Efficacy, duration of use and safety of glucocorticoids: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis

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ABSTRACT

This systematic literature review (SLR) regarding the efficacy, duration of use and safety of glucocorticoids (GCs), was performed to inform the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis (RA). Studies on GC efficacy were identified from a separate search on the efficacy of disease-modifying antirheumatic drugs (DMARDs). A combined search was performed for the duration of use and safety of GCs in RA patients. Dose-defined and time-defined GC treatment of any dose and duration (excluding intra-articular GCs) prescribed in combination with other DMARDs were considered. Results are presented descriptively. Two included studies confirmed the efficacy of GC bridging as initial therapy, with equal efficacy after 2 years of initial doses of 30 mg/day compared with 60 mg/day prednisone. Based on a recently performed SLR, in clinical trials most patients starting initial GC bridging are able to stop GCs within 12 (22% patients continued on GCs) to 24 months (10% patients continued on GCs). The safety search included 12 RCTs and 21 observational studies. Well-known safety risks of GC use were confirmed, including an increased risk of osteoporotic fractures, serious infections, diabetes and mortality. Data on cardiovascular outcomes were Inconsistent. Overall, safety risks increased with increasing dose and/or duration, but evidence on which dose is safe was conflicting. In conclusion, this SLR has confirmed the efficacy of GCs in the treatment of RA. In clinical trials, most patients have shown to be able to stop GCs within 12–24 months. Well-known safety risks of GC use have been confirmed, but with heterogeneity between studies.

INTRODUCTION

To inform the task force responsible for the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis (RA), three systematic literature searches (SLRs) were performed.[1 2] These included an update of the 2019 SLRs on safety and efficacy of disease-modifying antirheumatic drug (DMARD) treatments in RA, and a third SLR on the efficacy, safety and for the first time also duration of use (ie, the inability to stop) of glucocorticoids (GCs).[3 4]

GCs have been successfully used for the treatment of RA for decades. Because of their disease-modifying properties and rapid mode of action, they are still frequently used in current treatment strategies of RA.[5 6] However, it is also well known that the use of GCs is limited by a dose-dependent and duration-dependent risk of serious side effects.[7] Therefore, GCs are mainly used currently as short-term 'bridging' therapy, with the aim of rapidly suppressing disease activity until slower-acting DMARDs become clinically effective.[5] After this initial bridging phase, it has been recommended to taper and subsequently stop these GCs as rapidly as clinically feasible.[6]

In the SLRs in the context of the previous 2019 recommendations, GCs were included as part of the SLRs on safety and efficacy of DMARD treatment in RA.[3 4] However, since then specific concerns have been raised about the duration of use of GCs, specifically about difficulties to stop GCs after their use as initial bridging therapy, which may lead to a higher risk of (serious) side effects.[8] In the most recent update of the RA management guidelines of the American College of Rheumatology (ACR), the use of GCs—also as initial bridging therapy—is now specifically discouraged as it was argued that risks of GCs outweigh their benefits. This incentivised us to also investigate the duration of use (or the inability to stop) of GCs.[8]

Therefore, the aim of the current SLR is to update the evidence on the efficacy, safety and duration of use of GCs in RA, to inform the task force responsible for the update of the 2022 EULAR recommendations for the management of RA. For efficacy and safety, we focused on the effect newly started GCs (different routes of administration) as initial bridging therapy, rescue therapy and also the long-term effects of GCs in low doses. In addition, studies reporting the likelihood of long-term use of GCs after initial bridging (with or without protocolised tapering) compared with rescue therapy or reviewed. The results of two separate SLRs, on safety and on efficacy of treatment with DMARDs in RA, are published independently.[1 2]

METHODS

The steering committee of the EULAR task force for the 2022 update of the EULAR recommendations for the management of RA developed an SLR protocol covering three GC-related topics: efficacy, duration of use and safety. For each topic, research questions were defined according to the PICO (Population, Intervention, Comparator, Outcomes) principle. The complete list of research questions and PICOs is available in online supplemental file 1.

The population of interest was adult patients with a clinical diagnosis of RA. Different types of GCs and different routes of administration (of any dose and duration) were considered. GC treatment needed to be dose-defined and time-defined, and prescribed in combination with other DMARDs. Intra-articular GCs were not considered in this SLR.

Efficacy

We included studies investigating the efficacy of newly-started GCs in combination with DMARDs, as initial therapy or during follow-up. We also compared the efficacy of different routes of administration, protocolised versus non-protocolised tapering, and initial GC bridging versus rescue GC therapy in patients that did not start initial GC bridging. In addition, we studied the efficacy of long-term low dose GCs.

The prespecified comparator group varied per research question of interest, but in general included any other (combination of) DMARDs, or DMARD treatment in combination with a different type or dose of GCs. The efficacy outcomes of interest included core set measures, composite measures, physical functioning, other patient-reported outcomes, disease impact and structural damage (full list in online supplemental file 1). We included randomised controlled trials (RCTs) with >50 patients and ≥3 months follow-up. Studies on efficacy had to be published after 1 January 2019, as this study was an update of the previous EULAR SLR on the efficacy of pharmacological treatments in RA which had addressed GCs.[3]

Duration of use

We included studies investigating the likelihood of long-term continuation or restarting of GCs and the effects of withdrawal after initial GC bridging. Furthermore, we studied the likelihood of long-term use after initial GC bridging compared with rescue GCs, the influence of different routes of administration, and protocolised versus non-protocolised tapering. Recorded outcomes included GC use and dose during follow-up, disease activity, flare rate and DMARD changes after GC tapering. Randomised clinical trials with and without comparator group with >50 patients and ≥12 months of follow-up were included. Observational studies evaluating duration of use were not considered. A recent SLR (search performed on 9 February 2021) studied the likelihood of long-term continuation or restarting of GCs when used as initial bridging therapy in DMARD-naïve RA patients.[9] This search was updated, and the studies previously excluded as patients were not DMARD-naïve (which was not required for the current SLR), were reviewed. For the other questions addressing duration of use, no date limit was defined.

Safety

Studies investigating the safety of newly started GCs, as well as studies on chronic low-dose GCs, were included. Furthermore, we included studies comparing the safety of different routes of administration, studies investigating the safety of GCs combined with biological DMARDs (bDMARDs) and studies comparing continued GC use with GCs that are tapered and stopped. The comparator group was adjusted to the research question of interest but in general included any other (combination of) DMARDs, or DMARD treatment in combination with a different GC routine. An extensive list of safety outcomes was defined, including (serious) adverse events ((S)AEs) of specific interest for GC treatment (online supplemental file 1). We included cohort studies and registries, and (long-term extensions of) phases 3 and 4 clinical trials including >30 patients. Studies needed to be published after 1 January 2012, as an update to the previous SLR to inform the task force of the EULAR recommendations on the management of medium to high-dose GC therapy.[10]

Systematic literature review

An experienced librarian (JWS) conducted a combined literature search for the duration of use and safety of GCs on 14 January 2022, in the databases MEDLINE, Embase, Web of Science and the Cochrane Library. In addition, the EULAR and ACR 2020 and 2021 abstract databases were searched. Preprints of included abstracts were also searched. A detailed search strategy for each database is provided in online supplemental file 2. Studies on GC efficacy were identified from the separately performed search on the efficacy of DMARD treatment in RA.[1]

Two reviewers (SAB and AK) independently performed the title screening and abstract screening of a random selection of 10% of the included abstracts. In case of a high level of agreement, one reviewer (SAB) screened the remaining abstracts, and performed the full text screening, risk of bias (RoB) assessment and data extraction. Data on the predefined outcomes were extracted using a standardised data extraction form. RoB assessment was performed using the 'Hayden tool' for observational studies and the Cochrane Collaboration's tool for RCTs.[11 12] In case of doubt regarding any of the described steps, disagreements were discussed among the reviewers until consensus was reached, and a senior methodologist was consulted whenever necessary (RBML).

Due to a large heterogeneity in included studies and reported outcomes, all results are presented descriptively.

RESULTS

Efficacy

Article selection

Four studies were identified from the separate search on the efficacy of DMARD treatment and the GC search on duration of use and safety.[1] Three of these had a high RoB (online supplemental file 4).[13–15] One study was terminated early, and therefore, no data were extracted.[16] One additional conference abstract was identified, which did not report sufficient data for data extraction.[17] Extracted data are reported in online supplemental tables 5.1 and 5.2.

The efficacy of GC bridging as initial therapy

Two studies (both with high RoB) reported on the efficacy of GC bridging as initial therapy.[14 15] The CareRA trial was a pragmatic open-label randomised trial with 2 years follow-up.[14] Patients were stratified to high-risk or low-risk groups. For high-risk patients receiving COBRA classic (methotrexate (MTX)+sulfasalazine+GC initial dose 60 mg/day), COBRA slim (MTX+GC initial dose 30 mg/day) or COBRA Avant Garde (MTX+leflunomide+GC initial dose 30 mg/day) no significant differences were reported in ΔDAS28 (Disease Activity Score) (mean (SD) improvement −2.6 (1.2) to −2.7 (1.3)), DAS28 <2.6 (65% to 74%) or ΔHAQ (mean (SD) improvement −0.5 (0.7) to −0.7

(0.7)) at 24 months. Radiographic damage progression as measured by the Sharp/van der Heijde (SvdH) score was low in all treatment arms (mean progression between 0.5 (1.3) and 0.9 (1.7) at 2 years). In the second trial, patients started treatment with MTX+hydroxychloroquine, and either prednisone (initial dose 10 mg/day) or placebo. More improvement in ACR20 response, ΔDAS28 and ΔHAQ was shown for patients starting GC compared with placebo at 3 and 6 months, but not at 12 months.[15]

The efficacy of initial GC bridging compared with GCs used as rescue therapy

Low-risk patients included in the CareRA trial could be randomised to initial GC bridging (COBRA slim, MTX+GC initial dose 30 mg/day), or to MTX tight step-up treatment (no oral GCs allowed).[14] At 24 months, the COBRA slim and tight step-up treatment arms reported similar improvements in ΔDAS28 (mean (SD) −2.4 (1.7) and −2.2 (1.9)), DAS28<2.6 (67% and 72%), ΔHAQ (mean (SD) −0.6 (0.8) and −0.5 (0.7)) and low radiographic damage progression (mean progression 0.3 (0.7) and 0.5 (1.3) at 2 years). During follow-up (ie, not only considering the 24-month visit), patients on COBRA slim had lower values of DAS28 (mean (95% CI) difference: 0.37 (0.00 to 0.7)) and were less likely to receive GC injections (19% vs 47%) than patients on tight step-up.

The efficacy of long-term low-dose GC

The efficacy of long-term low-dose GC was investigated in the double-blind, placebo-controlled GLORIA trial in patients with active RA aged ≥65 years during 2 years follow-up.[13] Patients were randomised to prednisolone 5 mg/day or placebo, in addition to standard care antirheumatic treatment. Due to the pragmatic design of the trial, the study was assessed as having high RoB. At 3 months, ΔDAS28 improved more in patients on prednisolone compared with placebo (mean (SD) improvement −1.4 (1.1) and −0.7 (1.2), p<0.0001). The ΔHAQ improved in patients on prednisolone, but remained stable in patients on placebo (mean (SD) −0.2 (0.5) and 0.0 (0.4)). Also, patients on prednisolone more often achieved an ACR20 (36% vs 24%), 50 (20% vs 9%) or 70 response (8% vs 1%) and DAS28<2.6 (37% vs 14%), and slightly more often achieved Boolean remission (3.2% vs 0.7%). At 24 months, adjusted analyses showed that DAS28 was significantly lower for patients on prednisolone compared with placebo (2.97 vs 3.33), with similar HAQ (both groups 1.1) and significantly lower SvdH progression (0.3 vs 1.9 points).

One study was included on the efficacy of different routes of administration of GCs, but due to early termination of the study no data were extracted.[16] No studies were included on the efficacy of GC bridging during the follow-up, or on the efficacy of GC bridging with a protocolised versus a non-protocolised tapering protocol.

Duration of use

Article selection

The combined search identified 2977 articles (online supplemental figure 3.1). Of these, 10% were double-screened by two readers (SAB and AK) based on title and abstract, resulting in 95% agreement. The remaining abstracts were screened by a single reader (SAB). Two hundred and twenty out of 2977 articles were selected for detailed full-text review. Of these, 14 fulfilled all inclusion criteria. However, 13 of these were included in a recently published SLR.[9] Thus, the search identified only one new paper.[18] No additional meeting abstracts were identified. RoB assessments were provided in the original paper, and are in online supplemental file 4.[9] Baseline characteristics of included studies are provided in online supplemental table 5.1.

The likelihood of long-term continuation or restarting of GCs when used as initial bridging therapy

No additional articles were included on this topic after a recently published SLR.[9] In this previous SLR, 137 papers were included from 10 unique clinical trials. One of these studies was assessed as having a low RoB, nine of these studies were assessed as having a high RoB, mostly because they were single-blinded (Cochrane RoB tool 2).[9] Four of these studies (10 treatment arms) reported sufficient data to be included in a meta-analysis on GC use at 12 months follow-up, and 2 studies (4 treatment arms) on GC use at 24 months follow-up. In these four studies patients started with a dose of 30 or 60 mg/day of prednisone or prednisolone bridging, which was tapered to 5 or 7.5 mg/day and could be subsequently stopped between 20 and 32 weeks of follow-up in the different studies. The pooled proportions of patients taking GCs was 0.22 (95% CI 0.08 to 0.37) at 12 months and 0.10 (95% CI −0.01 to

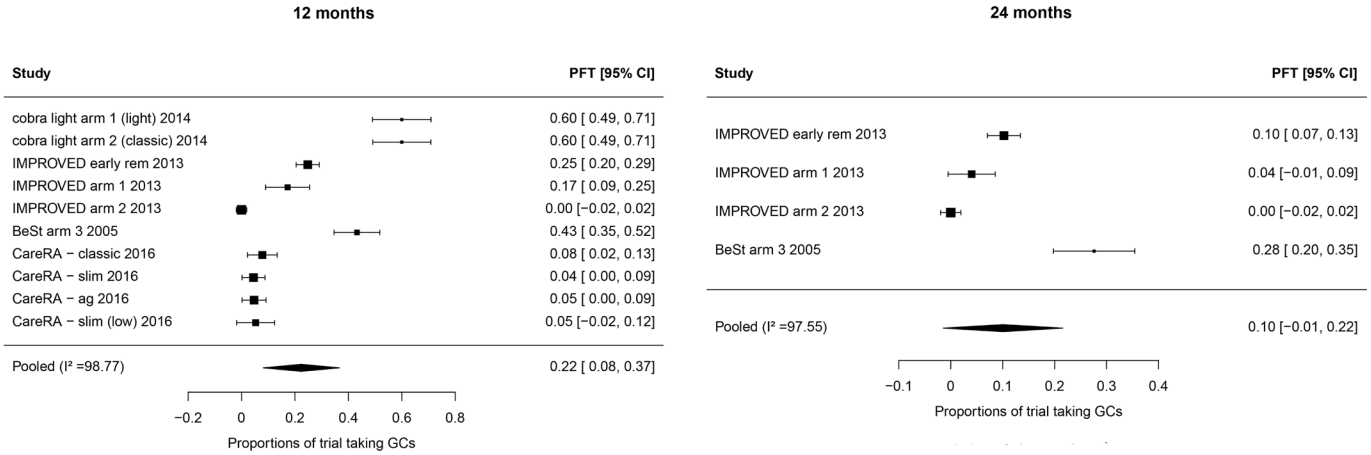

Figure 1 Proportion of patients using GCs at 12 months (A) and at 24 months (B) after initial GC bridging in clinical trials. Reproduced with permission from van Ouwerkerk *et al*.[9] CareRA COBRA ag, CareRA COBRA Avant Garde; CareRA COBRA slim (low), CareRA COBRA slim low-risk group, GC, glucocorticoids; IMPROVED early rem, IMPROVED early remission; PFT, proportions according to the Freeman Tukey transformation.

Table 1 GC status at predefined time points after the initial bridging strategy, based on an individual patient data meta-analysis of seven studies

GC status after bridging	All included treatment arms starting with GC bridging		Sensitivity analysis for oral GC use only (without IDEA and tREACH arm 1)	
	Odds (95% CI)	Probability	Odds (95% CI)	Probability
3 months	0.12 (0.06 to 0.23)	0.11	0.16 (0.09 to 0.29)	0.14
6 months	0.07 (0.03 to 0.19)	0.07	0.13 (0.05 to 0.29)	0.12
12 months	0.08 (0.03 to 0.21)	0.07	0.14 (0.06 to 0.32)	0.12
18 months	0.08 (0.03 to 0.25)	0.07	0.16 (0.06 to 0.40)	0.14

Data were pooled using a mixed effects logistic regression model with study arm as random effect, resulting in odds which were converted into probabilities. A description of the tapering schedules is provided in online supplemental table 5.3. Raw data for each individual study are presented in online supplemental table 5.4. Reproduced with permission.
GC, glucocorticoids.

0.22) at 24 months (figure 1).[9] Insufficient data were reported to compare other outcome measures between studies.

A follow-up study was performed in which individual patient data were combined from 7 out of 10 trials included in the original meta-analysis, to perform an individual patient data meta-analysis based on more detailed data.[19–25] At the time of publication of this SLR these data were yet unpublished, but the results of this effort were presented to the task force responsible for the update of the 2022 EULAR recommendations for the management of RA and partly reproduced here with permission (table 1 and online supplemental tables 5.3 and 5.4). The meta-analysis on individual data from the seven included trials (table 1) shows that at 6 months after the end bridging 7% of patients used GCs. After excluding trials which started with parenteral GCs (i.m. or i.v. GC once), this percentage was slightly higher (12%). At 12–18 months after bridging, these numbers were very similar.

The effects of withdrawal of GCs after use as bridging therapy

The SEMIRA study (low RoB) was the only included study which assessed the effects of withdrawal of GCs.[18] In this placebo-controlled study with 24 weeks follow-up, patients on tocilizumab and 5 mg/day prednisone with stable low disease activity were randomised to either continue or to taper prednisone to stop in 16 weeks. Patients who tapered prednisone had an increase in DAS28 of 0.54 (95% CI 0.35 to 0.73), whereas patients who continued prednisone had a decrease in DAS28 of −0.075 (95% CI −0.27 to 0.21) compared with baseline (p<0.001). The HR of being flare-free at 24 weeks was 2.77 (95% CI 1.47 to 5.25) for continuing versus stopping prednisone.

The likelihood of long-term use of GCs when used as bridging therapy, compared with GCs used as rescue therapy

Low-risk patients included in the CareRA study (high RoB, study described above) were randomised to COBRA slim, which consisted of MTX+prednisone bridging, or to MTX tight step-up, which consisted of MTX monotherapy without oral GC (i.m. GC allowed as rescue).[14] The mean cumulative prednisone dose in the first year was higher for COBRA slim (1554 mg (SD 308)) than for tight step-up (36 mg (SD 50)). However, in the second year the cumulative prednisone dose was higher for the tight step-up arm compared with the COBRA slim arm (235 mg (SD 696) vs 151 mg (SD 346)), suggesting that GC use was higher in patients who did not initially receive GC bridging. This was mainly explained by a higher proportion of patients receiving GC injections in the tight-step up arm (COBRA slim: 19%, tight step-up: 47%). The proportion of patients with at least 3 months GC use outside of the induction scheme was similar between the two treatment arms (COBRA slim: 12%, tight step-up 11%), with a slightly higher median daily dose in the tight step-up arm (COBRA slim: 5.4 mg (IQR 2.9), tight step-up: 6.7 mg (IQR 3.3)).

No studies were included on the influence of the route of administration of GCs or on the effects of protocolised versus non-protocolised tapering and stopping of GC bridging.

Safety

Article selection

From the 220 out of 2977 articles that were identified for full-text review, 42 papers fulfilling all selection criteria were included. In addition, three meeting abstracts were identified (online supplemental figure 3.2). From these conference abstracts, one full text of a subsequent full manuscript was available as a preprint.[13] The included studies reported on 12 unique RCTs and 21 observational studies. Two of these studies were not reported, 1 due to early termination,[16] and another because it was reporting on the same cohort with the same outcomes as another included paper.[26] RoB assessments are provided in online supplemental tables 4.1–4.3 (RCTs) (observational studies). Baseline characteristics of the included studies are provided in online supplemental tables 6.2 and 6.3 (RCTs) (observational studies).

Safety of therapy with GCs in RA

The number of included safety studies per outcome category is provided in online supplemental table 6.1. Observational studies were available for seven of the outcome categories (cardiovascular disease and hypertension, osteoporosis, infections, diabetes and hyperglycaemic, mortality, adverse pregnancy outcomes and glaucoma). These were considered the main study type. For outcome categories that are not reported in this table, no studies were included.

Cardiovascular disease and hypertension

Eleven observational studies reported on cardiovascular disease and/or hypertension (table 2, online supplemental tables 6.4 and 6.5).[27–37] Outcome definitions varied per included study. Four studies reported on hypertension separately.[27 29 34 35] Two studies, both at unclear RoB, reported an increased risk of hypertension.[34 35] One of these studies only reported an increased risk for recent GC treatment with a dose ≥7.5 mg/day and for cumulative GC doses between 5000 and 10 000 mg.[35] The other study reported an increased risk for all time-varying cumulative GC doses (adjusted HR, aHR 1.11, 1.39 (95% CI 1.03 to 1.48)), but not for different categories of daily GC doses, up to ≥7.5 mg/day.[34] The two other studies (both high RoB) reported no increased risk of hypertension for any GC use and for different cumulative GC doses,[27] or for daily versus alternate daily GC dosing.[29]

One study at high RoB reported no increased risk of a cerebrovascular accident after adjustment for potential confounders.[36]

The other observational studies reported on cardiovascular events in general.[27 28 30–33 37] Two studies (one high, one unclear RoB) reported an increased risk of cardiovascular events for any reported daily or cumulative dose (aHRs 1.02, 4.98 (95% CI 1.00 to 6.03)).[31 37] One study (high RoB) reported an increased risk for ever and current GC use and for most reported cumulative doses.[27] Three studies (2 unclear, 1 high RoB) only reported an increased

Table 2 Cardiovascular disease and hypertension, results of observational studies

Study ID	Registry	Type of ratio	Ref category	Exposure definition	Outcomes	RoB
Cerebrovascular accident						
Aviña-Zubieta *et al* 2011 Ann Rheum Dis[36]	Claims database	aHR	No GC use	Current GC use	1.41 (0.84; 2.37)	High
				Current mean daily dose (5 mg)	1.07 (0.94; 1.21)	
				Total cumulative duration of use (year)	1.11 (0.94; 1.32)	
				Total past cumulative dose (1 g)	1.04 (0.99; 1.08)	
				Current daily dose (5 mg) +	1.05 (0.92; 1.20)	
				cumulative duration (year)	1.10 (0.92; 1.31)	
Cardiovascular event						
Aviña-Zubieta *et al* 2013 Rheumatology[37]	Claims database	aHR	No GC use	Current GC use	**1.68 (1.14; 2.47)**	High
				Current mean daily dose (5 mg)	**1.14 (1.05; 1.24)**	
				Total cumulative duration of use (year)	**1.14 (1.00; 1.29)**	
				Total past cumulative dose (1 g)	**1.06 (1.02; 1.10)**	
				Current daily dose (5 mg) +	**1.13 (1.03; 1.24)**	
				cumulative duration (year)	1.10 (0.97; 1.26)	
Ocon *et al* 2021 Ann Rheum Dis[33]	CorEvitas	aHR	No GC use	Daily dose 1 -<5 mg/day	1.94 (0.55; 1.59)	Unclear
				≥5–9 mg/day	**1.56 (1.18; 2.05)**	
				≥10 mg/day	**1.91 (1.31; 2.79)**	
				Cumulative dose prec 6 months 1–380 mg	0.86 (0.53; 1.40)	
				381–750 mg	1.20 (0.81; 1.79)	
				751–1100 mg	**1.43 (1.04; 1.98)**	
				>1100 mg	**2.05 (1.42; 2.94)**	
				Cumulative dose prec 1 year 1–500 mg	0.93 (0.60; 1.45)	
				501–1100 mg	1.19 (0.83; 1.70)	
				1101–2100 mg	**1.47 (1.06; 2.03)**	
				>2100 mg	**1.74 (1.25; 2.43)**	
				Duration of use prec 6 months 1–80 days	0.72 (0.60; 1.45)	
				81–160 days	**1.54 (1.08; 2.20)**	
				161–181 days	1.56 (0.70; 3.48)	
				>181 days	**1.57 (1.20; 2.05)**	
				Duration of use prec 1 year 1–100 days	1.02 (0.68; 1.53)	
				101–220 days	**1.41 (1.03; 1.93)**	
				221–360 days	0.88 (0.54; 1.44)	
				>360 days	**1.88 (1.39; 2.56)**	
Ozen *et al* 2021 J Rheumatol[32]	FORWARD	aHR	No GC use	Ever GC use	**1.15 (1.11; 1.19)**	High
				<7.5 mg/day<3 months	0.90 (0.40; 2.01)	
				<7.5 mg/day ≥3 months	1.11 (0.99; 1.25)	
				≥7.5 mg/day<3 months	1.18 (0.63; 2.20)	
				≥7.5 mg/day≥3 months	**1.47 (1.26; 1.71)**	
Pujades-Rodriguez *et al* 2020 PloS Med[31]	CPRD	aHR	No GC use	Ever GC use	**1.63 (1.52; 1.73)**	Unclear
				Current GC use	**2.11 (1.98; 2.25)**	
				Current daily dose per 5 mg/day	**1.28 (1.25; 1.31)**	
				Current daily dose 1–4.9 mg	**1.84 (1.62; 2.10)**	
				5.0–14.9 mg	**2.00 (1.85; 2.15)**	
				15.0–24.9 mg	**2.79 (2.21; 3.51)**	
				≥25 mg	**4.98 (4.11; 6.03)**	
				Total cumulative dose per 1000 mg	**1.02 (1.02; 1.03)**	
				Total cumulative dose 1–959.9 mg	**1.47 (1.34; 1.61)**	
				960–3054.9 mg	**1.52 (1.36; 1.68)**	
				3055–7299.9 mg	**1.72 (1.55; 1.19)**	
				≥7300 mg	**1.80 (1.65; 1.97)**	
Roubille *et al* 2020 Rheumatology[30]	ESPOIR	N patients with event	No GC use	No GC use	3 (1.4%)	Unclear
				GC use	15 (3.8%), p=0.177	
				Cumulative dose>0–1842 mg	2 (2.2%)	
				1842–8421.5 mg	1 (0.7%)	
				≥8421.5 mg	12 (7.9%), **p<0.001**	
Suda *et al* 2018 Clin Rheumatol[29]	Hospital chart review	N pts with event	NA	Daily GC dosing	0	High
				Alternate daily GC dosing	2 (2.9%), p=0.16	

