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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 (I^2, 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 (I^2 = 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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CLINICAL SCIENCE

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 pre-designed 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 (>15% 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]).

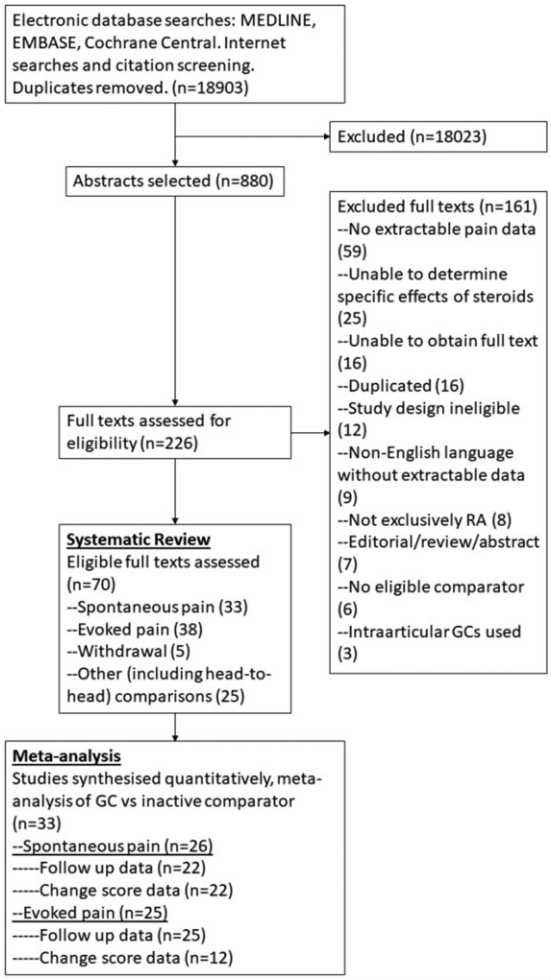
Types of interventions

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

Fig. 1 Flow diagram of searches and study selection



Flow diagram showing the search and selection strategy of studies. Studies may contribute to more than one outcome.

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× interquartile range [14]). 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

Table 1 Studies included in primary meta-analyses of pain and evoked pain

First author	Year	Country	Female (%)	Average age (years)	Total *N*	GC	Administration	Dose	Freq.	GC duration	Study duration	Risk of bias indicators								
												Randomization	Allocation concealment	Participants blinded	Physicians blinded	Assessors blinded	Attrition	Specified analysis	ITT	Reporting
Spontaneous pain																				
Bakker [22]	2012	Netherlands	71	54	236	Prednisolone	Oral	10 mg	Daily	2 y	2 y	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Bohm [23, 24]	1967	Germany	75	49	40	Prednisolone	Oral	2.5 mg	Unknown	8 d	8 d	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Corkill [25]	1990	UK	64	54	59	Depot methyl prednisolone	I.m.	120 mg	4 w	8 w	24 w	Yes	Yes	Unclear	Unclear	Yes	No	Yes	Yes	Yes
Kirwan [26]	1995	UK	64	49	128	Prednisolone	Oral	7.5 mg	Daily	2 y	2 y	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Lee [45]	1973	UK	Unknown	Unknown	141	Prednisolone	Oral	15 mg	Daily	2 w	2 w	Yes	Unclear	Unclear	Unclear	Unclear	No	Yes	No	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)	34 w	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Sheldon [31]	2003	UK	62	56	26	Budesonide	Oral	9 mg	Daily	4 w	4 w	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes
van Gestel [33]	1995	Netherlands	70	57	40	Prednisolone	Oral	10 mg, tapering	Daily	18 w	18 w	Unclear	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes
Spontaneous and evoked pain																				
Alten [34, 35]	2015	Germany	84	57	350	Prednisolone	Oral	5 mg	Daily	12 w	12 w	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Berry [36]	1974	UK	50	58	12	Prednisolone	Oral	15 mg	Daily	1 w	3 w	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes	No	Yes
Buttgereit [37]	2019	Germany	69	55	323	Fosdagrocorat (F)/prednisolone (P)	Oral	F 1, 5, 10, 15 mg and P 5, 10 mg	Daily	8 w	14 w	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Choy [38]	2005	UK	78	57	91	Depomedrone (methylpred)	I.m.	120 mg	Not sure	2 y	2 y	Unclear	Unclear	Unclear	Unclear	Yes	No	Yes	Yes	Yes
Harris [39]	1983	USA	68	55	34	Prednisolone	Oral	5 mg	Daily	24 w	32 w	Unclear	Yes	Yes	Yes	Yes	No	Unclear	No	Yes
Hua [40]	2020	China	78	47	59	Prednisone	Oral	10 mg daily for 12 w, 5 mg daily for next 8 w	Daily	6 m	6 m	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Jasani [41]	1968	UK	78	50	9	Prednisolone	Oral	15 mg	Daily	1 w	4 w?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Unclear
Jelinek [42]	1991	Australia	59	22–77 y range	22	Methyl prednisolone	I.v.	40 mg	Once	1 day	8 w	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes
Kennedy [43]	1973	UK	83	50	24	Triamcinolone acetonide (Kenalog)	I.m.	80 mg	Once	1 day	4 w	No	Yes	Yes	Yes	Yes	Yes	No	Unclear	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	Unclear	Unclear	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	No	Yes

