprednisolone in patients with rheumatoid arthritis: pharmacokinetics and clinical response. Eur J Clin Pharmacol 1992;42:85–8.

86 Radia M, Forst D. Comparison of three pulse methylprednisolone regimens in the treatment of rheumatoid arthritis. J Rheumatol 1988;15:242–6.

87 Scudeletti M, Puppo F, Lanza L, et al. Comparison of two glucocorticoid preparations (deflazacort and prednisone) in the treatment of immune-mediated diseases. Eur J Clin Pharmacol 1993;45(Suppl 1):S29–34.

88 Smith M, Ahern M, Roberts-Thomson P. Pulse steroid therapy in rheumatoid arthritis: can equivalent doses of oral prednisolone give similar clinical results to intravenous methylprednisolone? Ann Rheum Dis 1988;47:28–33.

89 Burmester GR, Buttgerit F, Bernasconi C et al. Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial. Lancet 2020;396:267–76.

90 Fleischmann R, Forst DE, Connolly-Strong E, Liu J, Zhu J, Brasington R. Repository Corticotropin Injection for Active Rheumatoid Arthritis Despite Aggressive Treatment: A Randomized Controlled Withdrawal Trial. Rheumatol Ther 2020;7:327–44.

91 Xiong J-H, Xue J, Ding Z-H. Evaluation of efficacy and safety of glucocorticoids combined with other drugs against rheumatoid arthritis. Chin J Hosp Pharm 2016;36:1582–84.

92 Pincus T, Swearingen CJ, Luta G, Sokka T. Efficacy of prednisone 1-4 mg/day in patients with rheumatoid arthritis: a randomised, double-blind, placebo controlled
93 Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain 2004;8:283–91.

94 Clarke L, Kirwan J. Efficacy, safety and mechanism of action of modified-release prednisone in rheumatoid arthritis. Ther Adv Musculoskelet Dis 2012;4:159–66.

95 Gron KL, Ornbjerg LM, Hetland ML et al. The association of fatigue, comorbidity burden, disease activity, disability and gross domestic product in patients with rheumatoid arthritis. Results from 34 countries participating in the Quest-RA program. Clin Exp Rheumatol 2014;32:869–77.

96 Witt KA, Sandoval KE. Steroids and the blood-brain barrier: therapeutic implications. Adv Pharmacol 2014;71:361–90.

97 Burston JJ, Valdes AM, Woodhams SG et al. The impact of anxiety on chronic musculoskeletal pain and the role of astrocyte activation. Pain 2019;160:658–69.

98 Felson DT, Anderson JJ, Boers M et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 1993;36:729–40.

99 Wallace BI, Wallace DM, Waljee AK, Clauw DJ. Evidence to support or guide glucocorticoid tapering in rheumatoid arthritis is lacking. Ann Rheum Dis 2019;78:1733–4.