Continued

Table 2 Continued

Study ID	Registry	Type of ratio	Ref category	Exposure definition	Outcomes	RoB
van Sijl *et al* 2014 PloS One[28]	CARRÉ cohort	aHR	No GC use	Ever GC use	0.89 (0.26; 3.09)	Unclear
				Recent (<1 year) GC use	1.11 (0.27; 4.53)	
				Current GC use	1.34 (0.31; 5.88)	
				Duration of GCs (years)	1.14 (0.83; 1.58)	
				Duration of GCs ≤5 years	0.71 (0.15; 3.27)	
				>5 years	1.48 (0.21; 10.45)	
				Cumulative use (g)	1.05 (0.99; 1.11)	
				Cumulative use ≤10 g	0.42 (0.05; 3.30)	
				>10 g	1.80 (0.37; 8.74)	
Wilson *et al* 2019 Arthritis Care Res[27]	CPRD	aOR	No GC use	GC use	**1.28 (1.07; 1.52)**	High
				Past GC use	1.09 (0.98; 1.21)	
				Current GC use	**1.31 (1.05; 1.64)**	
				Cumulative GC dose <700 mg	**1.35 (1.06; 1.72)**	
				700 to <3500 mg	1.03 (0.80; 1.32)	
				3500 to <7000 mg	**1.56 (1.14; 2.14)**	
				≥7000 mg	**1.60 (1.13; 2.28)**	
Hypertension						
Costello *et al* 2021 Rheumatology[35]	CPRD	aHR	No GC use	Recent GC use	**1.17 (1.10; 1.24)**	Unclear
				Recent GC dose >0–4.9 mg/day	1.10 (0.98; 1.24)	
				Recent GC dose 5–7.4 mg/day	1.07 (0.93; 1.23)	
				Recent GC dose 7.5–14.9 mg/day	**1.18 (1.08; 1.29)**	
				Recent GC dose ≥15 mg/day	**1.36 (1.18; 1.56)**	
				Cumulative GC dose>0–2.49 g	1.00 (0.92; 1.08)	
				Cumulative GC dose 2.5–4.99 g	0.99 (0.90; 1.08)	
				Cumulative GC dose 5–9.99 g	**1.12 (1.02; 1.22)**	
				Cumulative GC dose ≥10 g	1.07 (0.97; 1.17)	
Mebrahtu *et al* 2020 CMAJ[34]	CPRD	aHR	No GC use	Time-varying cumulative GC dose <0–959.9 mg	**1.11 (1.03; 1.21)**	Unclear
				960–3054.9 mg	**1.16 (1.05; 1.29)**	
				≥3055 mg	**1.39 (1.30; 1.48)**	
				Time-variant daily dose >0–4.9 mg	1.04 (0.89; 1.22)	
				5.0–7.4 mg	1.06 (0.93; 1.22)	
				≥7.5 mg	1.07 (0.96; 1.19)	
Suda et al 2018 Clin Rheumatol[29]	Hospital chart review	N patients with event	NA	Daily GC dosing	3 (4.4%)	High
				Alternate daily GC dosing	4 (5.7%), p=0.73	
Wilson *et al* 2019 Arthritis Care Res[27]	CPRD	aOR	No GC use	GC use	0.93 (0.85; 1.01)	High
				Past GC use	0.96 (0.91; 1.02)	
				Current GC use	1.02 (0.90; 1.16)	
				Cumulative GC dose <700 mg	0.93 (0.82; 1.06)	
				700 to <3500 mg	0.93 (0.82; 1.06)	
				3500 to <7000 mg	0.92 (0.76; 1.11)	
				≥7000 mg	0.91 (0.74; 1.12)	

Bold indicates statistically significant results at p<0.05.
aHR, adjusted HR; aOR, adjusted OR; GC, glucocorticoid; RoB, risk of bias.

risk for higher daily or cumulative doses (aHRs 1.41, 2.05 (95% CI 1.03 to 2.79)).[30 32 33] These were a daily dose ≥5 mg, cumulative doses >750 mg in the preceding 6 months or >1100 mg in the preceding year,[33] ≥7.5 mg/day for≥3 months,[32] or a cumulative dose ≥8421 mg over 10 years.[30] One study at unclear RoB reported no increased risk of cardiovascular events for any reported duration or cumulative dose, after adjustment for potential confounders.[28]

The number of events in the 12 included RCTs was low, and was therefore not further described (online supplemental table 6.6).[13 18 21 22 24 38–43]

Osteoporosis and osteoporotic fractures

Five observational studies reported on osteoporotic fractures,[26 29 30 32 44] and one on incident osteoporosis (table 3, online supplemental tables 6.7 and 6.8).[27] Three studies (two high, one unclear RoB) showed an increased risk for osteoporotic fractures.[26 32 44] This risk was only observed for higher daily or cumulative doses, although one study (unclear RoB) already reported an increased risk at 2.5 mg/day.[26] A second study (high RoB) reported an increased risk for GC use ≥3 months, independent of whether the daily dose was below or above 7.5 mg/day.[32] No difference for the risk of osteoporotic fractures was observed in another study, even with high cumulative doses (unclear RoB),[30] and between daily versus alternate daily GC dosing (high RoB).[29]

One study (high RoB) reported an increased risk of osteoporosis for current GC use, for all reported cumulative dose categories (adjusted ORs, aORs 1.31, 1.56 (95% CI 1.11 to 1.97)).[27]

Three additional RCTs reporting on osteoporotic fractures or osteoporosis are described in online supplemental table 6.9.[40 41 45]

Infections

Five observational studies reported on the risk of infections (table 4, online supplemental tables 6.10 and 6.11).[27 29 30 46 47]

Table 3 Osteoporotic fractures and osteoporosis, results of observational studies

Study ID	Registry	Type of ratio	Ref category	Exposure definition	Outcomes	RoB
Osteoporotic fractures						
Abtahi *et al* 2021 Rheumatology[26]	CPRD	aHR	Past GC use	Current GC use	**1.22 (1.06; 1.40)**	Unclear
				Recent GC use	0.71 (0.51; 1.00)	
				Non-use	0.94 (0.83; 1.07)	
				Current GC use mean daily dose ≤7.5 mg/day	1.14 (0.98; 1.33)	
				Dose 7.5–14.9 mg/day	**1.38 (1.11; 1.63)**	
				≥15 mg/day	**1.84 (1.23; 2.74)**	
				Current GC use, cumulative use ≤1 g	1.11 (0.86; 1.44)	
				>1 g	**1.24 (1.07; 1.44)**	
				Current GC use:		
				Cumul. Use ≤1 g and mean daily dose ≤7.5 mg/day	1.10 (0.83; 1.47)	
				Cumul. Use ≤1 g and mean daily dose >7.5 mg/day	1.15 (0.71; 1.87)	
				Cumul. Use >1 g and mean daily dose ≤7.5 mg/day	1.15 (0.98; 1.35)	
				Cumul. Use >1 g and mean daily dose >7.5 mg/day	**1.52 (1.22; 1.89)**	
				Current GC use ≤2.5 mg/day	1.00 (0.77; 1.31)	
				>2.5 mg/day	**1.27 (1.09; 1.47)**	
				Current GC use ≤5 mg/day	1.07 (0.89; 1.29)	
				>5 mg/day	**1.34 (1.14; 1.57)**	
Balasubramanian *et al* 2016 Osteoporosis Inc[44]	Claims database	aHR	No GC use	Current daily dose 0 mg/day	Ref	High
				>0 to <5 mg/day	1.37 (0.88; 2.13)	
				5 to <7.5 mg/day	1.20 (0.82; 1.77)	
				7.5 to <15 mg/day	1.01 (0.68; 1.49)	
				≥15 mg/day	**2.22 (1.51; 3.27)**	
				Cumulative dose 0 mg	Ref	
				>0 to <675 mg	0.93 (0.70; 1.25)	
				675 to <1350 mg	1.13 (0.81; 1.56)	
				1350 to <2700 mg	1.01 (0.72; 1.41)	
				2700 to <5400 mg	1.11 (0.77; 1.59)	
				≥5400 mg	**1.98 (1.37; 2.86)**	
		IR (95% CI)/1000 PY		Peak dose 0 mg	4.3 (3.4; 5.4)	
				>0 to <5 mg	4.8 (3.0; 7.2)	
				Five to <7.5 mg	4.8 (2.9; 7.5)	
				7.5 to <15 mg	5.7 (4.3; 7.4)	
				≥15 mg	6.0 (5.4; 6.7)	
				Cumulative days 0	4.3 (3.4; 5.4)	
				One to 90	4.8 (4.1; 5.5)	
				91 to 365	5.5 (4.6; 6.4)	
				>365	11.1 (9.1; 13.4)	
				Days since GC discontinuation (no exposure)	4.3 (3.4; 5.4)	
				Days since GC discontinuation 0 (current use)	9.0 (7.4; 10.8)	
				>0 to <60	7.2 (5.7; 8.9)	
				60 to <182	5.4 (4.2; 6.8)	
				182 to <365	5.0 (3.8; 6.4)	
				≥365	4.4 (3.7; 5.3)	
Ozen 2019 Ann Rheum Dis	FORWARD	aHR	No GC use	No GC use	Ref	High
				GC use <7.5 mg/day for <3 months	1.23 (0.65; 2.29)	
				GC use <7.5 mg/day for≥3 months	**1.26 (1.07; 1.48)**	
				GC use ≥7.5 mg/day for<3 months	1.66 (0.99; 2.77)	
				GC use≥7.5 mg/day for≥3 months	**1.57 (1.27; 1.94)**	
Roubille *et al* 2020 Rheumatology[30]	ESPOIR	N patients with event	No GC use	No GC use	15 (7.1%)	Unclear
				GC use	17 (4.3%), p=0.137	
				Cumulative dose>0–1842 mg	5 (5.4%)	
				1842–8421.5 mg	6 (3.9%)	
				≥8421.5 mg	6 (3.9%), p=0.475	
Suda *et al* 2018 Clin Rheumatol[29]	Hospital chart review	N events		Daily GC dosing	1 (1.5%)	High
				Alternate daily GC dosing	3 (4.3%), p=0.32	
Osteoporosis						
Wilson *et al* 2019 Arthritis Care Res[27]	CPRD	aOR	No GC use	Ever GC use	**1.41 (1.25; 1.59)**	High
				Past GC use	1.02 (0.95; 1.09)	
				Current GC use	**1.77 (1.54; 2.04)**	
				Cumulative GC dose <700 mg	**1.31 (1.11; 1.54)**	
				700 to <3500 mg	**1.52 (1.30; 1.77)**	
				3500 to <7000 mg	**1.43 (1.16; 1.76)**	
				≥7000 mg	**1.56 (1.24; 1.97)**	

Bold indicates statistically significant results at p<0.05.
aHR, adjusted HR; aOR, adjusted OR; cumul, cumulative; GC, glucocorticoid; IR, incidence rate; RoB, risk of bias.

Table 4 Infections, results of observational studies

Study ID	Registry	Type of ratio	Ref category	Exposure definition	Adjusted	RoB
Any infection						
Suda *et al* 2018 Clin Rheumatol[29]	Hospital chart review	aOR	Daily GC dosing	Alternate daily GC dosing	0.27 (0.12; 0.63)	High
Infection occurring during an acute care hospitalisation						
George *et al* 2020 Ann Int Med[47]	Claims database	Predicted 1-year incidence		**Medicare**		High
				No GC use	8.6	
				GC dose ≤5 mg/day	11.0 (10.6; 11.5)	
				5–10 mg/day	14.4 (13.8; 15.1)	
				≥10 mg/day	17.7 (16.5; 19.1)	
				Optum		
				No GC use	4	
				GC dose ≤5 mg/day	5.2 (4.7; 5.8)	
				5–10 mg/day	8.1 (7.0; 9.3)	
				≥10 mg/day	10.6 (8.5; 13.2)	
				Medicare		
				Cumulative dose ≤450 mg	0.97 (0.92; 1.01)	
				450–900 mg	0.94 (0.89; 0.99)	
				900–1350 mg	1.01 (0.95; 1.06)	
				1350–1800 mg	1.03 (0.96; 1.10)	
				1800–2250 mg	1.03 (0.95; 1.12)	
				2250–2700 mg	1.12 (1.03; 1.23) 1.01 (0.92; 1.12)	
				>2700 mg		
				Optum		
				Cumulative dose ≤450 mg	0.98 (0.86; 1.12)	
				450–900 mg	0.91 (0.77; 1.07)	
				900–1350 mg	0.97 (0.81; 1.15)	
				1350–1800 mg	0.99 (0.78; 1.24)	
				1800–2250 mg	1.31 (1.02; 1.68)	
				2250–2700 mg	1.31 (0.99; 1.75)	
				>2700 mg	1.28 (0.96; 1.70)	
Serious infections						
Dixon *et al* 2012 Ann Rheum Dis[46]	Claims database	aOR	No GC use	Current GC use	**1.84 (1.64; 2.06)**	High
				Any GC use past 30 days	**2.08 (1.86; 2.33)**	
				Any GC use past 90 days	**2.26 (2.02; 2.54)**	
				Ever GC use	**1.72 (1.53; 1.94)**	
				Current dose (per mg PEQ)	**1.04 (1.04; 1.05)**	
				Average dose in past 30 days (per mg PEQ)	**1.07 (1.06; 1.08)**	
				Average dose in past 90 days (per mg PEQ)	**1.09 (1.08; 1.11)**	
				Average dose since study entry (per mg PEQ)	**1.08 (1.06; 1.09)**	
				Peak dose past 30 days (per mg PEQ)	**1.03 (1.02; 1.03)**	
				Peak dose past 90 days (per mg PEQ)	**1.02 (1.01; 1.02)**	
*Roubille et a. 2020 Rheumatology*30	ESPOIR	N patients with event	No GC use	No GC use	5 (2.4%)	Unclear
				GC use	30 (7.6%), **p=0.009**	
				Cumulative GC dose>0–1842 mg	5 (5.4%)	
				1842–8421.5 mg	10 (6.6%)	
				≥8421.5 mg	15 (9.9%), **p=0.024**	
Suda *et al* 2018 Clin Rheumatol[29]	Hospital chart review	N patients with event	Daily GC dosing	Daily GC dosing	4 (5.9%)	High
				Alternate daily GC dosing	3 (4.3%), p=0.67	
Wilson *et al* 2019 Arthritis Care Res[27]	CPRD	aOR	No GC use	No GC use	Ref	High
				Ever GC use	**1.28 (1.11; 1.48)**	
				Past GC use	0.96 (0.88; 1.05)	
				Current GC use	**1.63 (1.37; 1.95)**	
				Cumulative GC dose <700 mg	1.11 (0.91; 1.36)	
				700 to <3500 mg	1.17 (0.93; 1.45)	
				3500 to <7000 mg	**1.30 (1.01; 1.68)**	
				≥7000 mg	**1.62 (1.23; 2.15)**	

Bold indicates statistically significant results at p<0.05.
aHR, adjusted HR; aOR, adjusted OR; GC, glucocorticoid; PEQ, prednisone equivalent dose; RoB, risk of bias.

Four of these reported on the risk of serious infections.[27 29 30 46] Three studies (two high RoB, one unclear RoB) reported an increased risk of serious infections for (current) GC use.[27 30 46] Two of these reported an increased risk with increasing dose.[46 47] The two studies investigating cumulative doses showed conflicting results.[27 30]

One study (high RoB) reported no difference in risk of serious infections for alternate daily GC dosing versus daily GC dosing.

However, the risk of any infection was lower with alternate daily GC dosing (aOR 0.27 (95% CI 0.12 to 0.63)).[29] Also, the risk of an infection occurring during an acute care hospitalisation was increased with increasing GC doses (one study at high RoB).[47]

Results of 11 additional RCTs reporting on infections, serious infections, tuberculosis or herpes zoster are described in online supplemental table 6.12.[13 14 18 21–24 40 48–50]

Diabetes and hyperglycaemia

Four observational studies reported on the risk of incident diabetes (table 5, online supplemental tables 6.13 and 6.14).[27 29 51 52] Three studies (two unclear RoB, one high RoB) reported an increased risk for ever or current GC use, with an increased risk for higher daily and for higher cumulative doses.[27 51 52] One of these studies (unclear RoB) reported no increased risk for daily doses <5 mg/d,[51] whereas a second study (unclear RoB) did report an increased risk of incident diabetes for the lowest daily dose category (<5 mg/day).[52]

One study (high RoB) reported no difference in the risk of diabetes for daily versus alternate daily dosing.[29]

Results of five RCTs reporting on diabetes and three RCTs reporting on hyperglycaemia or blood glucose fluctuation are described in online supplemental table 6.15.[13 18 22 24 40–42 50]

Mortality

Four observational studies reported on the risk of all-cause mortality (table 6, online supplemental tables 6.16 and 6.17).[27 30 51 53] One study (unclear RoB) reported no increased risk for ever use of GC or for different cumulative doses.[30] Two studies (one unclear, one high RoB) reported an increased risk for current GC use.[27 51] Two studies reported an increased risk with increasing daily dose, with one study (high RoB) reporting an increased risk starting at ≥8 mg/day and one study (unclear RoB) starting at ≥5 mg/day.[51 53] Three studies (two high, one unclear RoB) reported an increased risk with increasing cumulative doses.[27 51 53]

Three additional RCTs reporting on mortality are described in online supplemental table 6.18.[13 14 40]

Adverse pregnancy outcomes

One observational study (unclear RoB) reported on preterm birth (online supplemental tables 6.19 and 6.20).[54] An increased risk was shown for oral GC use ≥10 mg/day after gestational day 139 (aHR 2.47 (95% CI 1.32 to 4.63)).

Glaucoma

One observational study (high RoB) reported on the risk of glaucoma.[27] No higher risk was reported for current or past GC use. For some of the cumulative dose categories a higher risk was reported, but this was not consistently increased with increasing doses.

Three additional RCTs reporting on glaucoma are described in online supplemental table 6.23.[13 38 40]

Other safety outcomes

The remaining safety outcomes (online supplemental tables 6.24–6.33) were only reported in RCTs.[13 15 18 21–24 38–42 48 49] Due to a limited number of included studies per outcome and/or a limited number of events, the safety outcomes of these trials were not further discussed.

Safety outcomes of randomized trials investigating long-term GC treatment

Patients in the SEMIRA trial (low RoB) on tocilizumab with stable low disease activity were randomised to either taper and stop prednisone at 16 weeks, or to continue prednisone 5 mg/day.[18] At 24 weeks follow-up, both the number of patients with treatment emergent AEs (80 vs 64) and the number of patients with treatment emergent SAEs (7 vs 4) were higher for patients that tapered and stopped versus the patients that continued prednisone (online supplemental table 6.30).

The safety of prednisolone 5 mg/day in addition to standard care in patients with active RA aged ≥65 years was investigated in the double-blind placebo-controlled GLORIA trial (high RoB) during 2 years follow-up.[13] One of the main outcomes was the number of AEs of special interest. These included all SAEs, AEs leading to discontinuation and several GC-related AEs. More patients in the prednisolone (60%) than in the placebo (49%) group experienced this outcome (p=0.02, online supplemental table 6.30). The difference was mainly caused by a higher number of serious (26 vs 16) and non-serious (124 vs 91) infections in patients on prednisolone versus placebo (online supplemental table 6.12). The number of cardiovascular events was numerically higher for patients on prednisolone versus placebo (online supplemental table 6.6). The total number of patients with an SAE did not differ between the two groups (online supplemental table 6.30). Most GC-related AEs were rare (ie, newly occurring hypertension (online supplemental table 6.6), diabetes (online supplemental table 6.15), cataract (online supplemental table 6.32)), without relevant differences between groups.

No studies were included describing the safety of GC combined with bDMARDs compared with bDMARDs without GCs, or the safety of GCs with different routes of administration.

DISCUSSION

In this SLR, an overview was provided of the efficacy, duration of use and safety of GCs, with the aim of informing the task force responsible for the 2022 update of the EULAR recommendations for the management of RA. The results of this SLR suggest that GCs are effective as initial bridging therapy, with equal improvements over 2 years in disease activity, physical functioning and radiographic progression for moderate (30 mg/day) compared with high (60 mg/day) initial prednisone doses.[14] Studies about the efficacy of lower initial GC doses were not identified in the current SLR, but have been published previously and suggest benefits with doses ranging from 5 to 10 mg/day.[55] Another recently published study that was not included in the current SLR is the NORD-STAR trial.[56] In this RCT in patients with early RA, treatment with either abatacept, certolizumab or tocilizumab (all plus MTX) did not show superior efficacy compared with active conventional treatment consisting of conventional synthetic DMARDs+GCs. Since data on oral GCs and intra-articular GC use were not reported separately in the publication, this study could not be included.

For low-risk patients, after 2 years, efficacy outcomes were similar for patients starting initial GC bridging versus tight step-up treatment (without GCs).[14] However, disease activity during follow-up was lower for patients starting with bridging GCs, which can have positive effects. In fact, early control of disease activity has been shown to improve long-term outcomes (eg, fatigue), and to reduce the use of non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics.[57–59] In addition, in the second year of follow-up cumulative GC doses were higher for patients in the tight step-up treatment group, indicating

Table 5 Diabetes, outcomes of observational studies

Study ID	Registry	Type of ratio	Ref category	Exposure definition	Adjusted	RoB
Movahedi *et al* 2016 Arthritis Rheumatol[51]	CPRD and NDB	aHR	No GC use	**CPRD**		unclear
				Ever GC use	**1.35 (1.22; 1.48)**	
				Current GC use	**1.30 (1.17; 1.45)**	
				Current GC dosage (5 mg/day)	**1.25 (1.19; 1.31)**	
				Current GC dose 0–4.9 mg/day	1.06 (0.87; 1.28)	
				5–9.9 mg/day	**1.16 (1.00; 1.34)**	
				10–19.9 mg/day	**1.97 (1.61; 2.40)**	
				≥20 mg/day	**3.19 (2.22; 4.58)**	
				Cumulative GC dose last year per 1000 mg	**1.22 (1.17; 1.28)**	
				Cumulative GC dose since cohort entry per 1000 mg	**1.02 (1.01; 1.03)**	
				Cumulative GC dose since cohort entry 0–959.9 mg	**1.23 (1.08; 1.40)**	
				960–3054.9 mg	**1.41 (1.22; 1.62)**	
				3055–7298.9 mg	**1.35 (1.15; 1.57)**	
				≥7299 mg	**1.53 (1.30; 1.79)**	
				NDB		
				Ever GC use	**1.42 (1.22; 1.66)**	
				Current GC use	**1.61 (1.37; 1.89)**	
				Current GC dosage (5 mg/day)	**1.30 (1.21; 1.38)**	
				Current GC dose 0–4.9 mg/day	1.07 (0.80; 1.40)	
				5–9.9 mg/day	**1.58 (1.30; 1.93)**	
				10–19.9 mg/day	**2.24 (1.72; 2.93)**	
				≥20 mg/day	**3.06 (1.90; 4.91)**	
				Cumulative GC dose last year per 1000 mg	**1.19 (1.14; 1.24)**	
				Cumulative GC dose since cohort entry per 1000 mg	**1.03 (1.02; 1.05)**	
				Cumulative GC dose since cohort entry 0–959.9 mg	1.21 (0.97; 1.51)	
				960–3054.9 mg	**1.36 (1.08; 1.70)**	
				3055–7298.9 mg	**1.68 (1.35; 2.11)**	
				≥7299 mg	**1.67 (1.31; 2.12)**	
Suda *et al* 2018 Clin Rheumatol[29]	Hospital chart review	N events		Daily GC dosing	2 (2.9%)	high
				Alternate daily GC dosing	1 (1.4%), p=0.54	
Wilson *et al* 2019 Arthritis Care Res[27]	CPRD	aOR	No GC use	No GC use	Ref	high
				GC use	**1.33 (1.14; 1.56)**	
				Past GC use	1.09 (0.91; 1.29)	
				Current GC use	**2.24 (1.76; 2.83)**	
				Cumulative dose <700 mg	**1.14 (1.00; 1.53)**	
				700 to <3500	**1.35 (1.08; 1.69)**	
				3500 to <7000	**1.39 (1.03; 1.88)**	
				≥7000	**1.53 (1.12; 2.10)**	
Wu *et al* 2020 BMJ Open Diabetes Res Care[52]	CPRD	aHR	No GC use	Ever GC use	**1.41 (1.29; 1.54)**	unclear
				Current GC use	**2.01 (1.84; 2.20)**	
				Current daily dose per 5 mg/day	**1.03 (1.02; 1.04)**	
				Current daily dose >0–4.9 mg/day	**1.66 (1.37; 2.02)**	
				5.0–14.9 mg/day	**1.90 (1.71; 2.12)**	
				15.0–24.9 mg/day	**3.07 (2.28; 4.14)**	
				≥25.0 mg/day	**4.00 (3.08; 5.21)**	
				Cumulative dose per 1000 mg	**1.02 (1.01; 1.02)**	
				Cumulative dose 1.0–959.9 mg	**1.17 (1.04; 1.32)**	
				960.0–3054.9 mg	**1.44 (1.25; 1.65)**	
				3055.0–7299.9 mg	**1.58 (1.8; 1.82)**	
				≥7300 mg	**1.61 (1.42; 1.81)**	

Continued

Table 5 Continued

Study ID	Registry	Type of ratio	Ref category	Exposure definition	Adjusted	RoB

Bold indicates statistically significant results at p<0.05.
aHR, adjusted HR; aOR, adjusted OR; GC, glucocorticoid; RoB, risk of bias.

that also in terms of duration of use initial GC bridging may be advantageous in low-risk patients compared with 'rescue' treatment with GCs.[14] Further studies are needed to compare the efficacy, duration of use and safety of initial GC treatment versus rescue GC treatment in high-risk patients, especially in those starting a b/tsDMARD, and in larger patient groups. Also, studies comparing different routes of administration of GCs, the efficacy of GC bridging during follow-up, or the efficacy of GC bridging with a protocolised versus a non-protocolised tapering protocol, are currently lacking.

