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Effectiveness and safety of oral corticosteroids in the treatment of rheumatoid arthritis: a systematic review

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Abstract

Objective: This systematic review analyzed the effectiveness and the safety of oral corticosteroids in the treatment of rheumatoid arthritis. **Method:** The search sources were Cochrane **(**CENTRAL), MEDLINE, EMBASE, CINAHL, Web of Science, among other; in order to identify randomized controlled trials (RCT) that compared the oral use of corticosteroids to placebo or other treatments in adults. Reviewers, in pairs and independently, selected studies, performed data extraction and assessed the risk of bias. Narrative synthesis of data was performed. **Results:** Thirteen RCT were selected (n=2,393 patients) and more than 50% of them had some risk of bias. Prednisone 5mg and prednisolone 7.5mg seem to improve pain. Physical function improved with the use of prednisone 5mg, 10mg plus methotrexate (MTX) and 30mg plus MTX; and use of prednisolone 5mg, 7.5mg plus disease modifying anti-rheumatic drugs (DMARD). Prednisone 10mg and prednisolone 5mg, 7.5mg, 30mg and 60mg (alone or with DMARD) seems to improve radiological imaging. Prednisone 5mg and prednisolone 7.5mg reduced morning stiffness. Prednisone 5mg and 10mg (plus aurothioglucose), and prednisolone 7.5mg, budesonide 9mg seem to reduce the number swollen joints. Prednisone 5mg and 10mg, prednisolone 5mg and 7.5mg, and budesonide 9mg reduced the number tender joints. Prednisone 10mg and prednisolone 5mg improved grip strength. Prednisone 5mg, prednisolone (plus MTX and ciclosporin) and prednisolone 7.5mg improved quality of life. Prednisolone and budesonide showed larger numbers of common and serious adverse events. **Conclusion:** Prednisone 5mg and 10mg and prednisolone 5mg and 7.5mg seems to be effective, while prednisone appears to be safer anti-inflammatory to the treatment of rheumatoid arthritis. However, methodological limitations and the combination of different drugs and doses, contributed to limiting the conclusions on these findings.

Keywords: rheumatoid arthritis; adrenal cortex hormones; adverse effects; randomized clinical trial; systematic review.

Efetividade e segurança de corticosteroides orais no tratamento da artrite reumatoide: uma revisão sistemática

Resumo

Objetivo: Esta revisão sistemática analisou a efetividade e a segurança dos corticosteroides orais no tratamento da artrite reumatoide. **Método:** As fontes de busca foram Cochrane (CENTRAL), MEDLINE, EMBASE, CINAHL, Web of Science, entre outros; a fim de identificar ensaios clínicos randomizados (ECR) que compararam o uso oral de corticosteroides em relação ao placebo ou outro tratamento em adultos. Os revisores, em pares e independentemente, selecionaram estudos, realizaram a extração de dados e avaliaram o risco de viés. Uma síntese narrativa dos dados foi realizada. **Resultados:** Treze ECR foram selecionados (n=2.393 pacientes) e mais de 50% deles apresentaram algum risco de viés. Prednisona 5mg e prednisolona 7,5mg pareceu melhorar a dor. Função física melhorou com o uso de prednisona 5mg, 10mg com metotrexato (MTX) e 30mg com MTX; e com o uso de prednisolona 5mg, 7,5mg com drogas modificadores de doença anti-reumáticos (DMARD). Prednisona 10mg e prednisolona 5mg, 7,5mg, 30 mg e 60mg (sozinho ou com DMARD) pareceu melhorar a imagem radiológica. Prednisona 5mg e prednisolona 7,5mg reduziram a rigidez matinal. Prednisona 5mg e 10mg com aurotioglicose, e prednisolona 7,5mg, budesonida 9mg parecem reduzir o número de articulações inchadas. Prednisona 5mg e 10 mg, prednisolona 5 e 7,5mg, e budesonida 9mg reduziram o número de articulações dolorosas. Prednisona 10mg e prednisolona 5mg melhoraram a força de preensão. Prednisona 5mg, prednisolona (com MTX e ciclosporina) e prednisolona 7,5mg melhoraram a qualidade de vida. Prednisolona e budesonida mostraram o maior número de efeitos adversos comuns e graves. **Conclusão:** Prednisona 5mg e 10mg e prednisolona 5mg e 7,5mg parecem ser efetivos e prednisona parece ser o medicamento mais seguro no tratamento da artrite reumatoide. Entretanto, limitações metodológicas e a combinação de diferentes medicamentos e doses, contribuíram para limitar as conclusões desses achados.

Palavras-chave: artrite reumatoide; hormônios do córtex da adrenal; efeitos adversos; ensaio clínico randomizado; revisão sistemática.

Introduction

Rheumatoid arthritis is a chronic, autoimmune, systemic inflammatory disease with unknown causes that mainly affects joints and is characterized by symmetric synovial inflammation, resulting in joint damage, significant pain[1, 2] and serious incapacitation[3]. Around 1% of the world population suffers from it[4, 5], impacting the patient's quality of life and representing a great economic and psychological burden[6, 7]. Besides the associated morbidity of disease, there is an increase in the mortality, since their life expectancy is shortened, mainly due to cardiovascular alterations[8, 9].