(continued)

Table 1 Continued

First author	Year	Country	Female (%)	Average age (years)	Total *N*	GC	Administration	Dose	Freq.	GC duration	Study duration	Risk of bias indicators								
												Randomization	Allocation concealment	Participants blinded	Physicians blinded	Assessors blinded	Attrition	Specified analysis	ITT	Reporting
						Dexamethasone	Iontophoresis									Unclear				
Montecucco [27]	2012	Italy	64	60	220	Prednisolone	Oral	12.5 mg to 6.25 mg after 2 w	Daily	52 w	1 y	Yes	No	No	No	Yes	No	Yes	Yes	Yes
Pavelka [47]	1992	Czech Republic	Unknown	Unknown	34	Methylprednisolone	I.v.	1 g	3×		8 w	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Stenberg [48]	1992	USA	61	61	36	Prednisolone	Oral	5 mg	Daily	6 m	1 y	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	Yes
Stock [49]	2017	USA	59	56	86	Fosdagrocorat (F), prednisolone (P)	Oral	F 10 mg, F 25 mg, P 5 mg	Daily	2 w	2 w	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes
Taylor [50]	1999	New Zealand	75	55	36	Syncathen depot	I.m.	0.5 mg	Daily	2 d	6 m	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Unclear	No	Yes
van Everdingen [51–53]	2002	Netherlands	64	62	81	Prednisolone	Oral	10 mg	Daily	2 y	2 y	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Williams [54]	1982	UK	90	56	20	Methylprednisolone	I.v.	1 g	Once	1 d	6 w	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Evoked pain																				
Dick [55]	1970	UK	46	48	24	Prednisolone	Oral	10 mg	Daily	1 w	1 w	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear
Hansen [61]	1990	Denmark	73	60	97	methylprednisolone	I.v.	15 mg/kg	4 weeks	6 m	1 y	Yes	Yes	Unclear	Unclear	Yes	No	Unclear	No	Yes
Kazkaz [56]	1990	Syria	80	49	41	Methylprednisolone	I.v.	1 g	Once	1 day	8 w	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Unclear	No	Yes
Lee [57]	1974	UK	Unknown	Unknown	21	Prednisolone	Oral	2.5 mg	4× daily	1 w		No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear
Liebling [58]	1981	USA	70	55	10	Methylprednisolone	I.v.	1 g	Monthly	6 m	12 m	Unclear	Unclear	Yes	Yes	Unclear	No	No	No	Yes
Vershueren van der Elst 2019 (van der Elst 2019 [32])	2017	Belgium	79	51	91	Prednisone	Oral	30–20–12.5–10–7.5–5 mg tapering	Daily	2 y	2 y	Yes	No	No	No	No	Yes	No	Yes	Yes
Wang [60]	2017	China			112	Prednisone	Oral			3 m	3 m	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