Concerns have recently been expressed regarding the ability to stop GCs after initial GC bridging treatment.[8] We included data from a recently published SLR and meta-analysis, which concluded that in clinical trials at 12–24 months of follow-up with prespecified tapering and stopping of GCs, only a limited proportion of patients still used GCs, or resumed GC after initial stopping.[9]

These data suggest that in clinical trials with protocolised tapering schemes, tapering and stopping of GCs is feasible for most patients. This observation is in line with data from a study in real-world setting (not included in this SLR), in which most patients on a step-down strategy with protocolised tapering of GC could stop treatment after 2 years.[60] Even though protocolised tapering of GCs seems feasible, there might be challenges

Table 6 Mortality, results of observational studies

Study ID	Registry	Type of ratio	Ref category	Exposure definition	Adjusted	RoB
del Rincón *et al* 2014 Arthritis Rheumatol[53]	Observational database	aHR	No GC use	Daily dose none	Ref	High
				Daily dose <5 mg/day	1.19 (0.74; 1.90)	
				5–7 mg/day	1.21 (0.88; 1.66)	
				8–15 mg/day	**1.78 (1.22; 2.60)**	
				≥15 mg/day	**2.83 (1.41; 5.66)**	
				Cumulative dose none	Ref	
				Cumulative dose <9 mg	0.59 (0.36; 0.95)	
				9–39.9 mg	**1.12 (0.76; 1.64)**	
				≥40 mg	**1.74 (1.25; 2.44)**	
				Dose/time no GCs	Ref	
				<1.98 mg/year	0.48 (0.29; 0.80)	
				1.98–5.08 mg/year	0.99 (0.67; 1.45)	
				≥5.08 mg/year	**2.11 (1.51; 2.94)**	
Movahedi *et al* 2016 Eur J Epidemiol[51]	CPRD	aHR	No GC use	Never GC use	Ref	Unclear
				Ever GC use	**1.97 (1.81; 2.15)**	
				Current GC use	**1.77 (1.62; 1.93)**	
				Current GC dose per 5 mg/day	**1.33 (1.30; 1.35)**	
				Current dose >0–4.9 mg/day	1.02 (0.87; 1.20)	
				5.0–7.4 mg/day	**1.44 (1.26; 1.64)**	
				7.5–14.9 mg/day	**2.24 (1.98; 2.54)**	
				15.0–24.9 mg/day	**4.50 (3.61; 5.62)**	
				≥25 mg/day	**11.0 (8.87; 13.6)**	
				Cumulative dose since cohort entry (1000 mg/day)	**1.06 (1.05; 1.07)**	
				Cumulative dose >9–959.9 mg	**1.60 (1.42; 1.81)**	
				960–3054.9 mg	**1.83 (1.62; 2.07)**	
				3055–7299.9 mg	**2.11 (1.87; 2.39)**	
				≥7300 mg	**3.11 (2.74; 3.52)**	
Roubille *et al* 2020 Rheumatology[30]	ESPOIR	N patients with event	No GC use	No GC use	1 (0.5%)	Unclear
				GC use	9 (2.3%), p=0.103	
				Cumulative GC dose >0–1842 mg	1 (1.1%)	
				1842–8421.5 mg	4 (2.6%)	
				≥8421.5 mg	4 (2.6%) p=0.248	
Wilson *et al* 2019 Arthritis Care Res[27]	CPRD	aOR	No GC use	No GC use	Ref	High
				GC use	1.33 (1.19; 1.48)	
				Past GC use	1.03 (0.97; 1.10)	
				Current GC use	**1.80 (1.59; 2.04)**	
				Cumulative GC dose <700 mg	0.90 (0.76; 1.07)	
				700 to <3500 mg	**1.27 (1.10; 1.48)**	
				3500 to <7000 mg	**1.42 (1.18; 1.71)**	
				≥7000 mg	**2.33 (1.95; 2.77)**	

aHR, adjusted HR; aOR, adjusted OR; GC, glucocorticoid; RoB, risk of bias.

in implementing this strategy into clinical practice. Further research into possible barriers and facilitators of GC tapering in clinical practice will help in bridging this gap in the near future. Based on these RCTs, the recommendations on this point should clearly demand forced tapering and discontinuation of GCs in clinical practice. It should also be noted that although 12–24 months is longer than the maximum bridging period of 3 months that is advised in the 2019 EULAR recommendations, most trials included in this SLR only allowed stopping GCs after approximately 6 months, once the GC dose had first successfully been reduced to five or 7.5 mg/day within a timeframe of about 6 weeks.[6] Therefore, current data do not allow us to draw conclusions on whether stopping after 3 months is also feasible. However, it must be assumed that the effect of parenteral GC bridging does not last for more than 3 months and from this perspective 3 months appears to be a realistic target time.

The effects of withdrawal of GCs in patients with established RA (mean disease duration of 9.6 years) were studied in the SEMIRA trial.[18] Patients on tocilizumab with stable low disease activity who tapered prednisone had an increase in DAS28 and a lower likelihood of being flare-free, compared with patients who continued prednisone at 5 mg/day, suggesting that in advanced disease tapering might be more difficult.

The majority of studies included in this SLR reported on GC safety. Whereas we included both observational studies and (long-term extensions of) RCTs, we considered observational studies the main study type to evaluate safety in this SLR. Since RCTs are generally not powered to evaluate safety outcomes, often exclude patients with high risks of AEs and mostly have a relatively short follow-up, safety outcomes of RCTs can be difficult to interpret. Observational studies including large numbers of patients with longer follow-up allow a better interpretation of safety outcomes. However, due to non-random treatment allocation, a RoB such as confounding by indication may play a major role in the interpretation of the results. For this reason, all observational studies included in this SLR are evaluated to have an unclear or a high RoB.

Evidence from observational studies was available for 7 out of 21 outcomes reported in this SLR. In general, there is considerable heterogeneity in the definition of outcome measures and exposure categories across studies. Studies reporting on hypertension and cardiovascular events show conflicting results. In some studies a higher risk is only observed for higher cumulative or daily doses (≥5 to 7.5 mg/day prednisone equivalent dose (PEQ)).[32 33 35] One study showed no increased risk of cardiovascular events at all after adjusting for disease activity.[28] Of note, only one other study with cardiovascular events as an outcome directly adjusted for disease activity.[33] This study only found an increased risk for prednisone/prednisolone daily doses >5 mg/day or cumulative doses >750 mg in the preceding 6 months. This stresses the potential influence of confounding by indication in studies investigating the side effects of GC where patients who taper and flare and thus appear to be unable to stop or lower GC are different from those who can discontinue or were never exposed to GC. In addition, Information bias can also occur when defining exposure to GCs, which might further challenge the interpretation of treatment effects.[61]

The risk of osteoporotic fractures, serious infections and risk of diabetes was increased for GC users across all included studies. In general, this risk seemed increased for higher daily doses and longer durations, but results on a safe daily dose and/or duration are conflicting.

Only one out of four studies, which only reported unadjusted results, showed no increased risk of mortality.[30] The remaining studies showed an increased risk with increasing daily and/or cumulative doses, but again residual confounding (eg, by disease severity) cannot be ruled out.[27 51 53] None of the studies reported an increased risk of mortality for the lowest dose categories (<5 to 7 mg/day PEQ).

In conclusion, the results of this SLR confirm the efficacy of GC bridging as initial therapy. Moreover, the majority of patients who start GC bridging in clinical trials are able to stop GCs within 12–24 months. Also, long-term low-dose GC use seems efficacious, but with an increased risk of infections. In general, this SLR confirms well-known safety risks of GC use such as an increased risk of osteoporotic fractures, serious infections, diabetes, cardiovascular events and mortality, but with large heterogeneity between studies in terms of definitions of outcome measures and exposure categories, and particularly methods to cope with bias. Most studies show an increased risk with increasing daily dose and/or duration, but the currently available evidence is too equivocal to indicate which dose and duration are safe for different safety outcomes. The results of this SLR were used by the task force responsible for developing the update of the EULAR recommendations for the management of RA.

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SUPPLEMENTARY FILES: INDEX

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SUPPLEMENTARY FILE 1: Research questions and PICO's for the efficacy, safety and duration of use of glucocorticoids

EFFICACY

1. What is the efficacy of newly started GC in combination with other DMARDs as initial therapy?

Patient population: Newly diagnosed adult patients with RA.

Intervention: Newly started GC (prednisone, prednisolone, methylprednisolone, paramethasone, triamcinolone (hexa)acetonid, dexamethasone, deflazacort, cortivazol, betamethasone) – in combination with other DMARD(s) as initial therapy.
Dose and time defined: oral, intramuscular or intravenous, any dose and duration.

Comparator: Other DMARD(s) without GC.

Outcomes:

Signs and symptoms

Core set variables:

- SJC
- TJC
- Pain
- Patient global assessment
- Physician global
- HAQ
- CRP
- ESR

Composite measures:

- ACR 20/50/70
- DAS28-CRP
- DAS28-ESR
- DAS44
- CDAI
- SDAI
- EULAR responses (EULAR good or moderate response)
- ACR/EULAR remission

Physical Function

- Health assessment questionnaire Disability Index (HAQ-DI)
- Short Form 36 Physical Component Score (SF36-PCS)

Patient reported outcomes

- Mental component scores (MCS) of the Short Form-36 (SF-36) questionnaire
- Fatigue (FACIT-F)
- Pain (VAS score)
- Quality of life (RAQol, EQ5D)

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Impact of disease (RAID)

Structural damage

- Sharp scores (including modifications)
- Numbers of patients achieving radiographic non-progression (defined in individual studies)

2. What is the efficacy of newly started GC in combination with other DMARDs that are not started as initial therapy, but during follow-up?

P: Adult patients with existing RA.

I: Newly started GC – in combination with other DMARDs not started as initial therapy.
Dose and time defined: oral, intramuscular or intravenous, any dose and duration.

C: Other DMARD(s) without GC.

O: As in *1*.

3. What is the efficacy of different routes of administration of newly started GC in combination with other DMARDs?

P: Adult patients with RA.

I: Newly started GC in combination with other DMARD(s) .
Dose and time defined: oral, intramuscular or intravenous, any dose and duration.

C: Newly started GC with another route of administration, in combination with other DMARD(s).
Dose and time defined: oral, intramuscular or intravenous, any dose and duration.

O: As in *1*.

4. What is the efficacy of initial GC bridging in combination with DMARDs that is tapered and stopped versus initial DMARD therapy with rescue GC later during follow-up?

P: Adult patients with RA.

I: Newly started GC bridging that is tapered and stopped within 1 year of treatment start in combination with other DMARD(s).
Dose and time defined: oral, intramuscular or intravenous, any dose.

C: Newly started DMARD therapy, with rescue GC during follow-up

O: As in *1*.

5. What is the efficacy of long-term low dose GC?

P: Adult patients with RA.

I: Long-term (≥6 months) low dose (≤7.5 mg) GC in combination with other DMARDs
Dose and time defined: oral, intramuscular or intravenous.

C:
- DMARD therapy without GC
- DMARD therapy with GC that is tapered and stopped within 12 months.

O: As in *1*.

What is the efficacy of GC bridging with a protocolized tapering protocol versus non-protocolized tapering?

P: Adult patients with RA.

I: newly started GC bridging that is tapered and stopped within 1 year according to a study protocol, in combination with other DMARD(s).
Dose and time defined: oral, intramuscular or intravenous, any dose.

C: GC with non-protocolized tapering in combination with other DMARDs.

O: As in *1*.

DURATION OF USE

1. What is the likelihood of long-term continuation or restarting of GCs when used as initial bridging therapy?

P: Adult patients with RA.

I: GC (prednisone, prednisolone, methylprednisolone, paramethasone, triamcinolone (hexa)acetonid, dexamethasone, deflazacort, cortivazol, betamethasone) as initial bridging therapy that is tapered and stopped within 12 months, in combination with other DMARD(s).
Dose and time defined: oral, intramuscular or intravenous.

C:
- Treatment with DMARDs without GC
- Treatment with DMARDs with other GC
- No comparator

O:
- GC status (yes/no) 3, 6, 12 and 24 months follow-up after baseline / after the induction scheme.

- Cumulative GC dose at 6, 12, and 24 months follow-up after baseline / after the induction scheme.

- Having had at least 3 months of continuous GC use within 12 and 24 months of follow-up outside of the induction scheme (yes/no).
- Number of GC episodes within 12 and 24 months outside of the induction scheme.
- Mean or median GC dose in patients still using GCs 1, 3, 6 and 12 months after the induction scheme.
- Mean GC dose in patients who stopped GCs for the first time.
- Cumulative GC dose in patients who stopped GCs for the first time.
- Mean duration of GC therapy when stopping GCs for the first time.

2. What are the effects of withdrawal of GC after use as bridging therapy?

P: As in *1*.

I: GC bridging that is tapered and stopped within 12 months, in combination with other DMARD(s).

C:
- Treatment with DMARD(s) and continued GC
- Treatment with DMARD(s) without GC

O:
- Disease activity at 12 and 24 months of follow-up (at least 3 months after stopping in the patients who stop GC).
- Having a flare (yes/no) after the first attempt to stop GC, or at a comparable timepoint in patients who do not stop GC.
- Having a DMARD change (yes/no) after a flare after stopping GC treatment, or at a comparable timepoint in patients who do not stop GC.
- DMARD dose in patients who stopped vs. patients who continued GC at 12 and 24 months of follow-up.
- Treatment escalation, specifically having to start a b/tsDMARD

3. What is the likelihood of long-term use of GCs when used as bridging therapy, compared to GC used as rescue therapy?

P: As in *1*.

I: As in *1.*

C: Initial treatment with DMARD(s) without GC, with the possibility to start GC during follow-up.

O:
- GC status (yes/no) 3, 6, 12 and 24 months follow-up after baseline / after the induction scheme.
- Cumulative GC dose at 6, 12, and 24 months follow-up after baseline / after the induction scheme.

- Having had at least 3 months of continuous GC use within 12 and 24 months of follow-up outside of the induction scheme (yes/no).
- Number of GC episodes within 12 and 24 months outside of the induction scheme.
- Mean or median GC dose in patients still using GCs 1, 3, 6 and 12 months after the induction

scheme.
- Mean GC dose in patients who stopped GCs for the first time.
- Cumulative GC dose in patients who stopped GCs for the first time.
- Mean duration of GC therapy when stopping GCs for the first time.
- Treatment escalation, specifically having to start a b/tsDMARD

4. Are the long-term continuation or restarting and the effects of withdrawal of GCs influenced by route of administration?

P: As in *1*.

I: As in *2*.

C: Initial treatment with DMARDs with a GC with another route of administration (oral, intramuscular or intravenous)

O:
- GC status (yes/no) 3, 6, 12 and 24 months follow-up after baseline / after the induction scheme.
- Cumulative GC dose at 6, 12, and 24 months follow-up after baseline / after the induction scheme.

- Having had at least 3 months of continuous GC use within 12 and 24 months of follow-up outside of the induction scheme (yes/no).
- Number of GC episodes within 12 and 24 months outside of the induction scheme.
- Mean or median GC dose in patients still using GCs 1, 3, 6 and 12 months after the induction scheme.
- Mean GC dose in patients who stopped GCs for the first time.
- Cumulative GC dose in patients who stopped GCs for the first time.
- Mean duration of GC therapy when stopping GCs for the first time.

- Disease activity at 12 and 24 months of follow-up (at least 3 months after stopping in the patients who stop GC).
- Having a flare (yes/no) after the first attempt to stop GC, or at a comparable timepoint in patients who do not stop GC.
- Having a DMARD change (yes/no) after a flare after stopping GC treatment, or at a comparable timepoint in patients who do not stop GC.
- DMARD dose in patients who stopped vs. patients who continued GC at 12 and 24 months of follow-up.

5. What is the likelihood of long-term continuation and what are the withdrawal effects of GCs in protocolized versus non-protocolized tapering and stopping of GC bridging?

P: As in *1*.

I: GC bridging that is tapered and stopped within 12 months according to a protocolized tapering scheme, in combination with other DMARD(s). Any dose, oral, intramuscular or intravenous.

C: GC bridging tapered without a protocolized tapering scheme, in combination with other DMARD(s). Any dose, oral, intramuscular or intravenous.

O:

- GC status (yes/no) 3, 6, 12 and 24 months follow-up after baseline / after the induction scheme.
- Cumulative GC dose at 6, 12, and 24 months follow-up after baseline / after the induction scheme.

- Having had at least 3 months of continuous GC use within 12 and 24 months of follow-up outside of the induction scheme (yes/no).
- Number of GC episodes within 12 and 24 months outside of the induction scheme.
- Mean or median GC dose in patients still using GCs 1, 3, 6 and 12 months after the induction scheme.
- Mean GC dose in patients who stopped GCs for the first time.
- Cumulative GC dose in patients who stopped GCs for the first time.
- Mean duration of GC therapy when stopping GCs for the first time.

- Disease activity at 12 and 24 months of follow-up at least 3 months after stopping GC.
- Having a flare (yes/no) after the first attempt to stop GC
- Having a DMARD change (yes/no) after a flare after stopping GC treatment
- DMARD dose in patients who stopped vs. patients who continued GC at 12 and 24 months of follow-up.

SAFETY

1. What is the safety of therapy with glucocorticoids (GC) in RA?

P: Adult patients with RA.

I: Newly started GC (prednisone, prednisolone, methylprednisolone, paramethasone, triamcinolone (hexa)acetonid, dexamethasone, deflazacort, cortivazol, betamethasone) – in combination with other DMARD(s).
Dose and time defined: oral, intramuscular or intravenous, any dose and duration.

C:

- Another GC, in combination with other DMARD(s)
- DMARD(s) not in combination with GC
- None (if population-based incidence rates are reported)

O:

- Incidence of SAEs
- Deaths
- Withdrawals due to AEs
- Incidence of AEs
- Serious infections
- Tuberculosis
- Opportunistic infections
- Herpes zoster
- Malignancies (lymphoma, skin-cancer non-melanoma, solid tumours, other haematological malignancies, unspecified)

- Congestive heart failure
- Cardio-vascular disease (besides CHF): coronary heart disease including angina, MI, stroke, atrial fibrillation, venous thromboembolism, pulmonary embolism.
- Infusion/injection-site reactions
- Lipid levels
- Renal function (creatinine levels)
- Hepatic effects (elevation of transaminases and bilirubin)
- Haematological abnormalities (neutropenia)
- Gastro-intestinal effects
- Demyelinating disease
- Induction of auto-immune disease (including anti-nuclear antibodies, antibodies anti-dsDNA, anti-drug antibodies, anti-chimeric antibodies)
- Teratogenicity
- Fertility
- Adverse pregnancy outcomes
- Hyperglycemia / GC induced DM
- Osteoporosis
- Osteoporotic fractures
- Depression / depressive feelings / mood disturbances
- Avascular necrosis
- Cataract
- Glaucoma
- Cushing syndrome
- Malaise / unspecified wellbeing
- Fever
- Hypertension
- Non-infectious skin AEs
- Hair loss
- Headache
- Dizziness
- Anemia / leucopenia / thrombocytopenia
- Non-infectious pulmonary AEs, including dyspnea
- COVID19[1]

[1]Papers with as outcome COVID19 were included after November 2021, the search date of a recent EULAR SLR: Kroon FPB, et al. Ann Rheum Dis. 2022 Mar;81(3):422-432

2. What is the safety of GC that are tapered and stopped versus continued GC?

P: As in *1*.

I: Newly started GC that are tapered and stopped in combination with other DMARDs.
Dose and time defined: oral, intramuscular or intravenous, any dose and duration.

C: newly started GC that are continued, in combination with other DMARDs.
Dose and time defined: oral, intramuscular or intravenous, any dose and duration.

O: As in *1*.

3. Does safety differ by route of administration?

P: As in *1*.

I: As in *1*.

C: Newly started GC, in combination with other DMARDs.
Dose and time defined: any dose and duration, different mode of administration than the intervention (oral, intramuscular or intravenous).

O: As in *1*.

4. What is the safety of chronic low-dose GC?

P: As in *1*.

I: chronic low-dose GC (≥6 months, ≤7.5 mg) in combination with other DMARDs. Oral, intramuscular or intravenous.

C:
- DMARD treatment without GC.
- DMARD treatment with GC bridging that is tapered and stopped.

O: As in *1*.

5. What is the safety of GC combined with bDMARDs compared to bDMARDs without GC?

P: As in *1*.

I: Newly started GC in combination with a bDMARD
Dose and time defined: oral, intramuscular or intravenous, any dose and duration.

C: bDMARD treatment without GC (with or without csDMARDs).

O: As in *1*.