The treatment is based in pain relief, improvement on physical function and joint damage prevention[10]. According to the American College of Rheumatism (ACR) and the European League Against Rheumatism (EULAR), the current approach prioritizes the early treatment with synthetic or biological disease modifying anti-rheumatic drugs (DMARD), as soon as the diagnosis is completed[11, 12]. Methotrexate (MTX) is the drug of choice for most of the patients with early stage or stable disease[11, 13], but when used for long periods its toxicity can be limiting[14]. The concomitant use of corticosteroids and non-steroid anti-inflammatories (NSAID) can be used in order to control pain and inflammation[15, 16].

It is recommended the short-term use of low dose corticosteroids, if the disease is classified as moderate or severe, along with the current therapy[11]. The EULAR recommends the use of low dose corticosteroids as part of the initial treatment combined with DMARD, until six months and the doses should be reduced as soon as clinically possible[12].

Systematic reviews published on this subject are not recent. A systematic review verified that the use of low dose of prednisolone (15 mg/day) in patients with rheumatoid arthritis was superior to placebo and NSAID for control pain and improvement on articular sensitivity. However, the authors reported limitations to the study regarding to the adverse effects description, follow-up period and heterogeneity of the clinical trials[17]. Another systematic review published pointed out benefits to the concomitant use of corticosteroids in addition to standard therapy, in the inhibition of the progressive radiological damage caused by rheumatoid arthritis. The authors alerted to the need of more studies evaluating the safety profiles, in long-term treatments[18]. Then this review is justified since it found recent clinical trials in order to update the scientific evidence on effectiveness and safety of the oral corticosteroids in the treatment of rheumatoid arthritis.

Methods

Protocol and registration

The systematic review was performed according to the recommendations specified in the Cochrane Handbook for Interventional Reviews[19] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA statement)[20]. The protocol is available on the International Prospective Register of Systematic Review (PROSPERO) *https://www.crd.york.ac.uk/PROSPERO* (protocol: CRD42017073532). The present study carried out part of the objectives from the protocol published[21].

Eligibility Criteria

Inclusion criteria

Patients: adults (≥18 years old) diagnosed with rheumatoid arthritis according to the American College of Rheumatology[22] criteria and others[23];

Interventions: oral use of steroidal anti-inflammatory drugs (beclomethasone, betamethasone, budesonide, dexamethasone, flunisolide, fluticasone, fludrocortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone) alone or combined to other drugs;

Control/comparator group: placebo or any active control;

Outcomes: effectiveness and safety;

Types of studies: randomized controlled trials (RCT).

Exclusion criteria

Studies in which more than 20% of the patients suffered from another inflammatory disease, studies with combination of drugs in which it was not possible to measure the results for corticosteroids; crossover studies; and studies that evaluated the chronological differences in the administration of corticosteroids.

Outcome measures

Primary outcomes: pain (Visual Analogue Scale – VAS, patient global impression or other scale), physical function (measured using the Health Assessment Questionnaire – HAQ), number of swollen joints, number of painful joints; morning stiffness (time in minutes or hours), grip strength (indicator of general strength and general health), patients' and physicians' global assessment, disease progression (assessed based on radiological imaging of joints), quality of life (Short Form-36 and other scales).

Secondary outcome: adverse events and serious adverse events (such as death, life-threatening events, hospitalization, disability or permanent damage); and withdrawal from the study due to adverse events.

Selection of studies

Search

The following electronic databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via Ovid); Excerpta Medica Database (Embase, via Ovid); Cumulative Index to Nursing and Allied Health Literature (CINAHL, via Ovid); Web of Science; Virtual Health Library; ClinicalTrial.gov and WHO International Clinical Trials *Registry Platform*. The searching was carried up to December of 2019, no restrictions regarding publication status or language.

Other search resources

The reference list of all eligible studies was revised in order to identify other possible studies. When necessary, we contacted the authors of the studies in order to obtain information about some data.

Search strategy

The search strategy was performed using terms of the Medical Subject Headings (MeSH) and it was adapted for each database. The search strategy used in the MEDLINE (via Ovid) included the words: **#1** ((Arthritis, Rheumatoid)) AND **#2** ((Anti Inflammatory Agents, Non Steroidal OR Antiinflammatory Agents, Non Steroidal OR Antiinflammatory Agents, Nonsteroidal OR Nonsteroidal Anti-Inflammatory Agents OR Nonsteroidal Anti Inflammatory Agents OR NSAIDs OR Anti Inflammatory Agents, Nonsteroidal OR Non-Steroidal Anti-Inflammatory Agents OR Non Steroidal Anti Inflammatory Agents OR Aspirin-Like Agents OR Aspirin Like Agents OR Analgesics, Anti-Inflammatory OR Analgesics, Anti Inflammatory OR Anti-Rheumatic Agents, Non-Steroidal OR Agents, Non-Steroidal Anti-Rheumatic OR Anti Rheumatic Agents, Non Steroidal OR Antirheumatic Agents, Non-Steroidal OR Agents, Non-Steroidal Antirheumatic OR Antirheumatic Agents, Non Steroidal OR Non-Steroidal Antirheumatic Agents OR Nsaid OR Glucocorticosteroid)) AND **#3** (randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double blind method OR single blind method OR clinical trial OR clinical trials OR (clinical AND trial) OR single OR double OR treble OR triple OR placebos OR placebo OR random OR research design OR comparative study OR evaluation studies OR follow-up studies OR prospective studies OR control OR prospective OR volunteer)) AND limit to human.

Eligibility determination

Reviewers (RSI, MDGP, FBS), in pairs and independently, screened titles and abstracts and assessed the eligibility of each full-text article. Disagreements were resolved by consensus or by a third review author (CCB). In case of duplicate publications, we would include the article with most complete data, however, this situation did not occur.