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 = −0.65 (−0.82, −0.49) with significant heterogeneity [$I^2 = 56\%$, 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 for VAS pain showed improvements of −11 mm (−15, −7) 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 (–15mm) 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 =−0.57 (95% CI −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 (−0.75, −0.41) 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 of 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 −0.52 (−0.73, −0.31). Time-related changes in efficacy of oral GCs in higher quality studies are shown in supplementary Fig. S3B, available at *Rheumatology* online.

Different routes of GC administration derived evoked pain SMD (95% CI) for each route as oral −0.71 (−0.97, −0.45, $n = 15$ studies), i.m. −0.08 (−0.53, 0.35, $n = 3$ studies) and i.v. −0.33 (−0.76, 0.10, $n = 6$ studies) administration (heterogeneity between subgroups $P = 0.069$).

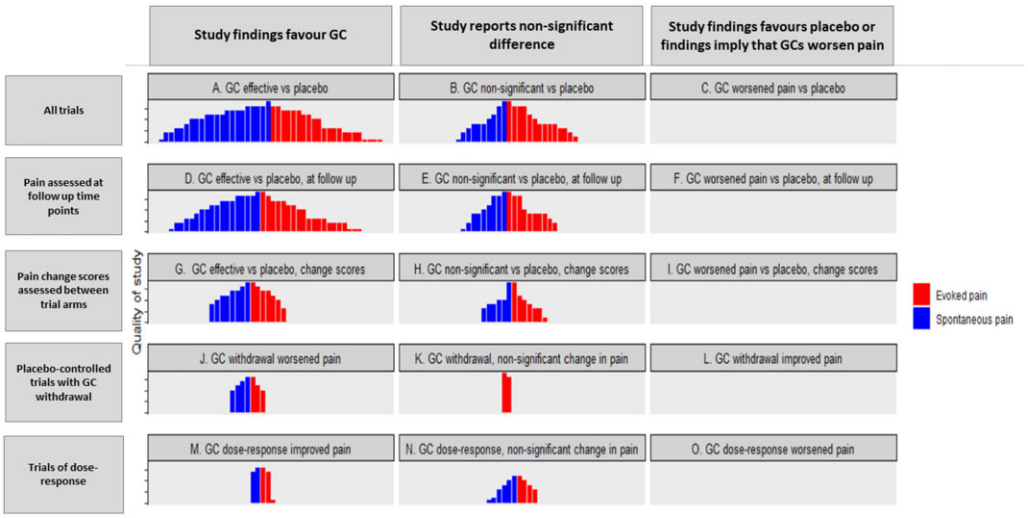
GC withdrawal studies and head-to-head comparisons between GCs or treatment regimens

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].

Fig. 2 Harvest plot showing reported efficacy of GC for pain outcomes



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.