SUPPLEMENTARY FILE 2: full search strategies

Total January 14, 2022: 2981 references, sourced from:

- MEDLINE (PubMed): 2289
- Embase: 1570 - 212 unique
- Web of Science: 1526 - 162 unique
- Cochrane Library: 665 - 318 unique

MEDLINE (PubMed)
https://pubmed.ncbi.nlm.nih.gov/

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Embase

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=main&MODE=ovid&D=oemezd

((*"Rheumatoid Arthritis"/ OR "rheumatoid arthritis".ti,ab OR "early rheumatoid arthritis".ti,ab OR "early rheum*".ti,ab OR "early arthritis".ti,ab OR "early arthri*".ti,ab OR "early RA".ti,ab OR "recent onset rheum*".ti,ab OR "recent onset arthri*".ti,ab OR "recent onset RA".ti,ab) NOT ((exp "Infant"/ OR "infant".ti OR "infants".ti OR "Child"/ OR "child".ti OR "children".ti OR "pediatric".ti OR "paediatric".ti OR exp "Adolescent"/) NOT (exp "Adult"/ OR "adult".ti OR "adults".ti)) AND (*"alclometasone dipropionate"/ OR "alclometasone dipropionate".ti,ab OR *"amcinonide"/ OR "amcinonide".ti,ab OR *"Beclomethasone"/ OR "Beclomethasone".ti,ab OR "betamethason*".ti,ab OR *"Betamethasone"/ OR "betamethasone".ti,ab OR *"Budesonide"/ OR "Budesonide".ti,ab OR *"ciclesonide"/ OR "ciclesonide".ti,ab OR *"Clobetasol"/ OR "Clobetasol".ti,ab OR *"clobetasone butyrate"/ OR "clobetasone butyrate".ti,ab OR *"clocortolone pivalate"/ OR "clocortolone pivalate".ti,ab OR *"clocortolone"/ OR "clocortolone".ti,ab OR *"cortivazol"/ OR "cortivazol".ti,ab OR "cortivazol*".ti,ab OR *"deflazacort"/ OR "deflazacort".ti,ab OR "deflazacort*".ti,ab OR *"Desoximetasone"/ OR "Desoximetasone".ti,ab OR "dexamethason*".ti,ab OR *"Dexamethasone"/

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((TI=("Rheumatoid Arthritis" OR "rheumatoid arthritis" OR "early rheumatoid arthritis" OR "early rheum*" OR "early arthritis" OR "early arthri*" OR "early RA" OR "recent onset rheum*" OR "recent onset arthri*" OR "recent onset RA") OR AK=("Rheumatoid Arthritis" OR "rheumatoid arthritis" OR "early rheumatoid arthritis" OR "early rheum*" OR "early arthritis" OR "early arthri*" OR "early RA" OR "recent onset rheum*" OR "recent onset arthri*" OR "recent onset RA") OR AB=("Rheumatoid Arthritis" OR "rheumatoid arthritis" OR "early rheumatoid arthritis" OR "early rheum*" OR "early arthritis" OR "early arthri*" OR "early RA" OR "recent onset rheum*" OR "recent onset arthri*" OR "recent onset RA")) NOT TI=(("Infant" OR "infant" OR "infants" OR "Child" OR "child" OR "children" OR "pediatric" OR "paediatric" OR "Adolescent") NOT ("Adult" OR "adult" OR "adults")) AND (TI=("alclometasone dipropionate" OR "alclometasone dipropionate" OR "amcinonide" OR "amcinonide" OR "Beclomethasone" OR "Beclomethasone" OR "betamethason*" OR "Betamethasone" OR "betamethasone" OR "Budesonide" OR "Budesonide" OR "ciclesonide" OR "ciclesonide" OR "Clobetasol" OR "Clobetasol" OR "clobetasone butyrate" OR "clobetasone butyrate" OR "clocortolone pivalate" OR "clocortolone pivalate" OR "clocortolone" OR "clocortolone" OR "cortivazol" OR "cortivazol" OR "cortivazol*" OR "deflazacort" OR "deflazacort" OR "deflazacort*" OR "Desoximetasone" OR "Desoximetasone" OR "dexamethason*" OR "Dexamethasone" OR "dexamethasone" OR "dichlorisone acetate" OR "dichlorisone acetate" OR "diflorasone" OR "diflorasone" OR "Diflucortolone" OR "Diflucortolone" OR "difluprednate" OR "difluprednate" OR "drocinonide phosphate potassium" OR "drocinonide phosphate potassium" OR "flumethasone pivalate" OR "flumethasone pivalate" OR "Flumethasone" OR "Flumethasone" OR "Fluocinolone Acetonide" OR "Fluocinolone Acetonide" OR "Fluocinonide" OR "Fluocinonide" OR "fluocortin butyl ester" OR "fluocortin butyl ester" OR "Fluocortolone" OR "Fluocortolone" OR "Fluorometholone" OR "Fluorometholone" OR "fluperolone acetate" OR "fluperolone acetate" OR "fluprednidene acetate" OR "fluprednidene acetate" OR "Fluprednisolone" OR "Fluprednisolone" OR "Flurandrenolone" OR "Flurandrenolone" OR "Fluticasone-Salmeterol Drug Combination" OR "Fluticasone-Salmeterol Drug Combination" OR "FX006" OR "FX006" OR "Glucocorticoid" OR "glucocorticoid*" OR "Glucocorticoid" OR "Glucocorticoids" OR "halometasone" OR "halometasone" OR "medrysone" OR "medrysone" OR "Melengestrol Acetate" OR "Melengestrol Acetate" OR "methylprednisolon*" OR "Methylprednisolone" OR "methylprednisolone" OR "paramethason*" OR "Paramethasone" OR "paramethasone" OR "prednicarbate" OR "prednicarbate" OR "prednisolon*" OR "Prednisolone" OR "prednisolone" OR "prednison*" OR "Prednisone" OR "prednisone" OR "rimexolone" OR "rimexolone" OR "terofenamate" OR "terofenamate" OR "Tobramycin, Dexamethasone Drug Combination" OR "Tobramycin, Dexamethasone Drug Combination" OR "triamcinolon*" OR "Triamcinolone Acetonide" OR "triamcinolone acetonide" OR "triamcinolone benetonide" OR "Triamcinolone" OR "triamcinolone") OR AK=("alclometasone dipropionate" OR "alclometasone dipropionate" OR "amcinonide" OR "amcinonide" OR "Beclomethasone" OR "Beclomethasone" OR "betamethason*" OR "Betamethasone" OR "betamethasone" OR "Budesonide" OR "Budesonide" OR "ciclesonide" OR "ciclesonide" OR "Clobetasol" OR "Clobetasol" OR "clobetasone butyrate" OR "clobetasone butyrate" OR "clocortolone pivalate" OR "clocortolone pivalate" OR "clocortolone" OR "clocortolone" OR "cortivazol" OR "cortivazol" OR "cortivazol*" OR "deflazacort" OR "deflazacort" OR "deflazacort*" OR "Desoximetasone" OR "Desoximetasone" OR "dexamethason*" OR "Dexamethasone" OR "dexamethasone" OR "dichlorisone acetate" OR "dichlorisone acetate" OR "diflorasone" OR "diflorasone" OR "Diflucortolone" OR "Diflucortolone" OR "difluprednate" OR "difluprednate" OR "drocinonide phosphate potassium" OR "drocinonide phosphate potassium" OR "flumethasone pivalate" OR "flumethasone pivalate" OR "Flumethasone"

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OR "FollowUp" OR "Longitudinal*" OR "Prospective*" OR "Retrospective*" OR "Register" OR "Registry" OR "Registries" OR "Register" OR "Registers" **OR** "phase 3 Clinical Trial" OR "phase 4 Clinical Trial" OR "phase 3" OR "phase 4" OR "phase III" OR "phase IV" OR "phase three" OR "phase four" OR "trial" OR "trials" OR "RCT" OR "randomized controlled trial" OR "controlled clinical trial" OR randomized OR placebo OR randomly OR trial OR groups OR "randomization" OR "double blind procedure" OR "single blind procedure" OR "clinical trial" OR ((singl* OR doubl* OR trebl* OR tripl*) NEAR/4 (mask* OR blind*)) OR "latin square" OR "placebo" OR placebo* OR random* OR "comparative study" OR "evaluation study" OR "crossover procedure" OR control OR controll*) AND PY=(2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020 OR 2021 OR 2022 OR 2023) NOT DT=(meeting abstract))

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(("Rheumatoid Arthritis" OR "rheumatoid arthritis" OR "early rheumatoid arthritis" OR "early rheum*" OR "early arthritis" OR "early arthri*" OR "early RA" OR "recent onset rheum*" OR "recent onset arthri*" OR "recent onset RA"):ti,ab,kw NOT (("Infant" OR "infant" OR "infants" OR "Child" OR "child" OR "children" OR "pediatric" OR "paediatric" OR "Adolescent") NOT ("Adult" OR "adult" OR "adults")):ti AND ("alclometasone dipropionate" OR "alclometasone dipropionate" OR "amcinonide" OR "amcinonide" OR "Beclomethasone" OR "Beclomethasone" OR "betamethason*" OR "Betamethasone" OR "betamethasone" OR "Budesonide" OR "Budesonide" OR "ciclesonide" OR "ciclesonide" OR "Clobetasol" OR "Clobetasol" OR "clobetasone butyrate" OR "clobetasone butyrate" OR "clocortolone pivalate" OR "clocortolone pivalate" OR "clocortolone" OR "clocortolone" OR "cortivazol" OR "cortivazol" OR "cortivazol*" OR "deflazacort" OR "deflazacort" OR "deflazacort*" OR "Desoximetasone" OR "Desoximetasone" OR "dexamethason*" OR "Dexamethasone" OR "dexamethasone" OR "dichlorisone acetate" OR "dichlorisone acetate" OR "diflorasone" OR "diflorasone" OR "Diflucortolone" OR "Diflucortolone" OR "difluprednate" OR "difluprednate" OR "drocinonide phosphate potassium" OR "drocinonide phosphate potassium" OR "flumethasone pivalate" OR "flumethasone pivalate" OR "Flumethasone" OR "Flumethasone" OR "Fluocinolone Acetonide" OR "Fluocinolone Acetonide" OR "Fluocinonide" OR "Fluocinonide" OR "fluocortin butyl ester" OR "fluocortin butyl ester" OR "Fluocortolone" OR "Fluocortolone" OR "Fluorometholone" OR "Fluorometholone" OR "fluperolone acetate" OR "fluperolone acetate" OR "fluprednidene acetate" OR "fluprednidene acetate" OR "Fluprednisolone" OR "Fluprednisolone" OR "Flurandrenolone" OR "Flurandrenolone" OR "Fluticasone Salmeterol Drug Combination" OR "Fluticasone Salmeterol Drug Combination" OR "FX006" OR "FX006" OR "Glucocorticoid" OR "glucocorticoid*" OR "Glucocorticoid" OR "Glucocorticoids" OR "halometasone" OR "halometasone" OR "medrysone" OR "medrysone" OR "Melengestrol Acetate" OR "Melengestrol Acetate" OR "methylprednisolon*" OR "Methylprednisolone" OR "methylprednisolone" OR "paramethason*" OR "Paramethasone" OR "paramethasone" OR "prednicarbate" OR "prednicarbate" OR "prednisolon*" OR "Prednisolone" OR "prednisolone" OR "prednison*" OR "Prednisone" OR "prednisone" OR "rimexolone" OR "rimexolone" OR "terofenamate" OR "terofenamate" OR "Tobramycin, Dexamethasone Drug Combination" OR "Tobramycin, Dexamethasone Drug Combination" OR "triamcinolon*" OR "Triamcinolone Acetonide" OR "triamcinolone acetonide" OR "triamcinolone benetonide" OR "Triamcinolone" OR "triamcinolone"):ti,ab,kw)

AND PY=(2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018 OR 2019 OR 2020 OR 2021 OR 2022 OR 2023) NOT DT=(meeting abstract)

MEETING ABSTRACTS

Total February 10, 2022: 303 references, sourced from:

- Embase: 299 - 297 unique
- Web of Science: 11 - 2 unique,
- Cochrane Library: 39 - 4 unique

The ACR 2021 abstract archive was searched manually.

Databases

Embase
http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=main&MODE=ovid&D=oemezd

(*"Rheumatoid Arthritis"/ OR "rheumatoid arthritis".ti,ab OR "early rheumatoid arthritis".ti,ab OR "early rheum*".ti,ab OR "early arthritis".ti,ab OR "early arthri*".ti,ab OR "early RA".ti,ab OR "recent onset rheum*".ti,ab OR "recent onset arthri*".ti,ab OR "recent onset RA".ti,ab) NOT ((exp "Infant"/ OR "infant".ti OR "infants".ti OR "Child"/ OR "child".ti OR "children".ti OR "pediatric".ti OR "paediatric".ti OR exp "Adolescent"/) NOT (exp "Adult"/ OR "adult".ti OR "adults".ti)) AND (*"alclometasone dipropionate"/ OR "alclometasone dipropionate".ti,ab OR *"amcinonide"/ OR "amcinonide".ti,ab OR *"Beclomethasone"/ OR "Beclomethasone".ti,ab OR "betamethason*".ti,ab OR *"Betamethasone"/ OR "betamethasone".ti,ab OR *"Budesonide"/ OR "Budesonide".ti,ab OR *"ciclesonide"/ OR "ciclesonide".ti,ab OR *"Clobetasol"/ OR "Clobetasol".ti,ab OR *"clobetasone butyrate"/ OR "clobetasone butyrate".ti,ab OR *"clocortolone pivalate"/ OR "clocortolone pivalate".ti,ab OR *"clocortolone"/ OR "clocortolone".ti,ab OR *"cortivazol"/ OR "cortivazol".ti,ab OR "cortivazol*".ti,ab OR *"deflazacort"/ OR "deflazacort".ti,ab OR "deflazacort*".ti,ab OR *"Desoximetasone"/ OR "Desoximetasone".ti,ab OR "dexamethason*".ti,ab OR *"Dexamethasone"/ OR "dexamethasone".ti,ab OR *"dichlorisone acetate"/ OR "dichlorisone acetate".ti,ab OR *"diflorasone"/ OR "diflorasone".ti,ab OR *"Diflucortolone"/ OR "Diflucortolone".ti,ab OR *"difluprednate"/ OR "difluprednate".ti,ab OR *"drocinonide phosphate potassium"/ OR "drocinonide phosphate potassium".ti,ab OR *"flumethasone pivalate"/ OR "flumethasone pivalate".ti,ab OR *"Flumethasone"/ OR "Flumethasone".ti,ab OR *"Fluocinolone Acetonide"/ OR "Fluocinolone Acetonide".ti,ab OR *"Fluocinonide"/ OR "Fluocinonide".ti,ab OR *"fluocortin butyl ester"/ OR "fluocortin butyl ester".ti,ab OR *"Fluocortolone"/ OR "Fluocortolone".ti,ab OR *"Fluorometholone"/ OR "Fluorometholone".ti,ab OR *"fluperolone acetate"/ OR "fluperolone acetate".ti,ab OR *"fluprednidene acetate"/ OR "fluprednidene acetate".ti,ab OR *"Fluprednisolone"/ OR "Fluprednisolone".ti,ab OR *"Flurandrenolone"/ OR "Flurandrenolone".ti,ab OR *"Fluticasone-Salmeterol Drug Combination"/ OR "Fluticasone-Salmeterol Drug Combination".ti,ab OR *"FX006"/ OR "FX006".ti,ab OR "Glucocorticoid".ti,ab OR "glucocorticoid*".ti,ab OR exp *"Glucocorticoid"/ OR "Glucocorticoids".ti,ab OR *"halometasone"/ OR "halometasone".ti,ab OR *"medrysone"/ OR "medrysone".ti,ab OR *"Melengestrol Acetate"/ OR

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((TI=("Rheumatoid Arthritis" OR "rheumatoid arthritis" OR "early rheumatoid arthritis" OR "early rheum*" OR "early arthritis" OR "early arthri*" OR "early RA" OR "recent onset rheum*" OR "recent onset arthri*" OR "recent onset RA") OR AK=("Rheumatoid Arthritis" OR "rheumatoid arthritis" OR "early rheumatoid arthritis" OR "early rheum*" OR "early arthritis" OR "early arthri*" OR "early RA" OR "recent onset rheum*" OR "recent onset arthri*" OR "recent onset RA") OR AB=("Rheumatoid Arthritis" OR "rheumatoid arthritis" OR "early rheumatoid arthritis" OR "early rheum*" OR "early arthritis" OR "early arthri*" OR "early RA" OR "recent onset rheum*" OR "recent onset arthri*" OR "recent onset RA")) NOT TI=(("Infant" OR "infant" OR "infants" OR "Child" OR "child" OR "children" OR "pediatric" OR "paediatric" OR "Adolescent") NOT ("Adult" OR "adult" OR "adults")) AND (TI=("alclometasone dipropionate" OR "alclometasone dipropionate" OR "amcinonide" OR "amcinonide" OR "Beclomethasone" OR "Beclomethasone" OR "betamethason*" OR "Betamethasone" OR "betamethasone" OR "Budesonide" OR "Budesonide" OR "ciclesonide" OR "ciclesonide" OR "Clobetasol" OR "Clobetasol" OR "clobetasone butyrate" OR "clobetasone butyrate" OR "clocortolone pivalate" OR "clocortolone pivalate" OR "clocortolone" OR

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"triamcinolone acetonide" OR "triamcinolone benetonide" OR "Triamcinolone" OR "triamcinolone") OR AB=("alclometasone dipropionate" OR "alclometasone dipropionate" OR "amcinonide" OR "amcinonide" OR "Beclomethasone" OR "Beclomethasone" OR "betamethason*" OR "Betamethasone" OR "betamethasone" OR "Budesonide" OR "Budesonide" OR "ciclesonide" OR "ciclesonide" OR "Clobetasol" OR "Clobetasol" OR "clobetasone butyrate" OR "clobetasone butyrate" OR "clocortolone pivalate" OR "clocortolone pivalate" OR "clocortolone" OR "clocortolone" OR "cortivazol" OR "cortivazol" OR "cortivazol*" OR "deflazacort" OR "deflazacort" OR "deflazacort*" OR "Desoximetasone" OR "Desoximetasone" OR "dexamethason*" OR "Dexamethasone" OR "dexamethasone" OR "dichlorisone acetate" OR "dichlorisone acetate" OR "diflorasone" OR "diflorasone" OR "Diflucortolone" OR "Diflucortolone" OR "difluprednate" OR "difluprednate" OR "drocinonide phosphate potassium" OR "drocinonide phosphate potassium" OR "flumethasone pivalate" OR "flumethasone pivalate" OR "Flumethasone" OR "Flumethasone" OR "Fluocinolone Acetonide" OR "Fluocinolone Acetonide" OR "Fluocinonide" OR "Fluocinonide" OR "fluocortin butyl ester" OR "fluocortin butyl ester" OR "Fluocortolone" OR "Fluocortolone" OR "Fluorometholone" OR "Fluorometholone" OR "fluperolone acetate" OR "fluperolone acetate" OR "fluprednidene acetate" OR "fluprednidene acetate" OR "Fluprednisolone" OR "Fluprednisolone" OR "Flurandrenolone" OR "Flurandrenolone" OR "Fluticasone-Salmeterol Drug Combination" OR "Fluticasone-Salmeterol Drug Combination" OR "FX006" OR "FX006" OR "Glucocorticoid" OR "glucocorticoid*" OR "Glucocorticoid" OR "Glucocorticoids" OR "halometasone" OR "halometasone" OR "medrysone" OR "medrysone" OR "Melengestrol Acetate" OR "Melengestrol Acetate" OR "methylprednisolon*" OR "Methylprednisolone" OR "methylprednisolone" OR "paramethason*" OR "Paramethasone" OR "paramethasone" OR "prednicarbate" OR "prednicarbate" OR "prednisolon*" OR "Prednisolone" OR "prednisolone" OR "prednison*" OR "Prednisone" OR "prednisone" OR "rimexolone" OR "rimexolone" OR "terofenamate" OR "terofenamate" OR "Tobramycin, Dexamethasone Drug Combination" OR "Tobramycin, Dexamethasone Drug Combination" OR "triamcinolon*" OR "Triamcinolone Acetonide" OR "triamcinolone acetonide" OR "triamcinolone benetonide" OR "Triamcinolone" OR "triamcinolone")) AND TS=("Cohort analysis" OR "Cohort Study" OR "Cohort" OR "Cohorts" OR "Follow up" OR "Follow-Up Studies" OR "Longitudinal Study" OR "Prospective Study" OR "Retrospective Study" OR "Longitudinal Studies" OR "Prospective Studies" OR "Retrospective Studies" OR "Follow-Up Study" OR "Longitudinal Study" OR "Prospective Study" OR "Retrospective Study" OR "Follow-Up" OR "Longitudinal" OR "Prospective" OR "Retrospective" OR "FollowUp" OR "Longitudinal*" OR "Prospective*" OR "Retrospective*" OR "Register" OR "Registry" OR "Registries" OR "Register" OR "Registers" **OR** "phase 3 Clinical Trial" OR "phase 4 Clinical Trial" OR "phase 3" OR "phase 4" OR "phase III" OR "phase IV" OR "phase three" OR "phase four" OR "trial" OR "trials" OR "RCT" OR "randomized controlled trial" OR "controlled clinical trial" OR randomized OR placebo OR randomly OR trial OR groups OR "randomization" OR "double blind procedure" OR "single blind procedure" OR "clinical trial" OR ((singl* OR doubl* OR trebl* OR tripl*) NEAR/4 (mask* OR blind*)) OR "latin square" OR "placebo" OR placebo* OR random* OR "comparative study" OR "evaluation study" OR "crossover procedure" OR control OR controll*) AND PY=(2020 OR 2021 OR 2022 OR 2023) AND DT=(meeting abstract) AND SO=(ANNALS OF THE RHEUMATIC DISEASES OR ARTHRITIS RHEUMATOLOGY))

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(("Rheumatoid Arthritis" OR "rheumatoid arthritis" OR "early rheumatoid arthritis" OR "early rheum*" OR "early arthritis" OR "early arthri*" OR "early RA" OR "recent onset rheum*" OR "recent onset arthri*" OR "recent onset RA"):ti,ab,kw NOT (("Infant" OR "infant" OR "infants" OR "Child" OR "child" OR "children" OR "pediatric" OR "paediatric" OR "Adolescent") NOT ("Adult" OR "adult" OR "adults")):ti AND ("alclometasone dipropionate" OR "alclometasone dipropionate" OR "amcinonide" OR "amcinonide" OR "Beclomethasone" OR "Beclomethasone" OR "betamethason*" OR "Betamethasone" OR "betamethasone" OR "Budesonide" OR "Budesonide" OR "ciclesonide" OR "ciclesonide" OR "Clobetasol" OR "Clobetasol" OR "clobetasone butyrate" OR "clobetasone butyrate" OR "clocortolone pivalate" OR "clocortolone pivalate" OR "clocortolone" OR "clocortolone" OR "cortivazol" OR "cortivazol" OR "cortivazol*" OR "deflazacort" OR "deflazacort" OR "deflazacort*" OR "Desoximetasone" OR "Desoximetasone" OR "dexamethason*" OR "Dexamethasone" OR "dexamethasone" OR "dichlorisone acetate" OR "dichlorisone acetate" OR "diflorasone" OR "diflorasone" OR "Diflucortolone" OR "Diflucortolone" OR "difluprednate" OR "difluprednate" OR "drocinonide phosphate potassium" OR "drocinonide phosphate potassium" OR "flumethasone pivalate" OR "flumethasone pivalate" OR "Flumethasone" OR "Flumethasone" OR "Fluocinolone Acetonide" OR "Fluocinolone Acetonide" OR "Fluocinonide" OR "Fluocinonide" OR "fluocortin butyl ester" OR "fluocortin butyl ester" OR "Fluocortolone" OR "Fluocortolone" OR "Fluorometholone" OR "Fluorometholone" OR "fluperolone acetate" OR "fluperolone acetate" OR "fluprednidene acetate" OR "fluprednidene acetate" OR "Fluprednisolone" OR "Fluprednisolone" OR "Flurandrenolone" OR "Flurandrenolone" OR "Fluticasone Salmeterol Drug Combination" OR "Fluticasone Salmeterol Drug Combination" OR "FX006" OR "FX006" OR "Glucocorticoid" OR "glucocorticoid*" OR "Glucocorticoid" OR "Glucocorticoids" OR "halometasone" OR "halometasone" OR "medrysone" OR "medrysone" OR "Melengestrol Acetate" OR "Melengestrol Acetate" OR "methylprednisolon*" OR "Methylprednisolone" OR "methylprednisolone" OR "paramethason*" OR "Paramethasone" OR "paramethasone" OR "prednicarbate" OR "prednicarbate" OR "prednisolon*" OR "Prednisolone" OR "prednisolone" OR "prednison*" OR "Prednisone" OR "prednisone" OR "rimexolone" OR "rimexolone" OR "terofenamate" OR "terofenamate" OR "Tobramycin, Dexamethasone Drug Combination" OR "Tobramycin, Dexamethasone Drug Combination" OR "triamcinolon*" OR "Triamcinolone Acetonide" OR "triamcinolone acetonide" OR "triamcinolone benetonide" OR "Triamcinolone" OR "triamcinolone"):ti,ab,kw)

Hand-limited to meeting abstracts.

SUPPLEMENTARY FILE 3: flow-charts for the duration of use and safety article selections

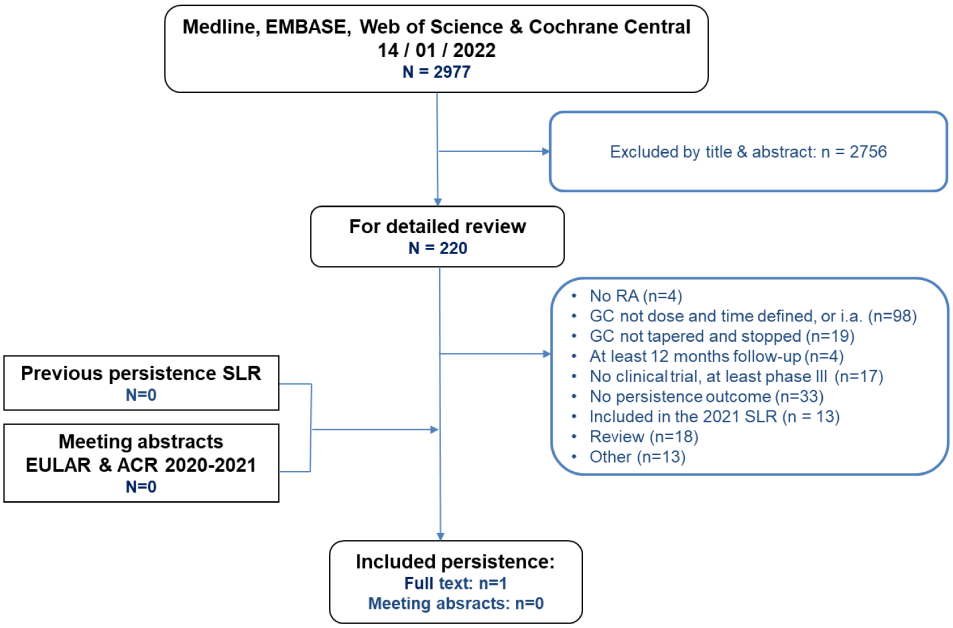

Figure 3.1 Flow-chart for the article selection of papers on GC duration of use.
One combined search was performed for duration of use and safety. Ten percent of titles and abstracts were screened by two readers, resulting in 95% agreement.

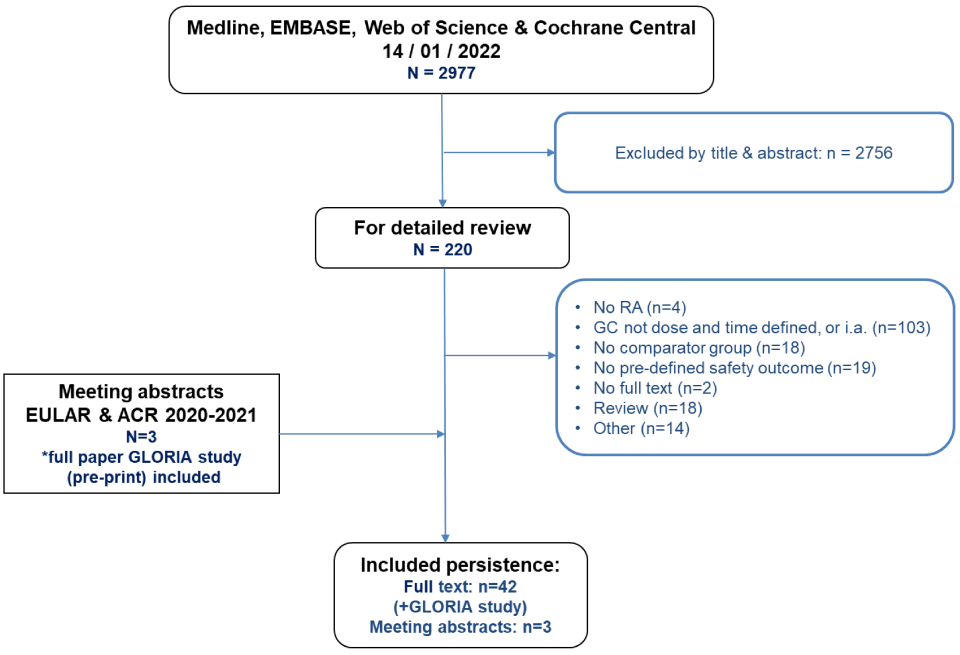

Figure 3.2 Flow-chart for the article selection of papers on GC safety.
One combined search was performed for duration of use and safety. Ten percent of titles and abstracts were screened by two readers, resulting in 95% agreement.