Data extraction

The same reviewers, in pairs and independently, extracted the data using standardized and pretested forms with instructions. Calibration exercises were conducted before starting data extraction to ensure consistency between reviewers.

Study information such as year and country of the publication, register protocol, characteristics of the population (diagnostic criteria, pain relief medications, number of patients, mean and standard deviation age, percentage of women), interventions and comparators (drug, daily dose, route of administration, duration of the treatment), risk of bias and outcomes were collected. Disagreements were resolved by consensus or by a third review author (CCB).

Risk of bias

Reviewers (RSI and MDGP), independently, assessed the risk of bias for each trial, using a modified version of the Cochrane collaboration risk of bias tool[19] according to the following criteria: random sequence; allocation concealment; blinding of the patients, care provider and outcome assessor; incomplete outcome data; selective outcome reporting; and other biases.

Was considered as 'definitely yes',' probably yes', 'probably no' and 'definitely no' for each of the domains; with 'definitely yes' and' probably yes' ultimately being assigned as low risk of bias and 'definitely no' and 'probably no' as high risk of bias[24]. Disagreements have been resolved by discussion and help of reviewer arbitrator.

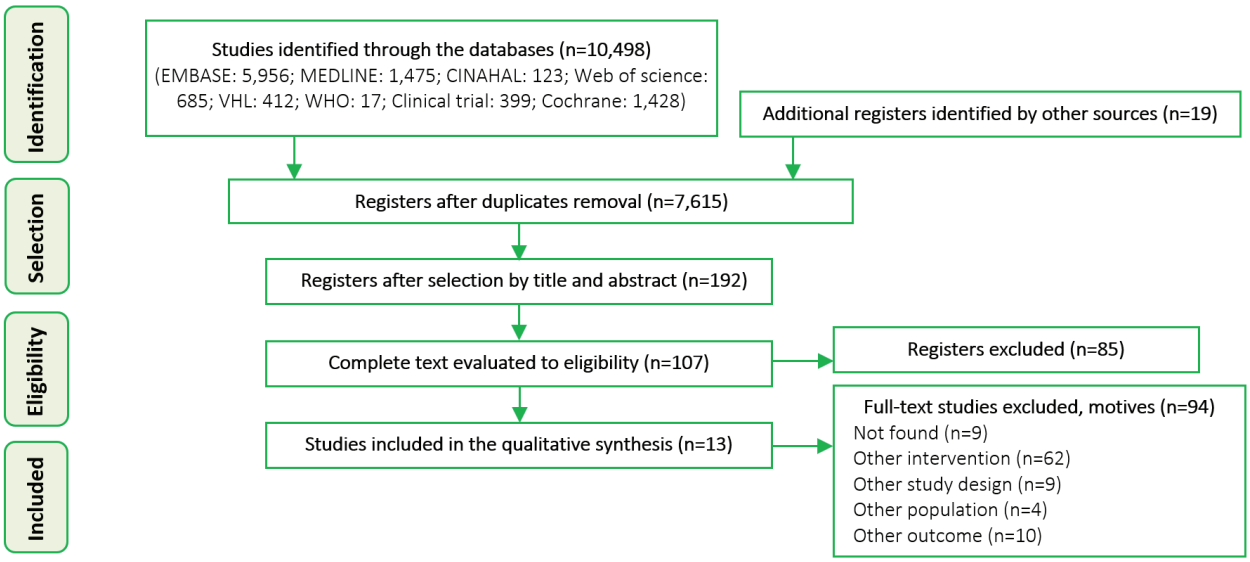
Summary measures

We provide summary tables and a narrative synthesis, since the meta-analysis was not appropriate due to excessive heterogeneity in populations, interventions, comparators and outcomes. Summary measures reported were those described in the primary studies.

Results

The search through the databases resulted in 10,498 studies, of which 108 were selected to full-text reading, resulting in 13 studies (Figure 1). Verschueren *et al*. (2004) complemented the outcomes data collected from Verschueren *et al*. (2002), since both studies used the same population. The list of excluded studies is in Appendix.

Figure 1. Study flow chart



Description of the studies

The 13 RCT (n=2,393 patients with rheumatoid arthritis) included in this review, evaluated the use of three corticosteroids: prednisone, prednisolone and budesonide. The duration of treatment was from 3 to 36 months and the follow-up was from 3 to 42 months. The lowest mean age of the participants was 43 years. Women were predominant in all studies, ranging from 60.5% to 85.4% of participants. Seven studies reported the concomitant use of DMARD. Some studies reported the use of NSAID (n=9), intra-articular corticosteroids (n=7) and analgesics (n=5) as rescue therapy. The follow-up time of studies containing prednisone ranged from 3 to 25.5 months, while the follow-up time of studies with prednisolone ranged from 4 to 42 months (Table 1).

Risk of bias of the included studies

Six of the 13 RCT were classified as low risk of bias in all the criteria[25-30]. The selection bias refers to the random sequence generation and allocation concealment. Five studies stated that the randomization occurred but did not describe how it was carried out[31-35]. Three studies also did not properly describe the allocation concealment[31, 34, 35]. One study was open-label[36].