Fatigue

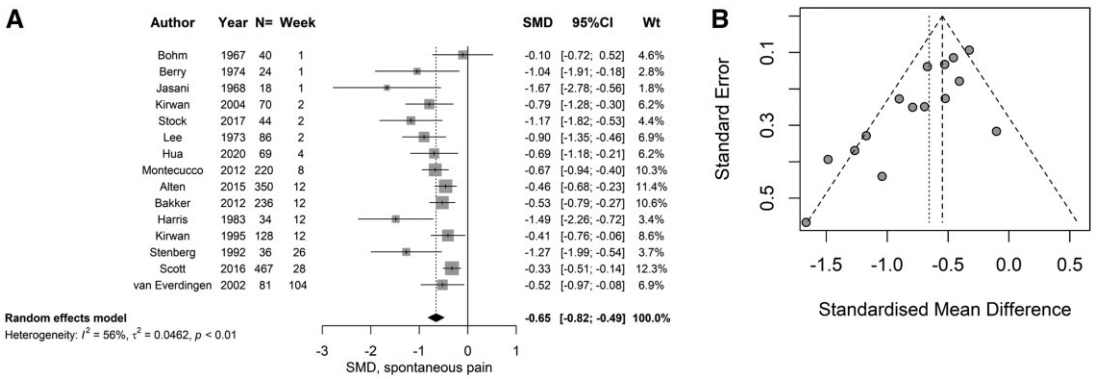
Five studies reported fatigue outcomes in response to systemic GCs [28, 32, 34, 35, 89, 92]. Fatigue was reported to improve with GC use in three trials verses placebo (two high-quality double-blind studies [28, 35] and one open-label [32]), using fatigue scales of functional assessment of chronic illness 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

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.

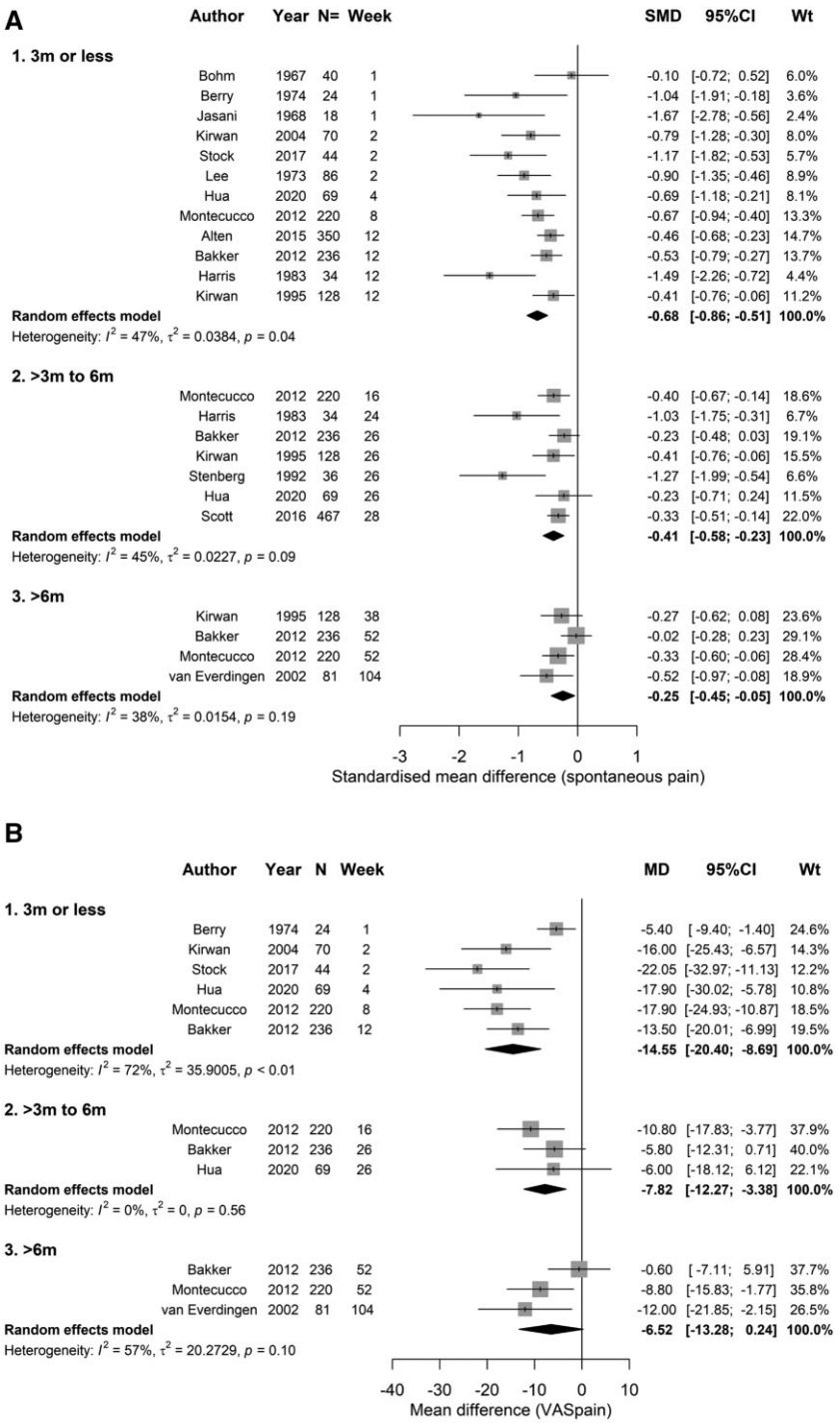
GCs, might suggest that maximum analgesic effect is achieved with low doses of oral prednisolone (possibly $\leq$15 mg daily). Long-term GC use, particularly at high doses, is associated with risk of adverse events, including total joint replacement, fracture risk, diabetes mellitus and cardiovascular 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