SUPPLEMENETARY FILE 4: Risk of bias assessments

Table 4.1 Risk of bias assessment of RCTs, according to the Cochrane Collaboration's tool

Study ID	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Overall
Efficacy							
Boers 2022 Ann Rheum Dis	Low	Low	Low	Low	Low	High	High
Hua 2020 Medicine	Low	Low	Low	High	Low	low	High
Stouten 2019 Rheumatology[α]	Low	High	Low	Low	Low	Low	High
Duration of use[θ]							
Burmester 2020 Lancet	Low	Low	Low	Low	Low	Low	Low
Safety							
Bakker 2012 Ann Int Med	Low	Low	Low	Low	Low	Low	Low
Boers 2022 Ann Rheum Dis	Low	Low	Low	Low	Low	High	High
Burmester 2020 Lancet	Low	Low	Low	Low	Low	Low	Low
Buttgereit 2013 Ann Rheum Dis	Unclear	Low	Low	Low	Low	Low	Low
De Jong 2013 Ann Rheum Dis	Low	High	High	Low	Low	Low	High
Den Uyl 2014 Ann Rheum Dis[γ]	Low	High	High	Low	Low	Low	High
Ding 2012 Curr Ther Res Clin Exp	Unclear	Low	Low	Unclear	Low	Low	Unclear
Hua 2020 Medicine	Low	Low	Low	High	Low	low	High
Nam 2014 Ann Rheum Dis	Low	Low	Low	Low	Low	Low	Low
Sadra 2014 Int J Rheum Dis	Unclear	Low	Low	Low	Low	Low	Low
Verschueren 2015 Ann Rheum Dis[α]	Low	High	Low	Low	Low	Low	High

[α]Multiple publications regarding the CareRA study and its long-term extension were included, which all received the same RoB assessment: Verschueren 2015 Ann Rheum Dis, Verschueren 2015 Arthritis Res Ther, Verschueren 2017 Ann Rheum Dis, Stouten 2021 Ann Rheum Dis, Stouten 2019 Rheumatology.

[γ]Multiple publications regarding the COBRA light study and its long-term extension were included, which all received the same RoB assessment: den Uyl 2014 Ann Rheum Dis, Konijn 2017 Rheumatol, Lucassen 2021 Osteoporosis Int.

[θ]RoB assessments for the other included articles on duration of use are reported in the original SLR on this topic.(Ouwerkerk et al. Ann Rheum Dis 2022, doi: 10.1136/annrheumdis-2022-222338).

Table 4.2: Risk of bias assessments of studies included in the previously published duration of use meta-analysis, reproduced with permission from Van Ouwerkerk et al. (2022).

	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall score
COBRA	Low	Low	High	Low	Low	High
BeSt	Low	Some concerns	Low	High	Some concerns	High
IDEA	Low	Low	Low	Low	Low	Low
COBRA-light	Low	High	Low	High	Low	High
IMPROVED	Low	Some concerns	Low	High	Some concerns	High
ARCTIC	Low	Low	Some concerns	High	Low	High
tREACH	Some concerns	Low	Low	High	Low	High
CareRA	Low	Some concerns	Low	High	Low	High
Hua et al.	Low	Low	High	Low	Low	High
NORD-STAR	Low	Low	Low	High	Low	High

This Risk of Bias (RoB) tool 2 uses 5 domains to assess bias: bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias due to selection of the reported results. Each domain can be scored as 'low risk', 'some concerns' or 'high risk', according to an algorithm incorporating all subparts of a domain. The overall score results in "low" if there is a low RoB for all domains. The overall score results in "some concerns" if there is at least one domain with some concerns. The overall score results in "high" if there is at least one domain with high risk or if there are several domains with some concerns in a way that it substantially lowers confidence in the results.

Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.

van Ouwerkerk L, Palmowski A, Nevins IS, Buttgereit F, Verschueren P, Smolen JS, et al. Systematic literature review of observational cohorts and clinical trials into the success rate of glucocorticoid discontinuation after their use as bridging therapy in patients with rheumatoid arthritis. Ann Rheum Dis. 2022;81(7):937-43.

Table 4.3 Risk of bias assessment of observational studies, according to the Hayden tool

Study ID	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall
Safety							
Abtahi 2022 Rheumatol	Low	Low	Low	Low	Unclear	Low	Unclear
Avina-Zubita 2011 Ann Rheum Dis	Low	Unclear	Low	Low	Unclear	Low	High
Avina-Zubieta 2013 Rheumatol	Low	Unclear	Unclear	Low	Unclear	Low	High
Balasubramanian 2016 Osteoporosis Inc	Low	High	Unclear	High	High	High	High
Costello 2021 Rheumatol	Low	Low	Low	Low	Unclear	Low	Unclear
Del Rincón 2014 Arthritis Rheumatol	High	Low	Low	Low	High	Low	High
Dixon 2012 Ann Rheum Dis	Low	High	Low	Low	High	Low	High
George 2020 Ann Int Med	Low	High	Unclear	Low	Unclear	Low	High
Mebrahtu 2020 CMAJ	Low	Low	Low	Low	Unclear	Low	Unclear

Movahedi 2016 Arthritis Rheumatol	Low	Low	Unclear	Low	Unclear	Low	Unclear
Ocon 2021 Ann Rheum Dis	Unclear	Low	Unclear	Low	Unclear	Low	Unclear
Ozen 2019 Ann Rheum Dis	Low	Low	High	Unclear	Unclear	Low	High
Ozen 2021 J Rheumatol	Low	Low	Low	Low	Unclear	Low	Unclear
Palmsten 2020 Rheumatol	Low	Low	Unclear	Ow	Unclear	Low	Unclear
Pujades-Rodriguez 2020 PloS Med	Low	Low	Low	Low	Unclear	Low	Unclear
Roubille 2020 Rheumatology	Low	Unclear	Low	Low	Unclear	Low	Unclear
Suda 2018 Clin Rheumatol	Unclear	High	Unclear	Low	High	Unclear	High
Van Sijl 2014 Plos One	Low	Low	Low	Low	Unclear	Low	Unclear
Wilson 2019 Arthritis Care Res	Low	High	Unclear	Low	Unclear	Low	High
Wu 2020 BMJ Open Diabetes Res Care	Low	Unclear	Low	Low	Unclear	Low	Unclear

Due to a risk of residual confounding, all observational studies were at least assessed as having an unclear risk of bias.

SUPPLEMENTARY FILE 5: Efficacy and duration of use, baseline characteristics and outcomes

Table 5.1 Baseline characteristics of included efficacy and duration of use studies

Study ID	Study acronym	Treatment	N pts	Age	Disease duration (weeks)	ACPA (% pos)	DAS28	HAQ	SvdH-score
Stouten 2019 Rheumatology	CareRA	- HR: MTX + SSZ + PRED 60 mg in 7 weeks to 7.5 mg,	98	53 (12)	22 (14; 44)[α]	78	5.0 (1.2)	1.2 (0.7)	
		- HR: MTX + PRED 30 mg in 6 weeks to 5 mg	98	52 (13)	24 (15; 39)	80	4.8 (1.1)	1.0 (0.7)	
		- HR: MTX + LEF + PRED 30 mg in 6 weeks to 5 mg all PRED tapered from week 28 to stop at week 34	93	51 (13)	25 (15; 51)	77	4.7 (1.2)	1.0 (0.6)	
		- LR: MTX + PRED 30 mg in 6 weeks to 5 mg PRED tapered from week 28 to stop at week 34	43	51 (14)	21 (14; 35)	28	4.5 (1.6)	0.9 (0.9)	
		- LR: MTX tight step up	47	51 (14)	19 (13; 33)	23	4.6 (1.6)	1.0 (0.7)	
Hua 2020 Medicine		- MTX + HCQ + PRED 10 mg, tapered to 5 mg/day from 4 months, stopped at 6 months	40	46 (13)	20.5 (13.5)		5.2 (1.0)	1.2 (0.7)	
		- MTX + HCQ + placebo	40	48 (12)	19.2 (13.1)		5.1 (1.5)	1.2 (0.7)	
Boers 2022 Ann Rheum Dis	GLORIA	- Standard of care + PRED 5 mg/d	224	73 (5)	10.8 (10.4)[β]	53	4.4 (1.0)	1.2 (0.7)	20.0 (34.6)
		- Standard of care + placebo	225	73 (5)	10.4 (10.2)	60	4.6 (1.1)	1.1 (0.7)	17.2 (33.4)
Burmester 2020 Lancet	SEMIRA	- Tocilizumab + continued PRED 5 mg/d	128	54 (13)	8.6 (7.4)[β]		1.95 (0.93)		
		- Tocilizumab + tapered PRED / placebo 5 mg/d PRED tapered to stop in 16 weeks	131	55 (14)	9.6 (8.0)		1.88 (0.81)		

Mean (SD) presented unless reported otherwise. HR = high risk, LR = low risk, MTX = methotrexate, SSZ = sulfasalazine, PRED = prednisone, HCQ = hydroxychloroquine, ACPA = anti-citrullinated protein antibodies, DAS = disease activity score, HAQ = health assessment questionnaire, SvdH = Sharp/van der Heijde.

[α]Median (IQR)

[β]Disease duration reported in years.

Table 5.2 Treatment outcomes of included efficacy studies

Study ID	Treatment	N pts	Timepoint	ACR20	ACR50	ACR70	ΔDAS28	DAS28<2.6 (%)	ACR/Boolean remission	ΔHAQ	ΔSvdH-score
Stouten 2019 CareRA	- HR: MTX + SSZ + PRED 60 mg in 7 weeks to 7.5 mg,	98	24 months				-2.7 (1.3)	65	21	-0.7 (0.7)	0.5 (1.3)
	- HR: MTX + PRED 30 mg in 6 weeks to 5 mg	98					-2.6 (1.2)	72	20	-0.5 (0.7)	0.9 (1.7)
	- HR: MTX + LEF + PRED 30 mg in 6 weeks to 5 mg	93					-2.6 (1.5)	74	23	-0.6 (0.7)	0.6 (1.2)

	all PRED tapered from week 28 to stop at week 34						p=0.58	p=0.36	p=0.94	p=0.18	p=0.23
	- LR: MTX + PRED 30 mg in 6 weeks to 5 mg PRED tapered from week 28 to stop at week 34 - LR: MTX tight step up	43 47	24 months				-2.4 (1.7) -2.2 (1.9) p=0.63	67 72 p=0.61	37 19 p=0.06	-0.6 (0.8) -0.5 (0.7) p=0.81	0.3 (0.7) 0.5 (1.3) p=0.60
Hua 2020 Medicine	- MTX + HCQ + PRED 10 mg, tapered to 5 mg/day from 4 months, stopped at 6 months - MTX + HCQ + placebo	40 40	3 months	85.0 47.5 p<0.05			-2.9 (1.0) -1.7 (1.2) p<0.001			-0.8 (0.6) -0.5 (0.5) p=0.003	
	- MTX + HCQ + PRED - MTX + HCQ + placebo		6 months	87.5 60.0 p<0.05			-3.4 (1.1) -2.4 (1.1) p<0.001			-0.9 (0.5) - 0.5 (0.4) p=0.002	
	- MTX + HCQ + PRED - MTX + HCQ + placebo		12 months	90.0 72.5 p<0.05			-3.6 (1.1) -3.6 (1.4) p=0.974			-0.9 (0.5) -0.9 (0.5) p=0.963	
Boers 2022 Ann Rheum Dis	- Standard of care + PRED 5 mg/d - Standard of care + placebo	224 225	3 months	36 24	20 9	8 1	-1.4 (1.1) -0.7 (1.2)	37 14	3.2 0.7	-0.2 (0.5) 0.0 (0.4)	
	- Standard of care + PRED 5 mg/d - Standard of care + placebo		24 months				2.97[γ] 3.33			1.1[γ] 1.1	0.3 (1.0) 1.9 (6.4) p=0.003

[γ]DAS28 and HAQ reported as predicted values at 24 months (no change scores), adjusted for country, prior GC exposure, and change of anti-rheumatic treatment at baseline

HR = high risk, LR = low risk, MTX = methotrexate, SSZ = sulfasalazine, PRED = prednisone, HCQ = hydroxychloroquine, ACPA = anti-citrullinated protein antibodies, DAS = disease activity score, HAQ = health assessment questionnaire, SvdH = Sharp/van der Heijde.

Table 5.3 Overview of study arms using GCs in clinical trials included in the unpublished individual patient data meta-analysis

Study (publication year)	**Type of GC**	**Initial GC dose**	**Tapering schedule**
COBRA (1997)	Prednisolone	60 mg/day	In 7 weeks to 7.5 mg/day. Stop after 35 weeks.**
BeSt (2005)	Prednisone	60 mg/day	In 7 weeks to 7.5 mg/day. Stop in 8 weeks after week 28 if DAS persistently ≤2.4
IDEA (2014)	Methylprednisolone	250 mg iv once	N.A.
COBRA-light (2015)	Prednisolone	arm 1 60 mg/day arm 2 30 mg/day	arm 1: in 7 weeks to 7.5 mg/day arm 2: in 9 weeks to 7.5 mg/day Stop after 32 weeks if DAS<1.6.
IMPROVED (2014)	Prednisone	60 mg/day	In 7 weeks to 7.5 mg/day. Stop after 20 weeks if DAS <1.6 at 4 months.
tREACH (2013)	Arm 1: methylprednisolone or kenacort arm 2 & 3: prednisone	arm 1: 120 mg or 80 mg im once (single dose) arm 2 & 3: 15 mg/day	In 10 weeks to 0 mg/day.**
CareRA (2017) - *COBRA Classic* - *COBRA Slim* - *COBRA Avant garde*	Prednisone	 - 60mg/day - 30mg/day - 30 mg/day	 - in 7 weeks to 7.5 mg/day, further tapered from week 28 and stop after 34 weeks. - in 6 weeks to 5 mg/day, further tapered from week 28 and stop after 34 weeks. - in 6 weeks to 5 mg/day, further tapered from week 28 and stop after 34 weeks. All if DAS28(CRP) ≤3.2.

Abbreviations: GC=glucocorticoid, im=intramuscular, iv=intravenous, mg=milligram, N.A.=not applicable
* replicated from *van Ouwerkerk et al. Ann Rheum Dis.* 2022
** GC tapered and stopped according to protocol, not depending on disease activity score.

Table 5.4 Oral GC use at predefined timepoints after the initial bridging strategy, for 7 out of 10 trials of which individual patient data was collected.

	COBRA (1997)		**BeSt (2005)**		**IDEA (2014)**		**COBRA light (2015)**				**IMPROVED (2014)***						**tREACH (2013)**						**CareRA (2017)**							
							Arm 1 (COBRA)		**Arm 2 (COBRA light)**		**Early remission**		**Arm 1**		**Arm 2**		**Arm 1**		**Arm 2**		**Arm 3**		**Arm 1 (classic)**		**Arm 2 (slim, high risk)**		**Arm 3 (avant garde)**		**Arm 4 (slim, low risk)**	
Participants (N)	76		133		57		81		83		387		83		78		91		93		97		98		98		93		43	
Duration induction scheme (weeks)	35		36		i.v. once		32		32		20		32		20		i.m. once		10		10		34		34		34		34	
*Oral GC use after bridging (% yes)**																														
	M		M		M		M		M		M		M		M		M		M		M		M		M		M		M	
3 months	0	4	5	32	0	0	0	35	1	37	1	15	11	20	3	3	0	3	0	1	0	7	0	19	0	15	0	21	0	14
6 months	0	5	11	16	0	0	-	ND	-	ND	3	37	36	20	19	4	0	1	0	3	0	3	ND	-	ND	-	ND	-	ND	-
12 months	-	ND	13	17	0	5	-	ND	-	ND	10	24	37	20	23	6	0	1	0	6	0	6	ND	-	ND	-	ND	-	ND	-
18 months	-	ND	-	ND	0	0	-	ND	-	ND	13	19	36	28	26	9	0	3	0	3	0	3	ND	-	ND	-	ND	-	ND	-

Abbreviations: M=missings (%); N=number; N.D.=no data

*All patients in IMPROVED started with MTX + prednisone 60 mg/d, which was tapered to 7.5 mg/d in 7 weeks. Patients with DAS<1.6 at 4 months (early remission) subsequently tapered prednisone to stop at 20 weeks. Patients not in remission at 4 months were randomized to arm 1 (MTX + SSZ + HCQ + prednisone 7.5 mg/d) or arm 2 (MTX + adalimumab, no oral GCs allowed).

SUPPLEMENTARY FILE 6: safety, baseline characteristics and outcomes

Table 6.1 Included safety studies per outcome category

	N observational	N RCT
Cardiovascular disease and hypertension	11	12
Osteoporosis / osteoporotic fractures	5	3
Infections	5	11
GC induced diabetes and hyperglycemia	4	8
Mortality	4	3
Adverse pregnancy outcomes	1	0
Glaucoma	1	3
Hair loss	0	2
Malaise	0	2
Cancer	0	2
Hematological	0	5
Renal and kidney function	0	6
Gastrointestinal	0	10
Non-infectious skin AE	0	2
Unspecified (S)AE	0	11
Depression and mood disturbances	0	1
Cataract	0	3
Dizziness	0	2
Headache	0	4
Flushing	0	1
Non-infectious pulmonary AEs	0	1

Number of RCTs refers to the number of papers that have been included, including multiple papers reporting on different timepoints of the same trial.

Baseline characteristics of included safety studies

Table 6.2 Baseline characteristics of included safety studies: clinical trials

Study ID	Study acronym	Treatment	N patients	Age (years)	Gender (% female)	Disease duration (weeks or years [β])	ACPA (% pos)	DAS28
Clinical trials								
Bakker 2012 Ann Int Med	CAMERA-II	- MTX + PRED 10 mg/d - MTX + placebo	117 119	54 (14) 53 (13)	60 61			5.8 (1.3) 5.5 (1.1)
Boers 2022 Ann Rheum Dis	GLORIA	- Standard of care + PRED 5 mg/d - Standard of care + placebo	224 225	73 (5) 73 (5)	71 69	10.8 (10.4)[β] 10.4 (10.2)	53 60	4.4 (1.0) 4.6 (1.1)
Burmester 2020 Lancet	SEMIRA	- Tocilizumab + continued PRED 5 mg/d - Tocilizumab + tapered PRED / placebo 5 mg/d PRED tapered to stop in 16 weeks	128 131	54 (13) 55 (14)	76 79	8.6 (7.4)[β] 9.6 (8.0)		1.95 (0.93) 1.88 (0.81)
Buttgereit 2013 Ann Rheum Dis	CAPRA-2	- Standard treatment + modified-release PRED 5 mg/d - Standard treatment + placebo	231 119	57 (9.9) 58 (9.6)	83 76	8.0[β] 7.9		5.2 (0.8) 5.1 (0.8)
De Jong 2013 Ann Rheum Dis	tREACH	- MTX + SSZ + HCQ + i.m. GCs (methylpred 120 mg or triamcinolone 80 mg) - MTX + SSZ + HCQ + oral GCs - MTX + oral GCs Oral GC 15 mg/d tapered in 10 wks to stop	91 93 97	53 (15) 54 (14) 54 (14)	60 72 70	23.1 (13.9) 26.3 (13.1) 22.0 (11.9)	65 54 58	4.8 (1.1) 4.8 (1.3) 4.8 (1.3)
Den Uyl 2014 Ann Rheum Dis[γ]	COBRA light	- MTX + PRED 30 mg/d, in 7 wks to 7.5 mg/d - MTX + SSZ + PRED 60 mg/d, in 9 wks to 7.5 mg/d stop after 32 wks if DAS<1.6	83 81	53 (13) 51 (13)	66 69	16 (9; 28)[α] 17 (8; 33)	62 66	5.7 (1.1) 5.5 (1.3)
Ding 2012 Curr Ther Res Clin Exp		- MTX + LEF + PRED 15 mg/d - MTX + LEF + PRED 7.5 mg/d - MTX + LEF + placebo	88 88 90	44 (14)[η] 40 (19) 45 (14)	74 76 77	2.7 (2.3)[β] 3.6 (2.1) 3.6 (2.1)		6.9 (3.5) 6.8 (2.5) 6.4 (2.1)
Hua 2020 Medicine		- MTX + HCQ + PRED 10 mg, tapered to 5 mg/day from 4 months, stopped at 6 months - MTX + HCQ + placebo	40 40	46 (13) 48 (12)	84 72	20.5 (13.5) 19.2 (13.1)		5.2 (1.0) 5.1 (1.5)
Nam 2014 Ann Rheum Dis	IDEA	- MTX + IFX - MTX + methylpred 250 mg i.v. once	55 57	53 (13) 54 (13)	66 72	30.1 (20.9; 42.7)[ε] 31.4 (22.2; 46.7)	75 64	3.6 (0.98)[δ] 4.1 (1.0)
Sadra 2014 Int J Rheum Dis		- Standard treatment + DEX 120 mg i.v. 3 consecutive days - standard treatment + methylpred 1 g 3 consecutive days Both followed by PRED 15 mg/d in 3 divided doses	14 16	49 (6) 43 (13)	86 75	6.7 (3.9)[β] 6.5 (5.1)	79 71	6.1 (0.6) 6.3 (0.8)
Verschueren 2015 Ann Rheum Dis[α]	CareRA	- HR: MTX + SSZ + PRED 60 mg, in 7 weeks to 7.5 mg, - HR: MTX + PRED 30 mg, in 6 weeks to 5 mg - HR: MTX + LEF + PRED 30 mg, in 6 weeks to 5 mg	98 98 93	53 (12) 52 (13) 51 (13)	65 64 69	22 (14; 44) [ε] 24 (15; 39) 25 (15; 51)	78 80 77	5.0 (1.2) 4.8 (1.1) 4.7 (1.2)

		all PRED tapered from week 28 to stop at week 34 if DAS28≤3.2						
		- LR: MTX + PRED 30 mg in 6 weeks to 5 mg PRED tapered from week 28 to stop at week 34	43	51 (14)	81	21 (14; 35) [ε]	28	4.5 (1.6)
		- LR: MTX tight step up	47	51 (14)	77	19 (13; 33)	23	4.6 (1.6)

Mean (SD) presented unless reported otherwise. MTX = methotrexate, SSZ = sulfasalazine, HCQ = hydroxychloroquine, PRED = prednisone, LEF = leflunomide, methylpred = methylprednisolone, i.m. = intramuscular, wks = weeks, mg/d = milligrams/day, DAS = disease activity score, HR = high risk, LR = low risk

[α]Multiple publications regarding the CareRA study and its long-term extension were included: Verschueren 2015 Ann Rheum Dis, Verschueren 2015 Arthritis Res Ther, Verschueren 2017 Ann Rheum Dis, Stouten 2021 Ann Rheum Dis, Stouten Rheumatology 2019.

[β]Disease duration presented in years.

[γ]Multiple publications regarding the COBRA light study and its long-term extension were included: den Uyl 2014 Ann Rheum Dis, Konijn 2017 Rheumatol, Lucassen 2021 Osteoporosis Int.

[δ]DAS44 instead of DAS28 reported.

[ε]Median (IQR) instead of mean (SD) reported.

[η]Age at onset of disease.