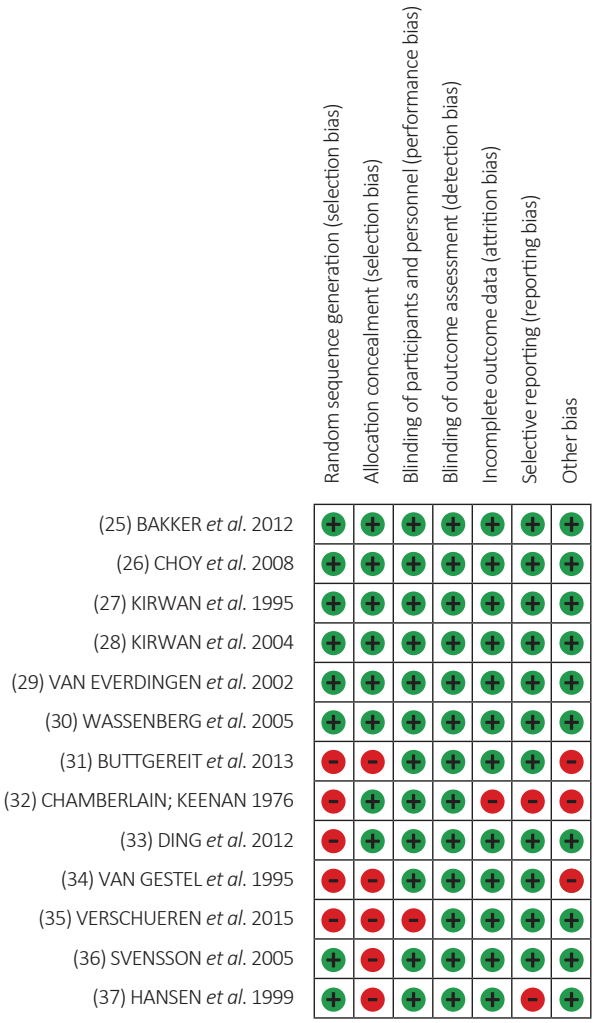
Other studies provided complete information about the randomization method (e.g. block randomization)[25-27, 36, 37]. They also secured that the participants had equal chances to be randomized among groups[28] or used software[29, 30]. The studies[25, 26-29, 30, 32, 33, 37] informed about allocation concealment.

Table 1. Characteristics of the 13 included studies (n=2,393 patients)

Study	Interventions vs comparators (mg/day)	Treatment duration (months)	Sample (N)	Lost to follow-up (%)	Rescue drug	Mean age (year)	Women (%)	Reported outcomes	Follow-up (months)
	PREDNISONE								
Bakker et al., 2012[25]	G1: MTX+Prednisone (10 mg) G2: MTX+Placebo	24	236	28.2	NSAID (IA), MTX (SC), CCS, ADA	53.5	60.5	1, 2, 3, 4, 5, 6, 7, 9	25.5 (median)
Buttgereit et al., 2013[31]	G1: DMARD+ Prednisone (5 mg-modified release) G2: DMARD+Placebo	3	350	7.7	Analgesic	57.3	84	1, 2, 4, 5, 6, 7, 9, 10, 11	4
Ding et al., 2012[33]	G1: MTX+LEF+Placebo G2: MTX+LEF+Prednisone (7,5 mg) G3: MTX+LEF+Prednisone (15 mg)	3	266	5.6	NSAID	43	85.3	4	3
Van Everdingen et al., 2002[29]	G1: Prednisone (10 mg) G2: Placebo	24	81	12.3	NSAID, Paracetamol, SSZ and corticosteroid (IA)	60	64	1, 2, 3, 4, 5, 6, 7, 8, 9*	24
Van Gestel, 1995[34]	G1: ATG IM+Prednisone (decreasing from 10-7.5-5-2.5-0 mg) G2: ATG IM+Placebo	5	40	52.5	NSAID corticosteroid (IA)	NR	70	1, 3, 4, 5, 6, 7, 8, 9	11
Verschueren et al., 2015[35]	G1: MTX G2: MTX+Prednisone (decreasing from 30-20-12.5-10-7.5-5 mg)	4	90	4.4	LEF, IM and corticosteroid (IA)	51.2	78.8	2, 4	4
	PREDNISOLONE								
Chamberlain; Keenan, 1976[32]	G1: Prednisolone (5 mg) G2: Prednisolone (3 mg) G3: Placebo	36	49	16.3	Analgesic	NR	85.4	2, 4, 5, 7, 8	42
Choy et al., 2008[26]	G1: MTX G2: MTX + CCS G3: MTX + Prednisolone (60 mg/6 weeks, 7.5 mg until 28th week, 0 mg at 34th week) Grupo 4: MTX+CCS+Prednisolone (NR)	24	467	18.8	Analgesic, NSAID, prednisolone 40 mg+lidocaine (IA) and prednisolone 120mg (IM)	54	69.6	2, 3, 4, 9	24
Hansen et al., 1999[37]	G1: DMARD G2: DMARD+Prednisolone (30 mg/2 weeks and after that patient chose a dose between 2 and 15 mg)	12	102	25.5	Analgesics, NSAID and prednisolone 20-80mg (IA)	NR	76.3	2, 3, 6, 8	12
Kirwan et al., 1995[27]	G1: Prenisolone (7.5 mg) G2: Placebo	25	128	17.1	NSAID and DMARD	49.2	64.1	1, 2, 3, 6, 7	24
Kirwan et al., 2004[28]	G1: Budesonide (3 mg) G2: Budesonide (9 mg) G3: Prednisolone (7.5 mg) G4: Placebo	3	142	16.2	Paracetamol and DMARD	55	71	1, 2, 4, 5, 6, 7, 9, 10, 11	4
Svensson et al., 2005[36]	G1: DMARD+Prednisolone (7.5 mg) G2: DMARD	24	250	3.2	NSAID and IA corticosteroid	55	64	2, 3, 4	24
Wassenberg et al., 2005[30]	G1: SAT/MTX+Prednisolone (5 mg) G2: SAT/MTX+Placebo	24	192	46.3	NSAID	51.8	70	1, 2, 3, 4, 6, 7	24