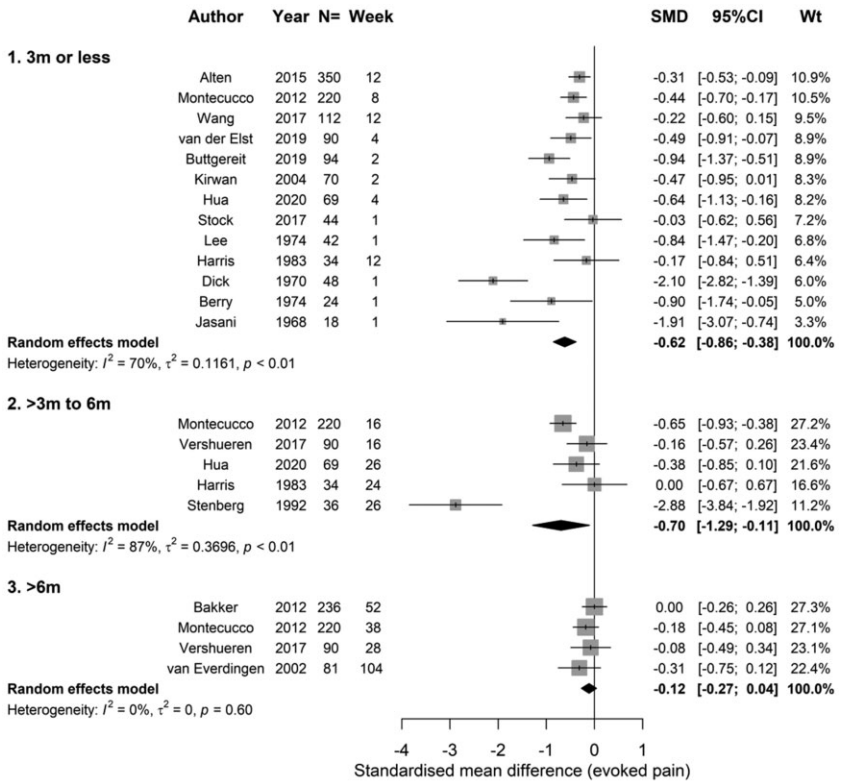
FIG. 4 Forest plot for subgroup analysis of pain stratified by duration of treatment with oral GCs



(**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.

FIG. 5 Forest plot of subgroup analysis of duration of treatment with oral GCs and evoked pain



SMDs of evoked pain in trials of oral GCs, stratified by duration of follow-up. Tender joints, Ritchie Aritcular Index and pain upon movement were included. 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; SMD: standardized mean difference.

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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.

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