Table 6.3 Baseline characteristics of included safety studies: observational studies

Study ID	Registry	Inclusion criteria	Exclusion criteria	Treatment / comparison groups	N patients	Age (years)	Gender (% female)	Disease duration (months)	DAS28
Observational studies									
Abtahi 2022 Rheumatol[η]	CPRD	RA diagnosed between 1 Jan 1997 and 31 Dec 2017, age ≥50 years	History of oral GC within 1 year before index date, or with OP fracture prior to index date	- Oral GC users - Non-users	7039 8084	68 (9) 69 (9)	67 70		
Avina-Zubita 2011 Ann Rheum Dis	Administrative billing data from the British Columbia Ministry of Health	First diagnosis of RA between Jan 1997 and Dec 2001 without a prior diagnosis of RA from Jan 1990 onwards	Oral GC exposure before the first RA diagnostic code, CVA before the index date	- GC users - Non-users	2844 4207	54 (18) 57 (17)	64 70		
Avina-Zubieta 2013 Rheumatol	Administrative billing data from the British Columbia	Incident RA, first diagnosis ≥ Jan 1997, ≥2 physician visits ≥2 months apart with RA diagnostic code ICD-9.	≥2 visits subsequent to the second RA visit with diagnoses of other inflammatory arthritides, an RA-coded visit by a non-	- GC users - Non-users	2783 8384	59 (17) 58 (17)	71 68		

	Ministry of Health		rheumatologist that was not confirmed on a subsequent rheumatologist visit, no subsequent RA-coded visits during the individual's last 5 years of follow-up.						
Balasubramanian 2016 Osteoporosis Inc	Marketscan Claims database	Adult RA, with 12-month baseline period prior to the first RA diagnosis. Patients with claims for any GC use had at least a 12-month GC-free clean period prior to their first GC claim in the study period.	Pre-index cancer	- Ever GC - Never GC	35,125 7002	50 (10) 49 (11)	74 74		
Costello 2021 Rheumatol	CPRD	incident RA according to validated algorithm	Diagnosis of hypertension before the RA diagnosis date	- Ever GC - Never GC	7421 10,339	58 (13) 55 (12)	67 69		
Del Rincón 2014 Arthritis Rheumatol	Observational database	RA patients fulfilling 1987 criteria from 6 rheumatology clinics, between Jan 1996 and Apr 2001		- GC at baseline - No GC at baseline	393 386	44 (13) 44 (14)	68 74	144 (120) 120 (120)	
Dixon 2012 Ann Rheum Dis	Administrative databases from Quebec, Canada	RA, ≥65 years, received ≥1 DMARD between 1 Jan 1985 and 31 Dec 2003	<3 months eligibility in the health insurance plan	- Cases (developing serious infection) - Controls	1947 9735	74 (70; 49)[ε] 74 (70; 79)	66 66		
George 2020 Ann Int Med	Medicare claims data	adult RA, stable DMARD course for ≥6 months	patients with PsA, AS, inflammatory bowel disease, SLE, cancer, HIV	GC use past 3 months - None -≤5 mg/d - 5 to 10 mg/d - >10 mg/d	 90,976 53,159 22,050 5856	 69 (12) 69 (12) 68 (12) 65 (13)	 82 81 77 73		
	Optum's Clinformatics Data Mart			GC use past 3 months - None -≤5 mg/d - 5 to 10 mg/d - >10 mg/d	 26,449 11,774 4632 1263	 57 (14) 57 (14) 59 (14) 59 (13)	 78 77 72 65		
Mebrahtu 2020 CMAJ	CPRD	Patients with chronic inflammatory diseases (IBD, SLE, PMR, GCA, RA, vasculitis),	Previous hypertension	- GC users - Non-users	4207 2844	57 (17) 54 (18)	70 64		

		registered in general practices for ≥1 year.							
Movahedi 2016 Arthritis Rheumatol	CPRD	Adult RA according to validated algorithm	Prevalent DM at study entry	- Never GC - Ever GC	12,066 9,896	58 (15) 62 (14)	71 70	24 (36) 24 (36)	
	US NDB			- Never GC - Ever GC	6,658 5,999	59 (13) 59 (14)	80 80	13 (12) 14 (11)	
Ocon 2021 Ann Rheum Dis	CorEvitas	clinical RA diagnosis	history of current or past GC therapy at or prior to enrolment, absence of follow-up, missing data for gender, age or RA duration, patients with >15 months between visits	- Cardiovascular event - No cardiovascular event	1106 18,796	65 (11) 58 (13)	67 78	144 (132) 108 (108)	
Ozen 2019 Ann Rheum Dis	FORWARD	RA ≥40 years, without prevalent fracture and completed ≥2 semiannual questionnaires from Jan 2003 through Dec 2017.		- All RA patients	11,412	61 (11)	80	187 (152)	
Ozen 2021 J Rheumatol	FORWARD	Adult RA, completed ≥2 semiannual questionnaires during the period Jan 1998 - Dec 2017.		- Cardiovascular disease - No cardiovascular disease	1801 16,953	68 (10) 58 (13)	70 81	204 (156) 168 (156)	
Palmsten 2020 Rheumatology	MotherToBaby Pregnancy Studies	Pregnant women with a last menstrual period between 2003–2014 who enrolled before gestational day 140 in either (i) MotherToBaby Autoimmune Diseases in Pregnancy Study and reported having RA or IBD or (ii) MotherToBaby Asthma Medications in Pregnancy Study and reported having asthma	Women who were lost to follow-up, withdrew, had an incomplete postpartum interview or had a spontaneous or therapeutic abortion.	- GC exposure - No GC exposure After gestational day 139	250 278	32 (5) 32 (5)	100 100		
Pujades-Rodriguez 2020 PloS Med	CPRD	Age≥18, diagnosed with IMID, treated with	Presence of CVD	- All RA patients	25,324	57 (46; 48)[e]	73		

		oral GC at or before start of follow-up							
Roubille 2021 Rheumatology	ESPOIR	RA 2010 criteria, DMARD and GC naïve	missing data for GC treatment, follow-up <1 year, past history of CVD, severe infection or fracture	- Ever GC - Never GC	397 211	47 (12) 48 (12)	77 82		5.3 (1.3) 4.8 (1.1)
Suda 2018 Clin Rheumatol	retrospective chart review Japanese tertiary hospital	RA 2010 criteria, ACPA positive, starting oral GC between 2005-2014	History of GC use for other diseases or lost to follow-up within the first year of GC therapy	- Daily dosing, 7.5 to 15 mg/d - Alternate-day dosing, 15 to 30 mg alternate daily Both tapered with good response	68 70	54 (15) 56 (15)	84 79	11.4 (35.4) 17.3 (52.7)	4.1 (1.2) 4.3 (1.5)
Van Sijl 2014 Plos One	CARRÉ cohort	Random sample of RA patients fulfilling the 1987 critera with age between 50 and 75, registered at the Jan van Breemen Research Institute - Reade in Amsterdam, the Netherlands.		- All RA patients	353				
Wilson 2019 Arthritis Care Res	CPRD	first-time Read code for RA between Jan 1995 and Jan 2015, ≥3 years recorded medial history prior to entry	Diagnosis of cancer, alcoholism, drug abuse, or HIV	- GC prescription - No GC prescription	13,770 20,280	56 (16) 56 (16)	71 70		
Wu 2020 BMJ Open Diabetes Res Care	CPRD	continuously registered in CPRD practices for ≥1 year, with a diagnosis of IBD, GCA, PMR, RA, SLE, or vasculitis.	History of diabetes	- All RA patients	28,365	59 (16)	71		

[ε]Median (IQR) instead of mean (SD) reported.

[η]A second identified study (Abtahi 2020 Ann Rheum Dis) described the same cohort with the same outcomes, but comparing different treatment groups. This study was not reported separately.

GC = glucocorticoid, RA = rheumatoid arthritis, CVA = cerebrovascular accident, PSA = psoriatic arthritis, AS = ankylosing spondylitis, SLE = systemic lupus erythematosus, DM = diabetes mellitus, IBD = inflammatory bowel disease, PMR = polymyalgia rheumatica, GCA = giant cell arteritis, IMID = immune-mediated inflammatory disease

Cardiovascular disease and hypertension

Table 6.4 Cardiovascular disease: outcome definition and statistical analyses of observational studies

Study ID	End of follow-up	Follow-up time (years)	Patient years	Outcome definition	GC naïve at baseline?	Type of analysis	Adjusted for
Avina-Zubieta 2011 Ann Rheum Dis	March 2006	Max. 9	- GC use: 3139 - No GC use: 40,216 - Total: 43,355	First cerebrovascular accident, identified from hospitalisation separation codes or death certification codes. Not including TIAs.	Yes	Cox regression	propensity score, unbalanced covariates (age, gender, hypertension, statins, diabetes, angina, chronic obstructive pulmonary disease, other cardiovascular drugs use, Charlson index, having seen a rheumatologist for rheumatoid arthritis, number of visits to a doctor per year), current use of COX-2 inhibitors, methotrexate and NSAIDs.
Avina-Zubieta 2013 Rheumatology	March 2006	Max. 9		- First myocardial infarction during follow-up, identified from hospitalization codes (ICD-9 code 410.x or ICD-10 code I21.x) either as cause of admission or as complication during hospitalization. - Death from MI, defined from a death certificate or any death within 30 days of the MI after being discharged from hospital.	NR	Cox regression	Propensity score, unbalanced covariates (age, gender, hypertension, statins, diabetes, angina, COPD, other cardiovascular drug use, Charlson index, having seen a rheumatologist for RA, number of MD visits per year) as fixed at the time of GC initiation, current use of Cox-2 inhibitors, MTX and NSAIDs as time-dependant covariates from index date to end of follow-up.
Costello 2021 Rheumatology	June 2019		Total: 97,547	Hypertension, as previously validated	Mixed	Cox regression	Baseline age, gender, BMI, ever smoking, Charlson comorbidity index, time-varying csDMARD use, NSAID use.
Mebrahtu 2020 CMAJ	Mar 2017	Median 6.5	Total: 94,781	The earliest date on which a diagnosis of hypertension, or ≥ 3 high systolic or diastolic blood pressure measures, was recorded within 12 months during follow-up.		Cox regression	Age, index of multiple deprivation, underlying inflammatory diseases (time-variant), non-oral GC use, cardiovascular disease, chronic renal disease stage 3 or 4 and scleroderma (time-variant).
Ocon 2021 Ann Rheum Dis	Mar 2018	>16	Total: 66,436	Cardiovascular event (cardiac death, myocardial infarction, stroke, hospitalisation for hypertension, coronary revascularisation procedures, ventricular arrhythmia, unstable angina, congestive heart failure, TIA, deep vein thrombosis, peripheral arterial thromobembolic event, urgent peripheral arterial revascularisation, peripheral arterial ischaemia, pulmonary	Yes	Cox regression	Age, sex, race, duration of RA, history of cardiovascular disease, diabetes mellitus, hyperlipidaemia, hypertension, statin use, NSAID use, tobacco use, year of enrolment, baseline modified HAQ, CDAI, (cs, b, ts) DMARD use

				embolism, acute coronary syndrome, other)			
Ozen 2021 J Rheumatol	Dec 2017	Median (IQR) 4.0 (1.7; 8.0)	- GC use: 32,287 - Total: 94,781	A composite of incident nonfatal and fatal cardiovascular events: (1) MI, (2) stroke, (3) hospitalized heart failure, (4) death from CVD.	No	Cox regression	Age, sex, ethnicity, location of residence (rural vs urban), education level (yrs), employment (yes/no), insurance type (Medicare vs others), BMI in WHO categories, ever smoking, Rheumatic Disease Comorbidity Index not including diabetes and hypertension, hypertension, diabetes, chronic kidney disease, prior CVD, RA duration, HAQ, pain and patient global scores, use of other drugs influencing the CVD risk (statins, acetylsalicylic acid, NSAIDs), number of previous csDMARD and bDMARDs, WCE-prednisone, and calendar year
Pujades-Rodriguez 2020 PloS Med	Mar 2017	Mean (SD) 6.2 (4.8)		Cardiovascular diseases	Mixed	Cox regression	Baseline age, sex, index of multiple deprivation, smoking, ethnicity, BMI, comorbidities, total cholesterol, HDL-cholesterol ,LDL-cholesterol, CRP, creatinine, number of hospital admissions in last year, prescribed non-oral GC, time-variant use of DMARDs and NSAIDs, random intercept for practice identifier
Roubille 2021 Rheumatology		Mean (SD) 8.66 (2.58)		Cardiovascular diseases (myocardial ischemia, stroke and heart failure)	Yes	Cox regression	None
Suda 2018 Clin Rheumatol	2015	Max. 1		Newly diagnosed cardiovascular events (angina pectoris, stroke, myocardial infarction, sub-arachnoid hemorrhage or intracranial hemorrhage defined according to ICD10-codes) added to the patient's chart within 1 year of starting GCs Newly diagnosed hypertension, diagnosis added to the patient's chart or the patient started any anti-hypertensive drug therapy within the first year of staring GCs	Yes	Not specified	
van Sijl 2014 PLoS One	Dec 2011	10	Total: 2361	cardiovascular event according to ICD-9 codes: myocardial infarction (410.0–9), stroke (436) or transient ischemic attack (TIA) (435.9), a history of peripheral arterial reconstruction, carotid	Mixed	Cox regression	Age, gender, SCORE (10-year estimated CV risk), DAS28, HAQ

				endarterectomy, percutaneous coronary intervention (PCI) (8036), coronary artery by-pass surgery (CABG) (8038) and sudden death, cause unknown (798)			
Wilson 2019 Arthritis Care Res		Mean (SD) 8.1 (5.7)	GC use: 73,568 No GC use: 119,677 Total: 193,245	incident hypertension code	Yes	Logistic regression	Alcohol status, smoking status, BMI, prior history of diabetes mellitus, cardiovascular disease, COPD, asthma, a prior prescription for opioid, statin, and COX-2 inhibitor
			GC use: 110,210 No GC use: 154,845 Total: 265,055	incident code for thrombotic stroke or MI			Alcohol status, smoking status, BMI, prior history of diabetes mellitus, hypertension, peripheral vascular disease, Charlson Comorbidity Index score, a prior prescription for a bisphosphonate, aspirin and DMARD.

BMI = body mass index, DMARD = disease-modifying anti-rheumatic drug, COPD = chronic obstructive pulmonary disease, DAS = disease activity score, HAQ = health assessment questionnaire, CRP = c-reactive protein, GC = glucocorticoid, RA = rheumatoid arthritis, CVD = cardiovascular disease, WCE = weighted cumulative exposure.

Table 6.5 Cardiovascular disease: outcomes of observational studies

Study ID	**N events**	**N pts with event**	**IR (95% CI) / 1000 PY**	**Type of ratio**	**Ref category**	**Exposure definition**	**Unadjusted**	**Adjusted**
Avina-Zubita 2011 Ann Rheum Dis			- GC use: 6.6 - No GC use: 3.9	HR	No GC use	Current GC use	**1.68 (1.06; 2.68)**	1.41 (0.84; 2.37)
						Current mean daily dose (5 mg)	1.11 (0.99; 1.23)	1.07 (0.94; 1.21)
						Total cumulative duration of use (year)	**1.18 (1.02; 1.35)**	1.11 (0.94; 1.32)
						Total past cumulative dose (1 g)	**1.06 (1.02; 1.10)**)	1.04 (0.99; 1.08)
						Current daily dose (5 mg) + cumulative duration (year)	1.08 (0.95; 1.23) 1.15 (0.99; 1.29	1.05 (0.92; 1.20) 1.10 (0.92; 1.31)
Avina-Zubieta 2013 Rheumatology				HR	No GC use	Current GC use	**1.94 (1.34; 2.80)**	**1.68 (1.14; 2.47)**
						Current mean daily dose (5 mg)	**1.17 (1.08; 1.27)**	**1.14 (1.05; 1.24)**
						Total cumulative duration of use (year)	**1.22 (1.09; 1.37)**	**1.14 (1.00; 1.29)**
						Total past cumulative dose (1 g)	**1.08 (1.04; 1.11)**	**1.06 (1.02; 1.10)**
						Current daily dose (5 mg) + cumulative duration (year)	**1.14 (1.04; 1.26)** **1.18 (1.04; 1.33)**	**1.13 (1.03; 1.24)** 1.10 (0.97; 1.26)
Costello 2021 Rheumatology			- GC use: 87.6 (83.0; 92.4) - No GC use: 49.7 (58.1; 61.4)	HR	No GC use	Recent GC use	**1.44 (1.35; 1.53)**	**1.17 (1.10; 1.24)**
						Recent GC dose >0 – 4.9 mg/d Recent GC dose 5 – 7.4 mg/d Recent GC dose 7.5 – 14.9 mg/d Recent GC dose ≥15 mg/d	**1.35 (1.21; 1.53)** **1.40 (1.22; 1.60)** **1.44 (1.33; 1.57)** **1.60 (1.40; 1.84)**	1.10 (0.98; 1.24) 1.07 (0.93; 1.23) **1.18 (1.08; 1.29)** **1.36 (1.18; 1.56)**
						Cumulative GC dose >0 – 2.49 g Cumulative GC dose 2.5 – 4.99 g Cumulative GC dose 5 – 9.99 g Cumulative GC dose ≥10 g	**1.14 (1.05; 1.23)** **1.16 (1.06; 1.27)** **1.36 (1.24; 1.48)** **1.35 (1.24; 1.49)**	1.00 (0.92; 1.08) 0.99 (0.90; 1.08) **1.12 (1.02; 1.22)** 1.07 (0.97; 1.17)

Mebrahtu 2020 CMAJ				HR	No GC use	Time-varying cumulative GC dose <0 – 959.9 mg 960 – 3054.9 mg ≥3055 mg		**1.11 (1.03; 1.21)** **1.16 (1.05; 1.29)** **1.39 (1.30; 1.48)**
						Time-variant daily dose >0 – 4.9 mg 5.0 – 7.4 mg ≥7.5 mg		1.04 (0.89; 1.22) 1.06 (0.93; 1.22) 1.07 (0.96; 1.19)
Ocon 2021 Ann Rheum Dis				HR	No GC use	Daily dose 1 - <5 mg/d ≥5 – 9 mg/d ≥10 mg/d	1.04 (0.61; 1.76) **1.78 (1.35; 2.35)** **2.09 (1.44; 3.05)**	1.94 (0.55; 1.59) **1.56 (1.18; 2.05)** **1.91 (1.31; 2.79)**
						Cumulative dose prec 6 months 1 – 380 mg 381 – 750 mg 751 – 100 mg >1100 mg	0.93 (0.56; 1.50) 1.31 (0.88; 1.95) **1.62 (1.18; 2.24)** **2.25 (1.57; 3.22)**	0.86 (0.53; 1.40) 1.20 (0.81; 1.79) **1.43 (1.04; 1.98)** **2.05 (1.42; 2.94)**
						Cumulative dose prec 1 year 1 – 500 mg 501 – 1100 mg 1101 – 2100 mg >2100 mg	0.99 (0.64; 1.54) 1.28 (0.89; 1.83) **1.63 (1.18; 2.25)** **1.97 (1.41; 2.74)**	0.93 (0.60; 1.45) 1.19 (0.83; 1.70) **1.47 (1.06; 2.03)** **1.74 (1.25; 2.43)**
						Duration of use prec 6 months 1 – 80 days 81 – 160 days 161 – 181 days >181 days	0.77 (0.46; 1.29) **1.66 (1.16; 2.36)** 1.71 (0.76; 3.81) **1.79 (1.38; 2.35)**	0.72 (0.60; 1.45) **1.54 (1.08; 2.20)** 1.56 (0.70; 3.48) **1.57 (1.20; 2.05)**
						Duration of use prec 1 year 1 – 100 days 101 – 220 days 221 – 360 days >360 days	1.08 (0.72; 1.62) **1.50 (1.10; 2.05)** 0.99 (0.60; 1.62) **2.15 (1.59; 2.92)**	1.02 (0.68; 1.53) **1.41 (1.03; 1.93)** 0.88 (0.54; 1.44) **1.88 (1.39; 2.56)**
Ozen 2021 J Rheumatol			- GC use: 2.25 (2.10; 2.42)	HR	No GC use	Ever GC use	**1.19 (1.16; 1.22)**	**1.15 (1.11; 1.19)**
						<7.5 mg/d <3 months <7.5 mg/d ≥3 months ≥7.5 mg/d <3 months ≥7.5 mg/d ≥3 months		0.90 (0.40; 2.01) 1.11 (0.99; 1.25) 1.18 (0.63; 2.20) **1.47 (1.26; 1.71)**
Pujades-Rodriguez 2020 PloS Med				HR	No GC use	Ever GC use		**1.63 (1.52; 1.73)**
						Current GC use		**2.11 (1.98; 2.25)**
						Current daily dose per 5 mg/d		**1.28 (1.25; 1.31)**
						Current daily dose 1 – 4.9 mg 5.0 – 14.9 mg 15.0 – 24.9 mg ≥25 mg		**1.84 (1.62; 2.10)** **2.00 (1.85; 2.15)** **2.79 (2.21; 3.51)** **4.98 (4.11; 6.03)**
						Total cumulative dose per 1000 mg		**1.02 (1.02; 1.03)**
						Total cumulative dose 1 – 959.9 mg 960 – 3054.9 mg 3055 – 7299.9 mg ≥7300 mg		**1.47 (1.34; 1.61)** **1.52 (1.36; 1.68)** **1.72 (1.55; 1.19)** **1.80 (1.65; 1.97)**
Roubille 2020 Rheumatology		3 15			No GC use	No GC use GC use	p=0.177	

		2 1 12				Cumulative dose >0 – 1842 mg 1842 – 8421.5 mg ≥8421.5 mg	**p<0.001**	
Suda 2018 Clin Rheumatol		0 2				**Incident CV event:** Daily GC dosing Alternate daily GC dosing	p = 0.16	
		3 4				**Incident hypertension:** Daily GC dosing Alternate daily GC dosing	p = 0.73	
van Sijl 2014 PLoS One			Total: 24.6	HR	No GC use	Ever GC use	1.77 (0.68; 4.63)	0.89 (0.26; 3.09)
						Recent (<1 year) GC use Current GC use	2.03 (0.72; 5.74) **2.91 (1.06; 8.00)**	1.11 (0.27; 4.53) 1.34 (0.31; 5.88)
						Duration of GCs (years)	1.18 (0.90; 1.41)	1.14 (0.83; 1.58)
						Duration of GCs ≤5 years >5 years	1.02 (0.28; 3.67) **4.33 (1.31; 14.29)**	0.71 (0.15; 3.27) 1.48 (0.21; 10.45)
						Cumulative use (g)	**1.04 (1.01; 1.07)**	1.05 (0.99; 1.11)
						Cumulative use ≤10 g >10 g	0.43 (0.06; 3.33) **3.88 (1.39; 3.33)**	0.42 (0.05; 3.30) 1.80 (0.37; 8.74)
Wilson 2019 Arthritis Care Res	1339 3101		18.2 (17.3; 19.2) 25.9 (25.0; 26.8)	OR	No GC use	**Hypertension:** GC use No GC use		 0.93 (0.85; 1.01) Ref
						Past GC use Current GC use		0.96 (0.91; 1.02) 1.02 (0.90; 1.16)
						Cumulative GC dose <700 mg 700 to <3,500 mg 3500 to <7000 mg ≥7000 mg		0.93 (0.82; 1.06) 0.93 (0.82; 1.06) 0.92 (0.76; 1.11) 0.91 (0.74; 1.12)
	426 560		3.9 (3.5; 4.3) 3.6 (3.3; 3.9)			**Thrombotic stroke or MI:** GC use No GC use		 **1.28 (1.07; 1.52)** Ref
						Past GC use Current GC use		1.09 (0.98; 1.21) **1.31 (1.05; 1.64)**
						Cumulative GC dose <700 mg 700 to <3,500 mg 3500 to <7000 mg ≥7000 mg		**1.35 (1.06; 1.72)** 1.03 (0.80; 1.32) **1.56 (1.14; 2.14)** **1.60 (1.13; 2.28)**

GC = glucocorticoid, mg = milligrams, g = grams, prec = preceding, MI = myocardial infarction, CV = cardiovascular, HR = hazard ratio, OR = odds ratio

Table 6.6: Cardiovascular disease: outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Bakker 2012 Ann Int Med	2008	2 years	yes	descriptive	Hypertension	MTX + PRED MTX + placebo	11 18	
Boers 2022 Ann Rheum Dis	Dec 2018	2 years	No GC at baseline	descriptive	Hypertension	**Hypertension AE of special interest** standard treatment + prednisolone standard treatment + placebo	 4 7	
						Hypertension SAE standard treatment + prednisolone standard treatment + placebo	 1 0	
					Cardiovascular, myocardial infarction, cerebrovascular event, peripheral arterial vascular event.	**Cardiovascular AE of special interest** standard treatment + prednisolone standard treatment + placebo	 2 0	
						Cardiovascular SAE standard treatment + prednisolone standard treatment + placebo	 8 6	
Burmester 2020 Lancet	Feb 2018	24 weeks	No	descriptive	Atrial fibrillation	tapered prednisone continued prednisone	1 0	
					Cerebrovascular accident	tapered prednisone continued prednisone	1 0	
Buttgereit 2013 Ann Rheum Dis	Feb 2009	12 weeks	No GC within 6 weeks from initiation	descriptive	Hypertension	standard treatment + MR prednisone standard treatment + placebo	5 1	
De Jong 2013 Ann Rheum Dis		3 months	Yes	descriptive	Hypertension	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		1 2 0
Den Uyl 2014 Ann Rheum Dis	Sep 2011	26 weeks	Yes	descriptive	Myocardial infarction	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	1 0	
					Arrhytmia requiring hospitalisation	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	0 1	
					Hypertension requiring treatment	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	1 2	
Konijn 2017 Rheumatology[a]		4 years	Yes	descriptive	Hypertension	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	7 5	
					Any cardiovascular event	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	6 7	
Ding 2012 Curr Ther Res Clin Exp	Jul 2011	12 weeks	No GC within 3 months before study start	Descriptive	Hypertension at 4 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		1 2 1
					Hypertension 4 to 12 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		4 3 2
Nam 2014 Ann Rheum Dis	Jul 2009	78 weeks	No GC within 1 month before study start	Descriptive	cardiac arrhythmia SAE	MTX + infliximab MTX + i.v. methylprednisolone	1 0	1 0

					Cardiac general SAE	MTX + infliximab MTX + i.v. methylprednisolone	2 2	1 2
Sadra 2014 Int J Rheum Dis	Jul 2022	30 days		Descriptive	Arrhythmia	standard treatment + methylprednisolone standard treatment + dexamethasone	0 0	
					Hypertension	standard treatment + methylprednisolone standard treatment + dexamethasone	2 0	
Verschueren 2017 Ann Rheum Dis	May 2014	1 year	Yes	descriptive	Hypertension	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up	5 3 1 0 0	
Stouten 2021 Ann Rheum Dis[b]		5 years	Yes	descriptive	Severe cardiovascular problems	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up	0 5 5 2 1	

[a]Long-term extension of the COBRA light trial (see Den Uyl 2014 Ann Rheum Dis).

[b]Long-term extension of the CareRA trial (see Verschueren 2017 Ann Rheum Dis).

MTX = methotrexate, SSZ = sulfasalazine, PRED = prednisone, LEF = leflunomide, HR = high risk, LR = low risk, AE = adverse event, SAE = serious adverse event.