ADA: Adalimumab. ATG: Aurothioglucose. CCS: Ciclosporin. DMARD: disease modifying anti-rheumatic drugs. G: Group. IA: Intra-articular. IM: Intramuscular. LEF: Leflunomide. MTX: Methotrexate. NR: not reported. NSAID: Non-steroidal anti-inflammatories. SAT: Sodium aurothiomalate. SSZ: Sulfasalazine. Outcomes reported: 1-Pain; 2-Physical function; 3-Radiographic progression; 4-Adverse events; 5-Morning stiffness; 6-Swollen joint count; 7-Tender joint count; 8-Grip strength; 9-Quality of life; 10-Physician's global assessment; 11-Patient's global assessment. *quality of life data was extracted from Van Everdingen et al. (2004)[38]

Figure 2. Risk of bias of the included studies (n=13)



Performance bias refers to the blinding of participants and personnel, and it was observed in 3 studies (did not specify any information regarding the blindness[35, 37] or the study was open-label[36]). Others stated the double-blindness[25-33] or the blinding of the participants[34].

Regarding the blinding of the outcome assessment, only 1 study had detection bias, since it did not thoroughly describe this topic[35]. One study had attrition bias since it did not report which method was used to deal with lost follow-up[32]. Most of the studies reported the intention-to-treat analysis[25, 27-31, 33, 35-37] and one per protocol[26]. Another study had less than 10% of the participants lost to follow-up[33].

One study did not thoroughly report all of the outcomes mentioned in "methods section"[32] and another study did not assess primary outcomes such as adverse events[37], resulting in reporting bias. Other biases could be observed in 3 studies[31, 32, 34] since the diagnosis criteria that was used differed from the *American College of Rheumatology*.

Primary outcomes

Prednisone 5mg+DMARD was superior to placebo+DMARD regarding all outcomes assessed pain improvement, physical function, reducing morning stiffness duration, number of swollen and tender joints, improvement on quality of life, physician's and patient's global assessment[31].

Prednisone 10mg was superior to placebo regarding to disease progression (radiological imaging of joints), the reduction of tender joints; and improvement on grip strength[29]. Prednisone 10mg+MTX was superior to placebo+MTX concerning improvement on physical function and radiographic progression of disease[25]. Prednisone 10mg+intramuscular aurothioglucose was superior to placebo+aurothioglucose in reducing the number of swollen joints and tender joints[34]. In general, prednisone showed no difference when referring to pain improvement[25, 29, 34], physical function[29], disease progression[34], morning stiffness duration[25, 29, 34], number of swollen[25, 29] and tender[25] joints, grip strength[34] and quality of life[25, 29, 34] relation to comparators. Prednisone 30mg (decreasing dose to 5 mg)+MTX was superior to MTX alone when assessing improvements on physical function[35].

Prednisolone 5mg was superior to both prednisolone 3mg and placebo regarding the improvement on physical function and grip strength, the reduction of morning stiffness duration and the number of tender joints[32]. Prednisolone 5mg+sodium aurothiomalate/MTX was superior to placebo+aurothiomalate/MTX only for outcome "radiological progression of the disease"[30]. Prednisolone 7.5mg was superior to placebo in improvement on radiographic progression [27], in physician's and patient's global assessment of disease, in reduction of morning stiffness duration and in number of swollen and tender joints[28]. Prednisolone 7.5mg was also superior to budesonide 3 and 9 mg concerning improvements of pain, physical function and quality of life[28]. Prednisolone 7.5mg+DMARD was superior to DMARD alone concerning the improvement on physical function and radiographic progression of the disease[36].

Prednisolone 30mg+DMARD (decreasing dose until 2mg) was superior to DMARD alone regarding the disease progression (assessed by radiographic evaluation). However, no differences were shown concerning physical function, number of swollen joints and grip strength[37]. Prednisolone 60mg+MTX (decreasing the dose to 0 mg, at 34th week) compared to MTX alone, MTX+cyclosporine and MTX+cyclosporine+prednisolone was superior to all other treatments in improvement on physical function and of quality of life. MTX+prednisolone was superior to the comparators concerning radiographic evaluation of the disease progression[26].

Budesonide 9mg was superior to budesonide 3mg and placebo regarding the reduction of morning stiffness duration, number of swollen and tender joints and the improvement on physician's and patient's global assessment of the disease[28].

Secondary outcomes

The secondary outcomes reported by clinical trials were adverse events, serious adverse events and withdrawals from the study due to adverse events. Adverse events were reported in 12 studies, but only six studies performed statistical analysis comparing groups for these outcomes. Besides, only four clinical trials compared corticosteroids versus placebo, since the others had more than one drug per group.

The percentage of adverse events to prednisone ranged from 40%[31, 34, 35] to 74%[25] of patients. The main adverse described events were: headache, nausea[25], arthralgia, aggravated rheumatoid arthritis[31], discomfort[35], hepatic toxicity[25, 33], mucocutaneous reactions, proteinuria[34], respiratory infections[29, 31], osteoporotic fractures, hypertension[29], gastrointestinal symptoms, diabetes and hyperlipidemia[33]. Considering the clinical trials[29, 31] that compared prednisone to placebo, the most reported adverse were arthralgia, rheumatoid arthritis flare-up/aggravated, respiratory tract infection and new osteoporotic fractures.

Table 2. Description of the primary outcomes regarding effectiveness of the interventions (n= 12*)

Study/ Sample (N)	Interventions (mg/day) vs comparators	Pain	Physical function	Radiographic progression	Morning stiffness	Number swollen joints	Number of tender joints	Grip strength	Quality of life	Physician's global assessment	Patient's global assessment
PREDNISONE											
Bakker et al., 2012[25] **(n=236)**	G1: MTX + Pred (10mg) G2: MTX + Placebo	NSD	Prednisone was superior	Prednisone was superior	NSD	NSD	NSD	-	NSD	-	-
Buttgereit et al., 2013[31] **(n=350)**	G1: DMARD+Pred. (5mg) G2:DMARD + Placebo	Prednisone was superior	Prednisone was superior	-	Prednisone was superior	Prednisone was superior	Prednisone was superior	-	Prednisone was superior	Prednisone was superior	Prednisone was superior
Van Gestel, 1995[34] **(n=40)**	G1: ATG IM+Pred. (10mg decreasing to 0 mg) G2: ATG IM+Placebo	NSD	-	NSD	NSD	Prednisone was superior	Prednisone was superior	NSD	NSD	-	-
Verschueren et al., 2015[35] **(n=90)**	G1: MTX G2: MTX+Pred. (30 mg decreasing to 5 mg)	-	Prednisone was superior	-	-	-	-	-	-	-	-
Van Everdingen et al., 2002[29] **(n=81)**	G1: Pred. (10mg) G2: Placebo	NSD	NSD	Prednisone was superior	NSD	NSD	Prednisone was superior	Prednisone was superior	NSD	-	-
PREDNISOLONE											
Chamberlain; Keenan, 1976[32] **(n=49)**	G1: Predni. (5mg) G2: Predni. (3mg) G3: Placebo	-	Predni. 5mg was superior until 1 year	-	Predni 5mg was superior until 1 year	-	Predni 5 mg was superior	Predni. 5 mg was superior until 2 years	-	-	-
Choy et al., 2008[26] **(n=467)**	G1: MTX G2: MTX + CCS G3: MTX + Predni. (60 mg decreasing 0 mg at week 34) G4:MTX+CCS+ Predni. (NR)	-	Triple therapy was superior	CCS and Predni. were superior	-	-	-	-	Triple therapy was superior	-	-
Hansen et al., 1999[37] **(n=102)**	G1: DMARD G2: DMARD+Predni. (30mg for 2 weeks, followed by patient's choice between 2 and 15 mg)	-	NSD	Predni. was superior	-	NSD	-	NSD	-	-	-
Kirwan et al., 1995[27] **(n=128)**	G1: Predni. (7.5 mg) G2: Placebo	NSD	NSD	Prednisolone was superior	-	NSD	NSD	-	-	-	-
Kirwan et al., 2004[28] **(n=142)**	G1: Budesonide (Bud) (3 mg) G2: Bud. (9 mg) G3: Predni. (7.5 mg) G4: Placebo	Prednisolone was superior	Predni. was superior	-	Predni. and Bud. 9 mg were superior	Predni. and Bud. 9mg were superior	Predni and Bud. 9 mg were superior	-	Predni. was superior	Predni and Bud. 9 mg were superior	Predni and Bud. 9 mg were superior
Svensson et al., 2005[36] **(n=250)**	G1:DMARD+ Predni. (7.5mg) G2: DMARD	-	Prednis. was superior	Prednis. was superior	-	-	-	-	-	-	-
Wassenberg et al., 2005[30] **(n=192)**	G1:SAT/ MTX+Predni. (5mg) G2:SAT/MTX+ Placebo	NSD	NSD	Prednis. was superior	-	NSD	NSD	-	-	-	-

ATG: Aurothioglucose. CCS: Ciclosporin. DMARD: Disease modifying anti-rheumatic drugs. G: Group. IA: Intra-articular. IM: Intramuscular. LEF: Leflunomide. MTX: Methotrexate. N:

Regarding prednisolone, one study[27] reported just 3% of the patients suffering from adverse events whereas the other studies[28, 30, 32] showed more than 70% of them. The main adverse events described for prednisolone were: mild dyspepsia, facial mooning[32], respiratory infections[26], nausea/vomit[26, 30], coughing, transient creatine elevation[26], hypertension[26, 27, 30], weight gain[27], insomnia, swollen ankle, depression[28], cutaneous eruptions, elevated hepatic enzymes, proteinuria, fever[36], exanthema, gastric distress and aggravated rheumatoid arthritis[30]. The use of budesonide 3 or 9mg showed small percentage of adverse events[28]. The main adverse advents described for budesonide were: insomnia, swollen ankle, bruising easily and depression[28]. Three clinical trials[27, 28, 32] compared prednisolone to placebo and the most reported adverse events were mild dyspepsia, facial mooning, transient bruising, bruising easily, insomnia, and depression.