Osteoporosis

Table 6.7 Osteoporosis: outcome definition and statistical analyses of observational studies

Study ID	End of follow-up	Follow-up time (years)	Patient years	Outcome definition	GC naïve at baseline?	Type of analysis	Adjusted for
Abtahi 2021 Rheumatology	Dec 2017	Mean (SD) GC users: 8.1 (4.9) Non-users: 6.2 (4.7)		Osteoporotic fractures identified through relevant READ codes.	No oral GC at least 1 year before index date	Cox regression	Baseline sex, BMI, smoking status, alcohol use, and during follow-up for age, history of AS, COPD, dementia falls, IBD, use of antidepressents in past 6 months, antihypertensives, proton pump inhibitors, paracetemol, non-selective NSAIDs, COX-2 selective inhibitors, tramadol, opioids, csDMARDs, recent use of oral GCs.
Balasubramanian 2016 Osteoporosis Inc	Dec 2012	Median 1.6		Osteoporotic fractures, Including closed fractures of the hip, distal radius/ulna, other parts of radius/ulna, pelvis, humerus, shaft/unspecified parts of femur, and clinically diagnosed vertebral fractures. The only open fracture site included was the distal radius/ulna. Identified by a relevant ICD-9-CM diagnosis code preceded by (1) ≥180 days with no diagnosis codes for the same fracture site or (2) appearing in conjunction with a surgical repair procedure	Yes	Cox regression	Sex, age, current daily dose or cumulative dose, anticonvulsant use, antidepressant use, osteoporosis agents, number of medications, Charlson Comorbidity Index Score, asthma/COPD, IBD, multiple sclerosis, pre-index fracture
Ozen 2019 Ann Rheum Dis	Dec 2017	10		Major osteoporotic fracture (hip, clinical spine, forearm or humerus) or hip fracture of patients with the US version of FRAX tool without bone mineral density results	Mixed	Cox regression	Age, sex, ethnicity, RA duration, educational level, insurance, rural residency, smoking, influenza vaccination, comorbidity index, BMI, HAQ, pain and patient global scores, prior osteoporosis diagnosis, use of osteoporosis specific medications, exercise, mental component score of SF-36, prior csDMARD and bDMARD counts, hospitalisation and calendar year
Suda 2018 Clin Rheumatol	2015	1		Osteoporotic fracture defined as femoral neck or vertebral fractures	Yes	Not described	
Wilson 2019 Arthritis Care Res		Mean (SD) 8.1 (5.7)	GC use: 152,751 No GC use: 103,636 All: 256,387	Incident osteoporosis	Yes	Logistic regression	Alcohol status, smoking status, BMI, RA disease duration, prior history of COPD, a past fracture, a prior prescription for a proton pump inhibitor, calcium supplement, and DMARD use.

BMI = body mass index, RA = rheumatoid arthritis, COPD = chronic obstructive pulmonary disease, DMARD = disease modifying anti-rheumatic drug, HAQ = health assessment questionnaire, GC = glucocorticoid, IBD = inflammatory bowel disease,

Table 6.8 Osteoporosis: outcomes of observational studies

Study ID	N events	N pts with event	IR (95% CI) / 1000 PY	Type of ratio	Ref category	Exposure definition	Unadjusted	Adjusted
Abtahi 2021 Rheumatology[α]	428 36 375 801		21.3 11.1 15.7 12.6	HR	Past GC use	Current GC use Recent GC use Past GC use Non-use		**1.22 (1.06; 1.40)** 0.71 (0.51; 1.00) ref 0.94 (0.83; 1.07)
	301 101 26		20.3 23.3 27.9			Current GC use mean daily dose ≤7.5 mg/d Dose 7.5 – 14.9 mg/d ≥15 mg/d		1.14 (0.98; 1.33) **1.38 (1.11; 1.63)** **1.84 (1.23; 2.74)**
	70 35		17.4 22.3			Current GC use, cumulative use ≤1 g >1 g		1.11 (0.86; 1.44) **1.24 (1.07; 1.44)**
	53 17 248 110		17.2 18.0 21.2 25.5			Current GC use cumulative use ≤1 g & mean daily dose ≤7.5 mg/d Cumulative use ≤1 g & mean daily dose >7.5 mg/d Cumulative use >1 g & mean daily dose ≤7.5 mg/d Cumulative use >1 g & mean daily dose >7.5 mg/d		1.10 (0.83; 1.47) 1.15 (0.71; 1.87) 1.15 (0.98; 1.35) **1.52 (1.22; 1.89)**
	63 365		16.8 22.4			Current GC use ≤2.5 mg/d >2.5 mg/d		1.00 (0.77; 1.31) **1.27 (1.09; 1.47)**
	165 263		18.5 23.6			Current GC use ≤5 mg/d >5 mg/d		1.07 (0.89; 1.29) **1.34 (1.14; 1.57)**
Balasubramanian 2016 Osteoporosis Inc	Total: n=519		5.0 (4.6; 5.6) 9.0 (5.7; 13.7) 7.8 (5.3; 11.1) 6.8 (4.6; 9.6) 16.0 (11.0; 22.6)	HR	No GC use	Current daily dose 0 mg/d >0 to <5 mg/d 5 to <7.5 mg/d 7.5 to <15 mg/d ≥15 mg/d		Ref 1.37 (0.88; 2.13) 1.20 (0.82; 1.77) 1.01 (0.68; 1.49) **2.22 (1.51; 3.27)**
			4.3 (3.4; 5.4) 4.6 (3.8; 5.4) 5.7 (4.6; 7.1) 5.3 (4.2; 6.7) 6.4 (4.9; 8.2) 13.4 (10.7; 16.7)			Cumulative dose 0 mg >0 to <675 mg 675 to <1350 mg 1350 to <2700 mg 2700 to <5400 mg ≥5400 mg		Ref 0.93 (0.70; 1.25) 1.13 (0.81; 1.56) 1.01 (0.72; 1.41) 1.11 (0.77; 1.59) **1.98 (1.37; 2.86)**
			4.3 (3.4; 5.4) 4.8 (3.0; 7.2) 4.8 (2.9; 7.5) 5.7 (4.3; 7.4) 6.0 (5.4; 6.7)			Peak dose 0 mg >0 to <5 mg 5 to <7.5 mg 7.5 to <15 mg ≥15 mg		
			4.3 (3.4; 5.4) 4.8 (4.1; 5.5) 5.5 (4.6; 6.4) 11.1 (9.1; 13.4)			Cumulative days 0 1 to 90 91 to 365 >365		
			4.3 (3.4; 5.4) 9.0 (7.4; 10.8) 7.2 (5.7; 8.9) 5.4 (4.2; 6.8)			Days since GC discontinuation (no exposure) Days since GC discontinuation 0 (current use) >0 to <60 60 to <182		

			5.0 (3.8; 6.4) 4.4 (3.7; 5.3)			182 to <365 ≥365		
Ozen 2019 Ann Rheum Dis			13.6 (12.5; 14.8) 14.4 (7.8; 26.8) 21.7 (19.0; 24.7) 22.7 (13.7; 37.7) 33.5 (28.0; 24.0)	HR	No GC use	No GC use GC use <7.5 mg/d for <3 months GC use <7.5 mg/d for ≥3 months GC use ≥7.5 mg/d for <3 months GC use ≥7.5 mg/d for ≥3 months	Ref 1.34 (0.72; 2.51) 1.59 (1.36; 1.86) 2.00 (1.20; 3.35) 2.46 (2.02; 3.00)	Ref 1.23 (0.65; 2.29) **1.26 (1.07; 1.48)** 1.66 (0.99; 2.77) **1.57 (1.27; 1.94)**
Suda 2018 Clin Rheumatol	1 3					Daily GC dosing Alternate daily GC dosing	p=0.32	
Wilson 2019 Arthritis Care Res	1151 1124		7.54 (7.11; 7.98) 10.85 (10.23; 11.49)	OR	No GC use	No GC use Ever GC use		Ref **1.41 (1.25; 1.59)**
						Past GC use Current GC use		1.02 (0.95; 1.09) **1.77 (1.54; 2.04)**
						Cumulative GC dose <700 mg 700 to <3500 mg 3500 to <7000 mg ≥7000 mg		**1.31 (1.11; 1.54)** **1.52 (1.30; 1.77)** **1.43 (1.16; 1.76)** **1.56 (1.24; 1.97)**

[α] A second identified study (Abtahi 2020 Ann Rheum Dis) described the same cohort with the same outcomes, but comparing different treatment groups. This study was not reported separately.

GC = glucocorticoid, mg = milligrams, mg/d = milligrams/day

Table 6.9: Osteoporosis: outcome definition and outcomes of clinical trials

Study ID	**End of follow-up**	**Follow-up time**	**GC naïve at baseline?**	**Type of analysis**	**Outcome definition**	**Exposure definition**	**N events**	**N pts with event**
Ding 2012 Curr Ther Res Clin Exp	Jul 2011	12 weeks	No GC within 3 months before study start	Descriptive	Non-traumatic fracture 4 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		0 0 0
					Non-traumatic fracture 4 to 12 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		1 0 0
Konijn 2017 Rheumatology[a]	2015	4 years	Yes	Descriptive	Osteoporosis at 4-year DEXA	MTX + PRED 30 mg/d MTX + SSZ + PRED 60 mg/d		1 4
Lucassen 2021 Osteoporosis Int[a]	Apr 2015	1 year	Yes	Descriptive	Osteoporosis	MTX + PRED 30 mg/d MTX + SSZ + PRED 60 mg/d	6 5	
		4 years				MTX + PRED 30 mg/d MTX + SSZ + PRED 60 mg/d	8 7	

[a] Both studies are long-term extension of the COBRA light trial.

MTX = methotrexate, SSZ = sulfasalazine, PRED = prednisone, mg/d = millirams/day, DEXA = dual energy X-ray absorptiometry

Infections

Table 6.10: Infections: outcome definition and statistical analyses of observational studies

Study ID	End of follow-up	Follow-up time (years)	Patient years	Outcome definition	GC naïve at baseline?	Type of analysis	Adjusted for
Dixon 2012 Ann Rheum Dis	Dec 2003	Mean 3.8		Serious infections, identified as the first occurrence of a primary hospital discharge diagnosis of infection		Logistic regression	Number of rheumatologist visits in the preceding year, current NSAID use, concomitant DMARD exposure in the 45 days before the index date, comorbidities, age, number of hospital admissions, number of GP and hospital specialist visits in the preceding year and concomitant use of gastric acid-suppressive drugs.
George 2020 Ann Int Med	2015	Median (IQR) Medicare: 180 days (90; 433 Optum: 148 days (90; 347)		Time to first infection occurring during an acute care hospitalization	No	Cause-specific proportional hazards model	Inverse probability weighting (variables not reported) + opioid use, outpatient visits, hospitalization (both data sets), emergency department visits (Medicare)
Roubille 2020 Rheumatology		Mean (SD) 8.66 (2.58)		Severe infection	Yes	Cox regression	None
Suda 2018 Clin Rheumatol	2015	1		Any infection, defined as the prescription of any antibiotic, anti-viral or anti-fungal medication, except for the use of anti-microbials for the prevention of pneumocystis pneumonia or isoniazid/rifampicin for latent tuberculosis Severe infection	Yes	Logistic regression	QOD dose, age, sex, baseline diabetes, baseline CRP level, presence of interstitial lung disease, mean daily dose of GC over 1 year and use of bDMARDs
Wilson 2019 Arthritis Care Res		Mean (SD) 8.1 (5.7)	GC use: 38,011 No GC use: 54,212 Total: 92,223	serious infection requiring hospitalization	Yes	Logistic regression	Alcohol status, smoking status, BMI, RA disease duration, prior history of COPD, a past fracture, a prior prescription for a proton pump inhibitor, calcium supplement, and DMARD use.

GP = general practitioner, GC = glucocorticoid, DMARD = disease modifying anti-rheumatic drug, QOD = every other day, COPD = chronic obstructive pulmonary disease, BMI = body mass index, RA = rheumatoid arthritis

Table 6.11 Infections: outcomes of observational studies

Study ID	N events	N pts with event	IR (95% CI) / 1000 PY	Type of ratio	Ref category	Exposure definition	Unadjusted	Adjusted
Dixon 2012 Ann Rheum Dis				OR	No GC use	Current GC use		**1.84 (1.64; 2.06)**
						Any GC use past 30 days		**2.08 (1.86; 2.33)**
						Any GC use past 90 days		**2.26 (2.02; 2.54)**
						Ever GC use		**1.72 (1.53; 1.94)**

						Current dose (per mg PEQ)		**1.04 (1.04; 1.05)**
						Average dose in past 30 days (per mg PEQ)		**1.07 (1.06; 1.08)**
						Average dose in past 90 days (per mg PEQ)		**1.09 (1.08; 1.11)**
						Average dose since study entry (per mg PEQ)		**1.08 (1.06; 1.09)**
						Peak dose past 30 days (per mg PEQ)		**1.03 (1.02; 1.03)**
						Peak dose past 90 days (per mg PEQ)		**1.02 (1.01; 1.02)**
George 2020 Ann Int Med				Predicted 1 year incidence		**Medicare**		
		130822				No GC use		8.6
		8363				GC dose ≤5 mg/d		11.0 (10.6; 11.5)
		31621				5 - 10 mg/d		14.4 (13.8; 15.1)
		76491				≥10 mg/d		17.7 (16.5; 19.1)
						Optum		
		35251				No GC use		4.0
		1635				GC dose ≤5 mg/d		5.2 (4.7; 5.8)
		5889				5 -10 mg/d		8.1 (7.0; 9.3)
		15504				≥10 mg/d		10.6 (8.5; 13.2)
						Medicare		
		44328				Cumulative dose ≤450 mg		0.97 (0.92; 1.01)
		35407				450 – 900 mg		0.94 (0.89; 0.99)
		33890				900 – 1350 mg		1.01 (0.95; 1.06)
		16978				1350 – 1800 mg		1.03 (0.96; 1.10)
		10590				1800 – 2250 mg		1.03 (0.95; 1.12)
		7833				2250 – 2700 mg		1.12 (1.03; 1.23)
		8331				>2700 mg		1.01 (0.92; 1.12)
						Optum		
		11481				Cumulative dose ≤450 mg		0.98 (0.86; 1.12)
		8558				450 – 900 mg		0.91 (0.77; 1.07)
		6603				900 – 1350 mg		0.97 (0.81; 1.15)
		3314				1350 – 1800 mg		0.99 (0.78; 1.24)
		1980				1800 – 2250 mg		1.31 (1.02; 1.68)
		1363				2250 – 2700 mg		1.31 (0.99; 1.75)
		1645S				>2700 mg		1.28 (0.96; 1.70)
Roubille 2020 Rheumatology		5			No GC use	No GC use	p=0.009	
		30				GC use		
		5				Cumulative GC dose >0 – 1842 mg	p=0.024	
		10				1842 – 8421.5 mg		
		15				≥8421.5 mg		
Suda 2018 Clin Rheumatol					Daily GC dosing	**Any infection**		
		34				Daily GC dosing	Ref	Ref
		17				Alternate daily GC dosing	0.32 (0.16; 0.66)	0.27 (0.12; 0.63)
						Severe infection	p=0.67	
		4				Daily GC dosing		
		3				Alternate daily GC dosing		
Wilson 2019 Arthritis Care Res	816		15.1 (14.1; 16.1)		No GC use	No GC use		Ref
	737		19.4 (18.1; 20.8)			Ever GC use		**1.28 (1.11; 1.48)**

						Past GC use Current GC use		0.96 (0.88; 1.05) **1.52 (1.15; 2.01)**
						Cumulative GC dose <700 mg 700 to <3500 mg 3500 to <7000 mg ≥7000 mg		1.15 (0.83; 1.59) 1.06 (0.79; 1.43) 1.38 (0.92; 2.09) 1.29 (0.84; 1.99)

PEQ = prednisone equivalent dose, mg = milligrams, mg/d = milligrams/day, GC = glucocorticoid

Table 6.12: Infections: outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Boers 2022 Ann Rheum Dis	Dec 2018	2 years	No GC at baseline	Descriptive	Infection, including urinary tract, pneumonia, other	**Infections AE of special interest** standard treatment + prednisolone standard treatment + placebo	 124 91	
						Infections SAE standard treatment + prednisolone standard treatment + placebo	 26 16	
Burmester 2020 Lancet	Feb 2018	24 weeks	No	descriptive	Serious infections or infestations	tapered prednisone continued prednisone	1 1	
De Jong 2013 Ann Rheum Dis		3 months	Yes	descriptive	Infections	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		3 4 9
Den Uyl 2014 Ann Rheum Dis	Sep 2011	26 weeks	Yes	descriptive	Infections	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	34 33	
Konijn 2017 Rheumatology[a]	2015	4 years	Yes	Descriptive	Tuberculosis	MTX + PRED 30 mg/d MTX + SSZ + PRED 60 mg/d		0 0
Nam 2014 Ann Rheum Dis	Jul 2009	78 weeks	No GC within 1 month before study start	Descriptive	Infection gastrointestinal SAE	**Infection gastrointestinal SAE** MTX + infliximab MTX + i.v. methylprednisolone	 0 1	 0 1
					infection - pulmonary/upper respiratory SAE	**Infection pulmonary SAE** MTX + infliximab MTX + i.v. methylprednisolone	 2 1	 2 !
Verschueren 2015 Ann Rheum Dis[b]	Sep 2013	4 months	Yes	Descriptive	Infection	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d	5 3 5	
Verschueren 2015 Arthritis Res Ther[b]						LR: MTX + PRED 30 mg/d LR: MTX tight step-up	0 1	
Verschueren 2017 Ann Rheum Dis[b]	May 2014	1 year	Yes	Descriptive	Herpes zoster	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up	1 0 0 0 0	

Stouten 2019 Rheumatology[b]		2 years	Yes	Descriptive	Serious infections	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up		2 4 3 4 1
Stouten 2021 Ann Rheum Dis[b]		2 till 5 years	Yes	descriptive	Severe infections	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up	16 18 17 1 6	

[a]Long-term extension of the COBRA light trial (see Den Uyl 2014 Ann Rheum Dis).

[b]These studies refer to different follow-up durations (including a long-term extension, Stouten 2021 Ann Rheum Dis) of the CareRA trial.

MTX = methotrexate, LEF = leflunomide, SSZ = sulfasalazine, PRED = prednisone, HR = high risk, LR = low risk, i.v. = intravenous, i.m. = intramuscular, mg/d = milligrams/day, AE = adverse event, SAE = serious adverse event.

GC induced diabetes and hyperglycemia

Table 6.13: Diabetes mellitus: outcome definition and statistical analyses of observational studies

Study ID	End of follow-up	Follow-up time (years)	Patient years	Outcome definition	GC naïve at baseline?	Type of analysis	Adjusted for
Movahedi 2016 Arthritis Rheumatol	Dec 2009	median 5.4	**CPRD** Ever used GC: 48,300 Never used GC: 86,706 **NDB** Ever used GC: 5999 Never used GC: 9002	1) Read code for type 2 DM, 2) at least 2 prescriptions for oral antidiabetic medication (2 different medications or the same medication on 2 different dates), or 3) fasting blood sugar ≥7.0 mmoles/liter, random glucose level ≥11.1 mmoles/liter, glucose tolerance test result ≥11.1 mmoles/liter, or glycosylated hemoglobin (HbA1c) level ≥7%.	Mixed	Cox regression	Sex, age, history of hypertension, ever use of NSAIDs at cohort entry, concomitant time-varying use during follow-up of 4 main DMARDs, use of GCs in the 3 years prior to cohort entry; additionally adjusted for family history of diabetes mellitus in the CPRD.
Suda 2018 Clin Rheumatol	2015	1		Incident diabetes	Yes	Not specified	
Wilson 2019 Arthritis Care Res		Mean (SD) 8.1 (5.7)	GC use: 102,632 No GC use: 146,058 All: 248,690	Incident diabetes	Yes	Logistic regression	Alcohol status, smoking status, BMI, RA disease duration, prior history of osteoporosis, coronary heart disease, asthma, a prior prescription for a proton-pump inhibitor, diuretic, statin, and opioid.
Wu 2020 BMJ Open Diabetes Res Care	March 2017	Median (IQR) 4.9 (2.1; 6.0)		Incidence of type 2 diabetes, defined by the date of the first recorded diagnosis (Read and ICD10-codes, a recording of glycated hemoglobin (HbA1c) ≥7.0% (53 mmol/mol), or a fasting glucose result ≥7.0 mmol/L.	Mixed	Cox regression	Baseline age, sex, hypertension, prescribed non-oral GCs, blood pressure-lowering medication, underlying inflammatory disease type, time-variant use of DMARDs and NSAIDs; general practice identifier included as a random intercept to account for clustering effect.

GC = glucocorticoid, SD = standard deviation, IQR = inter quartile range, DM = diabetes mellitus, DMARD = disease modifying anti-rheumatic drugs, BMI = body mass index, RA = rheumatoid arthritis. CPRD and NDB are individual databases.

Table 6.14: Diabetes mellitus: outcomes of observational studies

Study ID	N events	N pts with event	IR (95% CI) / 1000 PY	Type of ratio	Ref category	Exposure definition	Unadjusted	Adjusted
Movahedi 2016 Arthritis Rheumatol				HR	No GC use	**CPRD** Ever GC use		**1.35 (1.22; 1.48)**
						Current GC use		**1.30 (1.17; 1.45)**
						Current GC dosage (5 mg/d)		**1.25 (1.19; 1.31)**
						Current GC dose 0 – 4.9 mg/d 5 – 9.9 mg/d		1.06 (0.87; 1.28) **1.16 (1.00; 1.34)**

						10 – 19.9 mg/d ≥20 mg/d		**1.97 (1.61; 2.40)** **3.19 (2.22; 4.58)**
						Cumulative GC dose last year per 1000 mg		**1.22 (1.17; 1.28)**
						Cumulative GC dose since cohort entry per 1000 mg		**1.02 (1.01; 1.03)**
						Cumulative GC dose since cohort entry 0 - 959.9 mg 960 – 3054.9 mg 3055 – 7298.9 mg ≥7299 mg		**1.23 (1.08; 1.40)** **1.41 (1.22; 1.62)** **1.35 (1.15; 1.57)** **1.53 (1.30; 1.79)**
						NDB Ever GC use		 **1.42 (1.22; 1.66)**
						Current GC use		**1.61 (1.37; 1.89)**
						Current GC dosage (5 mg/d)		**1.30 (1.21; 1.38)**
						Current GC dose 0 – 4.9 mg/d 5 – 9.9 mg/d 10 – 19.9 mg/d ≥20 mg/d		1.07 (0.80; 1.40) **1.58 (1.30; 1.93)** **2.24 (1.72; 2.93)** **3.06 (1.90; 4.91)**
						Cumulative GC dose last year per 1000 mg		**1.19 (1.14; 1.24)**
						Cumulative GC dose since cohort entry per 1000 mg		**1.03 (1.02; 1.05)**
						Cumulative GC dose since cohort entry 0 - 959.9 mg 960 – 3054.9 mg 3055 – 7298.9 mg ≥7299 mg		1.21 (0.97; 1.51) **1.36 (1.08; 1.70)** **1.68 (1.35; 2.11)** **1.67 (1.31; 2.12)**
Suda 2018 Clin Rheumatol	2 1					Daily GC dosing Alternate daily GC dosing	P=0.54	
Wilson 2019 Arthritis Care Res	908 554		6.22 (5.83; 6.63) 5.40 (4.97; 5.87)	OR	No GC use	No GC use GC use		Ref **1.33 (1.14; 1.56)**
						Past GC use Current GC use		1.09 (0.91; 1.29) **2.24 (1.76; 2.83)**
						Cumulative dose <700 mg 700 to <3500 3500 to <7000 ≥7000		**1.14 (1.00; 1.53)** **1.35 (1.08; 1.69)** **1.39 (1.03; 1.88)** **1.53 (1.12; 2.10)**
Wu 2020 BMJ Open Diabetes Res Care				HR	No GC use	Ever GC use		**1.41 (1.29; 1.54)**
						Current GC use		**2.01 (1.84; 2.20)**
						Current daily dose per 5 mg/d		**1.03 (1.02; 1.04)**
						Current daily dose >0 – 4.9 mg/d 5.0 – 14.9 mg/d 15.0 – 24.9 mg/d ≥25.0 mg/d		**1.66 (1.37; 2.02)** **1.90 (1.71; 2.12)** **3.07 (2.28; 4.14)** **4.00 (3.08; 5.21)**
						Cumulative dose per 1000 mg		**1.02 (1.01; 1.02)**
						Cumulative dose 1.0 – 959.9 mg 960.0 – 3054.9 mg 3055.0 – 7299.9 mg ≥7300 mg		**1.17 (1.04; 1.32)** **1.44 (1.25; 1.65)** **1.58 (1.8; 1.82)** **1.61 (1.42; 1.81)**

GC = glucocorticoid, mg = milligrams, mg/d = milligrams/day. CPRD and NDB are individual databases.

Table 6.15: Diabetes mellitus: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Boers 2022 Ann Rheum Dis	Dec 2018	2 years	No GC at baseline	Descriptive	Diabetes	standard treatment + prednisolone standard treatment + placebo		2 1
Burmester 2020 Lancet	Feb 2018	24 weeks	No	descriptive	Blood glucose fluctuation	tapered prednisone continued prednisone	1 0	
De Jong 2013 Ann Rheum Dis		3 months	Yes	descriptive	Hyperglycemia	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs	0 1 0	
Den Uyl 2014 Ann Rheum Dis	Sep 2011	26 weeks	Yes	descriptive	Incident diabetes	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d		2 0
Konijn 2017 Rheumatology[a]		4 years	Yes	descriptive	Diabetes	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d		1 3
Ding 2012 Curr Ther Res Clin Exp	Jul 2011	12 weeks	No GC within 3 months before study start	Descriptive	Diabetes 4 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		4 3 4
					Diabetes 4 to 12 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		13 8 4
Sadra 2014 Int J Rheum Dis	Jul 2022	30 days		Descriptive	Hyperglycemia	standard treatment + methylprednisolone standard treatment + dexamethasone	2 0	
Stouten 2021 Ann Rheum Dis[b]		2 till 5 years	Yes	descriptive	Diabetes	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up		2 1 0 0 0

[a]Long-term extension of the COBRA light trial (see Den Uyl 2014 Ann Rheum Dis).