Seven studies evaluated serious adverse events. The use of prednisone was not associated to serious adverse events[33, 35] or just reported by 1-2% of the patients[25, 31]. The described events were death, hospitalization[25], joint sprain and arthralgia[31]. Prednisolone accounted for most of the serious adverse events, ranging from 5% to 29% of the patients[26, 28, 30]. The described events were death[26, 28], hospitalization[28], myocardial infarctions/angina/strokes, infections and upper gastrointestinal complications[26]. The use of budesonide 3 mg compared to 9mg[28] showed more events of hospitalization and angina.

Patients withdrawing from the study due to adverse events were reported by nine studies. Few (less than 2% of the participants)[31, 33] or none[29] of the participants left the study due to adverse events while using prednisone, except for one study[25] that reported 13% of withdrawals. Prednisolone presented less than 2% of withdrawal in two studies[27, 28] whereas, in the other three studies[26, 30, 36], the percentage varied between 11% and 48%. Budesonide had low withdrawal rate for both doses[28].

Table 3. Description of the secondary outcomes related to safety of the interventions (n= 12*)

Study	Interventions (mg/day) vs comparators	Follow-up (months)	Number of participants adverse events/total (%)	N. of participants serious adverse events/total (%)	N. of participants withdrawn due to adverse events/ total (%)
	PREDNISONE				
#Bakker et al., 2012[25]	G1: MTX+Pred.10mg G2: MTX+Placebo	25.5 (median)	86/117 (74) 94/119 (79)	2/117 (2) 5/119 (4)	16/117 (13) 20/119 (17)
#Buttgereit et al., 2013[31]	G1: DMARD+Pred. 5mg G2: DMARD+Placebo	4	99/231 (43) 58/119 (49)	3/231 (1) 5/119 (4)	5/231 (2) 1/119 (1)
#Ding et al., 2012[33]	G1: MTX+LEF+Placebo G2: MTX+LEF+Pred.7.5mg G3: MTX+LEF+Pred. 15mg	3	NR	No SAE	6/90 (7) 1/88 (1) 2/88 (2)
#Van Everdingen et al., 2002[29]	G1: Pred. 10 mg G2: Placebo	24	NR	NR	No withdrawal
#Van Gestel, 1995[34]	G1: ATG IM+Pred. 10mg/12 weeks, 7.5 mg/2 weeks, 5mg/2 weeks, 2.5 mg/2 weeks and 0mg/2 weeks) G2: ATG IM+Placebo	11	8/20 (40) 6/20 (30)	NR	NR
#Verschueren et al., 2015[35]	G1: MTX G2: MTX+Pred. (decreasing 30 to 5 mg)	4	21/47 (45) 17/43 (40)	No SAE	NR
	PREDNISOLONE				
#Chamberlain; Keenan, 1976[32]	G1: Predni. 5mg G2: Predni. 3mg G3: Placebo	42	10/20 (50) 7/10 (70) 6/19 (34)	NR	NR
#Choy et al., 2008[26]	G1: MTX G2: MTX + CCS G3: MTX + Predni. (decreasing 60 to 0mg at 34th) G4: MTX+CCS+Predni. (NR)	24	NR	21/117 (18) 18/119 (15) 19/115 (16) 23/116 (20)	20/117 (17) 30/119 (25) 36/115 (31) 56/116 (48)
#Kirwan et al., 1995[27]	G1: Predni. 7.5mg G2: Placebo	24	2/61 (3) 2/67 (3)	NR	1/61 (1) 5/67 (7)
#Kirwan et al., 2004[28]	G1: Budesonide 3mg G2: Bud. 9mg G3: Predni. 7.5mg G4: Placebo	4	33/37 (89) 33/35 (94) 33/39 (85) 28/31 (90)	2/37 (5) 0/35 (0) 2/39 (5) 2/31 (6)	1/37 (3) 2/35 (6) 1/39 (2) 2/31 (6)
#Svensson et al., 2005[36]	G1: DMARD+Predni. 7.5mg G2: DMARD	24	NR	NR	26/119 (22) 24/131 (18)
#Wassenberg et al., 2005[30]	G1: SAT/MTX+Predni. 5mg G2: SAT/MTX+Placebo	24	66/94 (71) 71/98 (74)	27/94 (29) 31/98 (33)	10/94 (11) 12/98 (12)

ATG: Aurothioglucose. CCS: Ciclosporin. DMARD: Disease modifying anti-rheumatic drugs. G1-4: Group. IM: Intramuscular. LEF: Leflunomide. MTX: Methotrexate. NR: Not reported. SAT: Sodium aurothiomalate.*Hansen et al. 1999[37] did not report adverse events. The symbol # means that the study not report statistical analysis to this outcome.

Discussion

Summary of evidence and comparison of findings to previous studies

This systematic review evaluated the available evidence concerning the effectiveness and safety of oral corticosteroids in the treatment of rheumatoid arthritis. The main methodological flaws were lack of details about the random sequence generation and/or presence of open-label studies, observed in six clinical trials. It is important to highlight the divergence observed between the doses as well as the outcome measures in studies, making the meta-analyses impracticable.

In general, prednisone (in doses of 5, 10 or 30mg) was studied mainly in combination with other drugs, such as DMARD or MTX. The results suggest improvement on the efficacy outcomes in the groups that included this corticosteroid, implicating in the benefits of using prednisone in doses of 5 and 10 mg in comparison with higher doses. Prednisolone (in the doses of 5, 7.5, 30 and 60mg) was evaluated alone or in combination with DMARD, MTX or aurothioglucose; and in general, this drug was superior to placebo in several efficacy outcomes. Budesonide 9mg was superior to placebo and budesonide 3mg for most of efficacy outcomes.

Half of clinical trials compared corticosteroids to placebo, other six studies there was a combination of drugs and thus, the adverse events refer to the group, and not in specified to the corticosteroid. Fewer frequency of adverse events was observed in the patients of groups that contain prednisone than to the patients of groups with prednisolone and budesonide. Larger number of serious adverse events were observed in prednisolone groups. The main serious adverse events were infections, hospitalizations, cardiovascular and gastrointestinal complications and death.

Systematic reviews approaching the effectiveness of corticosteroids in this group of patients were published until the year of 2008. A review found a sample of 508 patients. After six months of follow-up, the effects of prednisone (maximum 15mg/day) were superior to placebo, reducing the number of tender and swollen joints and pain and improving physical function of patients; however, this information should be confirmed due to the low quality of the evidence observed[39]. Other review (total of 462 patients) verified that the use of low dose prednisolone (up to 15 mg/day) was superior to placebo and NSAID regarding joint tenderness and pain in patients with rheumatoid arthritis. However, the authors showed some limitations of RCT concerning the description of adverse events, short-term follow-up and heterogeneity of the trials[17]. Our study added five RCT evaluating the use of prednisolone, a larger sample size (2,393) and evaluated other outcomes showing divergent results regarding pain improvement; and pointing out that prednisolone 5mg and budesonide 9mg are significant for reducing the number of tender joints.

The benefits of using prednisone and prednisolone in addition to standard therapy (mainly DMARD) were observed in other systematic review. The use of corticosteroids reduced the erosion progression caused by arthritis. The authors alerted to the need of more studies to evaluate the safety of these drugs on the long term and at low doses[18]. The present study included more RCT besides the ones that were part of both reviews[27, 29, 30, 34, 36, 37] and our results reinforce the benefits of corticosteroids on inhibiting radiological damage.

Systematic review of international guidelines and consensus statements showed a possible benefit of use for short-term (≤ 6 months) and at low doses of corticosteroids for treatment of rheumatoid arthritis[40]. However, less than half of the guidelines explicitly recommended the use of corticosteroids, as well as not specified the duration of the treatment and dosages recommendations. The summary of the results of the present study tended to demonstrate that corticosteroids, in lower doses, demonstrated benefits for most of the evaluated outcomes. Regarding the follow-up time, the studies were quite heterogeneous, ranging from 3 to 42 months of follow-up.

In the present study, seven RCT had long-term follow-up periods (24 to 42 months)[25-27, 29, 30, 32, 36] and they presented the largest numbers of adverse events and serious adverse events, in relation to those in a short-term follow-up period (3 to 11 months). Among the RCT that evaluated prednisolone, only one of them was a short-term follow-up period, while most studies with prednisone was short-term follow-up. This fact may affect the different safety profile of corticosteroids presented in this study.

Studies discussed the importance of evaluate parameters specific of patient with rheumatoid arthritis such as lifestyle, age, time of diagnosis, disease activity, co-medication, risk factors and comorbidities and how they could affect the course of the treatment strategies. They considered such parameters decisive in the safety profile of long-term and in low-doses corticosteroid treatment, but they are scarcely considered by most guidelines and studies[40, 41].

Strengths and limitations of this study

The methodology employed in this review includes explicit eligibility criteria, comprehensive and extensive database searches and independent and paired evaluation to select studies, as well as robust assessment of risk of bias. Meticulous search and selection processes were carried out, and we are confident that all trials meeting the inclusion criteria were included in the review.

This study carried out a broad search strategy and did not exclude any studies due to language barriers or date of publication. Some studies did not record the concomitant use of other analgesic agents or used dose, which can mislead outcomes for pain measurement. It is also important to mention that most of the studies allowed the use of other drugs for rheumatoid arthritis, and in some cases, there was drug combination (corticosteroids and DMARD, for example) which should be taken into account when analyzing the results of effectiveness and safety outcomes.

The quality of the primary studies included in this review was a limiting factor for proper analysis to be carried out. Besides that, the diversity of drugs and used doses may decrease the quality of our findings, turning impossible carrying out the meta-analysis.

Implications for clinical practice and research

Prednisone and prednisolone are the main corticosteroids studied for the treatment of rheumatoid arthritis and seem to be effective to improve most of the outcomes, causing mild adverse events. However, prednisolone has shown to cause larger numbers of adverse events, which can be explained by the fact that studies with longer follow-up periods shown more cases of adverse events, including serious adverse events.

The methodological limitations, the differences regarding to corticosteroids and their doses, concurrent use of other drugs and different outcomes; contributed to limiting the conclusions based on our findings. Future trials should consider these limitations.

Conclusion

The findings suggested that prednisone 5mg and 10mg and prednisolone 5mg and 7.5mg seem to improve most of the effectiveness outcomes; and prednisolone seem to be less safety drug. However, methodological limitations, different drugs and doses, the concurrent use of other drugs and different outcomes reported, contributed to limiting the conclusions on our findings.

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Collaborators

RSI and CCB: participated in development of the study and elaboration of the article (conception of the project, data analysis and interpretation, writing of the article and relevant critical review of the intellectual content, as well as review of the final paper to be published).

MDGM and FBS: participated in development of the study and elaboration of the article (data analysis and interpretation, writing of the article and review of the final paper to be published).

Conflict of interest statement

The authors declare no conflict of interest.

Availability of data and material

Not applicable.

Code availability
Not applicable.

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