[b]Long-term extension of the CareRA trial (see Verschueren 2017 Ann Rheum Dis.

MTX = methotrexate, SSZ = sulfasalazine, HCQ = hydroxychloroquine, i.m. = intramuscular, GC = glucocorticoid, PRED = prednisone, HR = high risk, LR = low risk.

Mortality

Table 6.16: Mortality: outcome definition and statistical analyses of observational studies

Study ID	End of follow-up	Follow-up time (years)	Patient years	Outcome definition	GC naïve at baseline?	Type of analysis	Adjusted for
del Rincón 2014 Arthritis Rheumatol	April 2001	median 10.3 (range 1 day - 14.2 years)	No GC use: 2535 GC use: 4668	Mortality, reported by family, friends, obituaries, neighbors, physicians, and the public health department. Online mortality databases were searched monthly. Further efforts were made to ascertain vital status by contacting patients directly. For remaining cases medical records were reviewed. All deaths were confirmed by death certificate.	Mixed	Cox regression	GC propensity score, predicted using age at RA onset, RA duration, sex, race, socioeconomic status, counts of tender, swollen, and deformed joints, presence of subcutaneous nodules, presence of rheumatoid factor, ESR, RA severity, presence of diabetes mellitus, hypercholesterolemia, hypertension, cigarette smoking and BMI.
Movahedi 2016 Eur J Epidemiol	October 2011	Median 6.1	No GC use: 66,650 GC use: 44,538	All-cause mortality: ICD10 codes with a specified underlying cause of death.	Mixed	Cox regression	Gender, age, BMI, smoking status, socioeconomic status, prior 1 year cumulative GC dose at baseline, baseline Charlson comorbidity index, time-varying use of the DMARDs MTX, HCQ, SSZ and LEF, use of other DMARDs (penicillamine, azathioprine, cyclosporin, injectable gold) and time-varying use of NSAIDs
Roubille 2020 Rheumatology		Mean (SD) 8.66 (2.58)		All-cause mortality	Yes	Cox regression	None
Wilson 2019 Arthritis Care Res		Mean (SD) 8.1 (5.7)	No GC use: 159,402 GC use: 116,715	Death	Yes	Logistic regression	Alcohol status, smoking status, BMI, prior history of diabetes mellitus, COPD, CCI score, a prior prescription for aspirin, opioid, PPI, and bisphosphate

SD = standard deviation, GC = glucocorticoid, RA = rheumatoid arthritis, BMI = body mass index, DMARD = disease modifying anti-rheumatic drugs, MTX = methotrexate, HCQ = hydroxychloroquine, SSZ = sulfasalazine, LEF = leflunomide, COPD = chronic obstructive pulmonary disease, PPI = proton pump inhibitor.

Table 6.17: Mortality: outcomes of observational studies

Study ID	N events	N pts with event	IR (95% CI) / 1000 PY	Type of ratio	Ref category	Exposure definition	Unadjusted	Adjusted
del Rincón 2014 Arthritis Rheumatol		95 22 69 42 9		HR	No GC use	Daily dose none Daily dose <5 mg/d 5 – 7 mg/d 8 – 15 mg/d ≥15 mg/d	Ref 1.38 (0.87; 2.20) **1.51 (1.11; 2.06)** **2.58 (1.79; 3.71)** **3.98 (2.01; 7.90)**	Ref 1.19 (0.74; 1.90) 1.21 (0.88; 1.66) **1.78 (1.22; 2.60)** **2.83 (1.41; 5.66)**
		61 23 50 103				Cumulative dose none Cumulative dose <9 mg 9 – 39.9 mg ≥40 mg	Ref 0.63 (0.39; 1.03) 1.38 (0.95; 2.01) **2.46 (1.78; 3.39)**	Ref 0.59 (0.36; 0.95) **1.12 (0.76; 1.64)** **1.74 (1.25; 2.44)**
		61 20 48 108				Dose/time no GCs <1.98 mg/year 1.98 – 5.08 mg/year ≥5.08 mg/year	Ref 0.51 (0.30; 0.85) 1.23 (0.84; 1.80) **2.93 (2.14; 4.03)**	Ref 0.48 (0.29; 0.80) 0.99 (0.67; 1.45) **2.11 (1.51; 2.94)**
Movahedi 2016 Eur J Epidemiol		1034 1962	15.5 (14.6; 16.5) 44.0 (42.1; 46.0)	HR	No GC use	Never GC use Ever GC use		Ref **1.97 (1.81; 2.15)**
						Current GC use		**1.77 (1.62; 1.93)**
						Current GC dose per 5 mg/d		**1.33 (1.30; 1.35)**
						Current dose >0 – 4.9 mg/d 5.0 – 7.4 mg/d 7.5 – 14.9 mg/d 15.0 – 24.9 mg/d ≥25 mg/d		1.02 (0.87; 1.20) **1.44 (1.26; 1.64)** **2.24 (1.98; 2.54)** **4.50 (3.61; 5.62)** **11.0 (8.87; 13.6)**
						Cumulative dose since cohort entry (1000 mg/d)		**1.06 (1.05; 1.07)**
						Cumulative dose >9 – 959.9 mg 960 – 3054.9 mg 3055 – 7299.9 mg ≥7300 mg		**1.60 (1.42; 1.81)** **1.83 (1.62; 2.07)** **2.11 (1.87; 2.39)** **3.11 (2.74; 3.52)**
Roubille 2020 Rheumatology		1 9			No GC use	No GC use GC use	P=0.103	
		1 4 4				Cumulative GC dose >0 – 1842 mg 1842 – 8421.5 mg ≥8421.5 mg	P=0.248	
Wilson 2019 Arthritis Care Res		1579 2074	9.9 (9.4; 10.4) 17.8 (17.0; 18.5)	OR	No GC use	No GC use GC use		Ref 1.33 (1.19; 1.48)
						Past GC use Current GC use		1.03 (0.97; 1.10) **1.80 (1.59; 2.04)**
						Cumulative GC dose <700 mg 700 to <3500 mg 3500 to <7000 mg ≥7000 mg		0.90 (0.76; 1.07) **1.27 (1.10; 1.48)** **1.42 (1.18; 1.71)** **2.33 (1.95; 2.77)**

HR = hazard ratio, OR = odds ratio, GC = glucocorticoid, mg = milligrams, mg/d = milligrams/day.

Table 6.18: Mortality: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Boers 2022 Ann Rheum Dis	Dec 2018	2 years	No GC at baseline	descriptive	Death	standard treatment + prednisolone standard treatment + placebo		3 2
Konijn 2017 Rheumatology[a]	2015	4 years	Yes	descriptive	Deceased	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d		2 3
Stouten 2019 Rheumatology[b]		2 years	Yes	descriptive	Deceased	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up		1 1 0 0 0

[a]Long-term extension of the COBRA light trial (see Den Uyl 2014 Ann Rheum Dis).

[b]Long-term extension of the CareRA trial (see Verschueren 2017 Ann Rheum Dis).

MTX = methotrexate, SSZ = sulfasalazine, LEF = leflunomide, PRED = prednisone, mg/d = milligrams/day.

Adverse pregnancy outcomes

Table 6.19: Adverse pregnancy outcomes: outcome definition and statistical analyses of observational studies

Study ID	End of follow-up	Follow-up time (years)	Patient years	Outcome definition	GC naïve at baseline?	Type of analysis	Adjusted for
Palmsten 2020 Rheumatology	2014	Duration of pregnancy	No GC use: 7415 weeks GC use: 4530 weeks	Preterm birth, delivery between 140 and <259 gestational days.	Mixed	Cox regression	Quintiles of the propensity score: last menstrual period year, maternal age, race and ethnicity, multiple gestation, ≥5 servings of alcohol in the first trimester, autoimmune disease comorbidity (IBD, lupus or ankylosing spondylitis), oral corticosteroid cumulative dose trajectory before gestational day 110, NSAID before gestational day 110, HAQ, pain score and global score at enrolment.

GC = glucocorticoid, IBD = inflammatory bowel disease, HAQ = health assessment questionnaire.

Table 6.20: Adverse pregnancy outcomes: outcomes of observational studies

Study ID	N events	N pts with event	IR (95% CI) / 1000 PY	Type of ratio	Ref category	Exposure definition	Unadjusted	Adjusted
Palmsten 2020 Rheumatology		31 51	4.2 11.3 (per 1000 weeks)	HR	No GC use	No oral GC use Oral GC use after gestational day 139	Ref **2.81 (1.80; 4.39)**	Ref **1.83 (1.01; 3.32)**
		19 32	7.3 17.4 (per 1000 weeks)			Oral GC use <10 mg/d after gestational day 139 Oral GC use ≥10 mg/d after gestational day 139	**1.80 (1.02; 3.19)** **4.57 (2.79; 7.49)**	1.23 (0.63; 2.41) **2.47 (1.32; 4.63)**

HR = hazard ratio, GC = glucocorticoid, mg/d = milligrams/day.

Glaucoma

Table 6.21: Glaucoma: outcome definition and statistical analyses of observational studies

Study ID	End of follow-up	Follow-up time (years)	Patient years	Outcome definition	GC naïve at baseline?	Type of analysis	Adjusted for
Wilson 2019 Arthritis Care Res		Mean (SD) 8.1 (5.7)	GC use: 109,086 No GC use: 152,824	Glaucoma	Yes	Logistic regression	Alcohol status, smoking status, BMI, RA disease duration, prior history of asthma, autoimmune disease, a prior prescription for a DMARD, and ocular steroid use.

SD = standard deviation, GC = glucocorticoid, BMI = body mass index, RA = rheumatoid arthritis, DMARD = disease modifying anti-rheumatic drugs.

Table 6.22: Glaucoma: outcomes of observational studies

Study ID	N events	N pts with event	IR (95% CI) / 1000 PY	Type of ratio	Ref category	Exposure definition	Unadjusted	Adjusted
Wilson 2019 Arthritis Care Res	278 195		1.82 (1.62; 2.05) 1.79 (1.55; 2.06)	OR	No GC use	No GC use GC use		Ref 1.26 (0.98; 1.62)
						Past GC use Current GC use		1.25 (0.95; 1.64) 1.27 (0.87; 1.84)
						Cumulative dose <700 mg 700 to <3500 mg 3500 to <7000 mg ≥7000 mg		1.07 (0.74; 1.55) **1.53 (1.10; 2.13)** 0.76 (0.45; 1.28) **1.71 (1.07; 2.72)**

OR = odds ratio, GC = glucocorticoid, mg = milligrams.

Table 6.23: Glaucoma: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Bakker 2012 Ann Int Med	2008	2 years	yes	descriptive	Glaucoma	MTX + PRED MTX + placebo	0 1	
Boers 2022 Ann Rheum Dis	Dec 2018	2 years	No GC at baseline	descriptive	Glaucoma	standard treatment + prednisolone standard treatment + placebo	1 3	
Konijn 2017 Rheumatology[a]		4 years	Yes	descriptive	Glaucoma	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	0 1	

[a]Long-term extension of the COBRA light trial (see Den Uyl 2014 Ann Rheum Dis).

MTX = methotrexate, PRED = prednisone, SSZ = sulfasalazine, GC = glucocorticoid, mg/d = milligrams/day.

Hair loss

Table 6.24: Hair loss: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Bakker 2012 Ann Int Med	2008	2 years	yes	descriptive	Hair loss	MTX + PRED MTX + placebo	10 17	
De Jong 2013 Ann Rheum Dis		3 months	Yes	descriptive	Hair loss	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		3 2 6

MTX = methotrexate, PRED = prednisone, SSZ = sulfasalazine, HCQ = hydroxychloroquine, i.m. = intramuscular, GC = glucocorticoid.

Malaise

Table 6.24: Malaise: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
De Jong 2013 Ann Rheum Dis		3 months	Yes	Descriptive	Malaise	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		11 8 9
Verschueren 2015 Ann Rheum Dis[a]	Sep 2013	4 months	Yes	Descriptive	Discomfort	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d	111 50 96	
Verschueren 2015 Arthritis Res Ther[a]						LR: MTX + PRED 30 mg/d LR: MTX tight step-up	0 0	
Verschueren 2017 Ann Rheum Dis[a]	May 2014	1 year	Yes	Descriptive	General malaise, including excessive warmth/sweating, palpitations, nervousness, general malaise, fatigue, headache, vertigo, insomnia, shortness of breath, energy loss, euphoria, migraine.	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up	52 22 30 11 12	

[a]These studies refer to different follow-up durations of the CareRA trial.

MTX = methotrexate, SSZ = sulfasalazine, HCQ = hydroxychloroquine, i.m. = intramuscular, GC = glucocorticoid, HR = high risk, LR = low risk, mg/d = milligrams/day.

Cancer

Table 6.25: Cancer: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Boers 2022 Ann Rheum Dis	Dec 2018	2 years	No GC at baseline	descriptive	Cancer, lung, basal cell carcinoma, meningioma	**Neoplasms SAE** standard treatment + prednisolone standard treatment + placebo	 2.5/100 PY 2.0/100 PY	
						Neoplasms other AESI standard treatment + prednisolone standard treatment + placebo	 1.1/100 PY 0.3/100 PY	
Konijn 2017 Rheumatology[a]	2015	4 years	Yes	Descriptive	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	MTX + PRED 30 mg/d MTX + SSZ + PRED 60 mg/d	5 2	

[a]Long-term extension of the COBRA light trial (see Den Uyl 2014).

PY = patient years, GC = glucocorticoid, SAE = serious adverse event, AESI = adverse event of special interest, PRED = prednisone, pts = patients

Hematological

Table 6.26: Hematological: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Bakker 2012 Ann Int Med	2008	2 years	yes	descriptive	Leukopenia	MTX + PRED MTX + placebo	0 1	
					Thrombocytopenia	MTX + PRED MTX + placebo	0 1	
					Anemia	MTX + PRED MTX + placebo	0 0	
Burmester 2020 Lancet	Feb 2018	24 weeks	No	descriptive	Neutropenia	tapered prednisone continued prednisone	1 0	
Ding 2012 Curr Ther Res Clin Exp	Jul 2011	12 weeks	No GC within 3 months before study start	Descriptive	Leukocyte decrease 4 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		2 2 7
					Leukocyte decrease 4 to 12 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		2 2 10
Hua 2020 Medicine	May 2016	1 year	Yes	descriptive	Leukopenia	MTX + HCQ + PRED MTX + HCQ + placebo	0 3	
Verschueren 2017 Ann Rheum Dis	May 2014	1 year	Yes	descriptive	Blood level related AEs ,including anemia, leukopenia, calcemia, iron deficiency, pancytopenia	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up	7 3 4 0 2	

MTX = methotrexate, PRED = prednisone, HCQ = hydroxychloroquine, HR = high risk, LR = low risk, mg/d = milligrams/day.

Renal and kidney function

Table 6.27: Renal and kidney function: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Bakker 2012 Ann Int Med	2008	2 years	yes	Descriptive	liver toxicity, including alanine aminotransferase levels >ULN, aspartate aminotransferase level >ULN, y-glutamyltransferase levels >ULN, alkaline phsophate levesl >ULN	MTX + PRED MTX + placebo	15 33	
					Creatinine level increase	MTX + PRED MTX + placebo	2 1	
De Jong 2013 Ann Rheum Dis		3 months	Yes	Descriptive	High creatinine	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		0 6 3
					Raised liver enzymes	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		4 7 9
Ding 2012 Curr Ther Res Clin Exp	Jul 2011	12 weeks	No GC within 3 months before study start	Descriptive	alanine aminotransferase 4 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		6 5 9
					alanine aminotransferase 4 to 12 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		8 6 17
Hua 2020 Medicine	May 2016	1 year	Yes	Descriptive	Liver dysfunction	MTX + HCQ + PRED MTX + HCQ + placebo	4 4	
Nam 2014 Ann Rheum Dis	Jul 2009	78 weeks	No GC within 1 month before study start	Descriptive	hepatobiliary/pancreas SAE	MTX + infliximab MTX + i.v. methylprednisolone	1 1	1 1
Verschueren 2017 Ann Rheum Dis	May 2014	1 year	Yes	Descriptive	Kidney function abnormality	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up	1 0 0 2 0	
					Liver function abnormality	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up	17 17 22 6 3	

MTX = methotrexate, PRED = prednisone, SSZ = sulfasalazine, HCQ = hydroxychloroquine, i.m. = intramuscular, GC = glucocorticoid, LEF = leflunomide, HR = high risk, LR = low risk, SAE = serious adverse event.

Gastrointestinal

Table 6.28: Gastrointestinal: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Bakker 2020 Ann Int Med	2008	2 years	yes	descriptive	Gastrointestinal, including nausea, diarrhea and stomachache	MTX + PRED MTX + placebo	46 69	
Boers 2020 Ann Rheum Dis	Dec 2018	2 years	No GC at baseline	descriptive	Gastrointestinal disorders SAE	standard treatment + prednisolone standard treatment + placebo	1.7/100 PY 2.0/100 PY	
					Gastrointestinal disorders any AE	standard treatment + prednisolone standard treatment + placebo	6.2/100 PY 5.6/100 PY	
Burmester 2020 Lancet	Feb 2018	24 weeks	No	descriptive	Gastrointenstinal perforations	tapered prednisone continued prednisone	0 0	
De Jong 2013 Ann Rheum Dis		3 months	Yes	descriptive	Gastrointestinal complaints	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		43 46 25
Den Uyl 2014 Ann Rheum Dis	Sep 2011	26 weeks	Yes	descriptive	Mild gastrointestinal problems	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	34 35	
Konijn 2017 Rheumatology[a]	2015	4 years	Yes	Descriptive	Any gastrointestinal event	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	1 3	
Ding 2012 Curr Ther Res Clin Exp	Jul 2011	12 weeks	No GC within 3 months before study start	Descriptive	Gastrointestinal 4 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		8 8 6
					Gastrointestinal 4 to 12 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		10 10 8
Hua 2020 Medicine	May 2016	1 year	Yes	descriptive	Gastrointestinal reactions	MTX + HCQ + PRED MTX + HCQ + placebo	5 3	
Nam 2014 Ann Rheum Dis	Jul 2009	78 weeks	No GC within 1 month before study start	Descriptive	Gastrointestinal SAE	MTX + infliximab MTX + i.v. methylprednisolone	0 1	0 1
Verschueren 2017 Ann Rheum Dis	May 2014	1 year	Yes	Descriptive	Gastrointestinal tract related AEs, including abdominal pain/upset, nausea, diarrhoea, constipation, reflux/heartburn, vomiting, flatulence	HR: MTX + SSZ + PRED 60 mg/d HR: MTX + PRED 30 mg/d HR: MTX + LEF + PRED 30 mg/d LR: MTX + PRED 30 mg/d LR: MTX tight step-up	45 48 67 20 15	

[a]Long-term extension of the COBRA light trial (see Den Uyl 2014 Ann Rheum Dis).

GC = glucocorticoid, MTX = methotrexate, PRED = prednisone, SSZ = sulfasalazine, HCQ = hydroxychloroquine, i.m. = intramuscular, LEF = leflunomide, mg/d = milligrams/day, AE = adverse event, SAE = serious adverse event, HR = high risk, LR = low risk, PY = person years.

Non-infectious skin AE

Table 6.29: Non-infectious skin AE: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Den Uyl 2014 Ann Rheum Dis	Sep 2011	26 weeks	Yes	Descriptive	Skin problems	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	30 36	
Ding 2012 Curr Ther Res Clin Exp	Jul 2011	12 weeks	No GC within 3 months before study start	Descriptive	Rash 4 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		0 2 7
					Rash 4 to 12 weeks	MTX + LEF + PRED 15 mg/d MTX + LEF + PRED 7.5 mg/d MTX + LEF + placebo		0 2 9

MTX = methotrexate, SSZ = sulfasalazine, PRED = prednisone.

Unspecified (S)AE

Table 6.30: Unspecified (S)AE: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Boers 2022 Ann Rheum Dis	Dec 2018	2 years	No GC at baseline	descriptive	Number of adverse events of special intereest	standard treatment + prednisolone standard treatment + placebo		134 111
					Number of SAEs	standard treatment + prednisolone standard treatment + placebo		25 25
Burmester 2020 Lancet	Feb 2018	24 weeks	No	descriptive	Any treatment emergent AE	tapered prednisone continued prednisone		80 64
					Any treatment emergent SAE	tapered prednisone continued prednisone	7 4	
Buttgereit 2013 Ann Rheum Dis	Feb 2009	12 weeks	No GC within 6 weeks from initiation	descriptive	Number of AEs	standard treatment + MR prednisone standard treatment + placebo	99 58	
					Number of SAEs	standard treatment + MR prednisone standard treatment + placebo	1 2	
de Jong 2013 Ann Rheum Dis		3 months	Yes	descriptive	Patients with AEs	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		61 67 50
					Patients with SAEs	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		1 4 6
den Uyl 2014 Ann Rheum Dis	Sep 2011	26 weeks	Yes	descriptive	SAE (non-planned)	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	1 2	

Nam 2014 Ann Rheum Dis	Jul 2009	78 weeks	No GC within 1 month before study start	Descriptive	Number of AEs	MTX + infliximab MTX + i.v. methylprednisolone	369 372	54 54
					Number of SAEs	MTX + infliximab MTX + i.v. methylprednisolone	20 9	13 9
Verschueren 2015 Ann Rheum Dis[a]	Sep 2013	4 months	Yes	Descriptive	Therapy-related AEs	High risk: MTX + SSZ + PRED 60 mg/d High risk: MTX + PRED 30 mg/d High risk: MTX + LEF + PRED 30 mg/d	148 70 130	
Verschueren 2015 Arthritis Res Ther[a]						Low risk: MTX + PRED 30 mg/d Low risk: MTX tight step-up	30 32	
					Therapy-related SAEs	High risk: MTX + SSZ + PRED 60 mg/d High risk: MTX + PRED 30 mg/d High risk: MTX + LEF + PRED 30 mg/d	2 1 3	
						Low risk: MTX + PRED 30 mg/d Low risk: MTX tight step-up	0 0	
Verschueren 2017 Ann Rheum Dis[a]	May 2014	1 year	Yes	Descriptive	Total number of AEs	High risk: MTX + SSZ + PRED 60 mg/d High risk: MTX + PRED 30 mg/d High risk: MTX + LEF + PRED 30 mg/d Low risk: MTX + PRED 30 mg/d Low risk: MTX tight step-up	394 353 452 150 150	
					GC related AEs	High risk: MTX + SSZ + PRED 60 mg/d High risk: MTX + PRED 30 mg/d High risk: MTX + LEF + PRED 30 mg/d Low risk: MTX + PRED 30 mg/d Low risk: MTX tight step-up	9 5 7 0 0	
					Total number of SAEs	High risk: MTX + SSZ + PRED 60 mg/d High risk: MTX + PRED 30 mg/d High risk: MTX + LEF + PRED 30 mg/d Low risk: MTX + PRED 30 mg/d Low risk: MTX tight step-up	15 15 10 7 7	
Stouten 2019 Rheumatology[a]		2 years	Yes	descriptive	Total number of AEs	High risk: MTX + SSZ + PRED 60 mg/d High risk: MTX + PRED 30 mg/d High risk: MTX + LEF + PRED 30 mg/d Low risk: MTX + PRED 30 mg/d Low risk: MTX tight step-up	209 164 208 63 69	72 69 74 28 34
					Total number of SAEs	High risk: MTX + SSZ + PRED 60 mg/d High risk: MTX + PRED 30 mg/d High risk: MTX + LEF + PRED 30 mg/d Low risk: MTX + PRED 30 mg/d Low risk: MTX tight step-up	29 29 25 10 11	21 22 16 9 7
Stouten 2021 Ann Rheum Dis		2 till 5 years	Yes	descriptive	Total number of AEs	High risk: MTX + SSZ + PRED 60 mg/d High risk: MTX + PRED 30 mg/d High risk: MTX + LEF + PRED 30 mg/d Low risk: MTX + PRED 30 mg/d Low risk: MTX tight step-up	70 95 80 18 36	36 48 36 10 17

					Total numbrer of SAEs	High risk: MTX + SSZ + PRED 60 mg/d High risk: MTX + PRED 30 mg/d High risk: MTX + LEF + PRED 30 mg/d Low risk: MTX + PRED 30 mg/d Low risk: MTX tight step-up	9 20 11 3 6	7 15 11 2 6

[a]These studies refer to different follow-up durations of the CareRA trial, includings its long-term follow-up.

MTX = methotrexate, SSZ = sulfasalazine, HCQ = hydroxychloroquine, i.m. = intramuscular, GC = glucocorticoid, PRED = prednisone, LEF = leflunomide, HR = high risk, LR = low risk, AE = adverse event, SAE = serious adverse event, mg/d = milligrams/day.

Depression and mood disturbances

Table 6.31: Depression/mood disturbances: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
De Jong 2013 Ann Rheum Dis		3 months	Yes	Descriptive	Feeling sad	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		2 9 8

MTX = methotrexate, SSZ = sulafsalazine, HCQ = hydroxychloroquine, i.m. = intramuscular, GC = glucocorticoid.

Cataract

Table 6.32: Cataract: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Bakker 2012 Ann Int Med	2008	2 years	yes	descriptive	Cataract	MTX + PRED MTX + placebo	1 0	
Boers 2022 Ann Rheum Dis	Dec 2018	2 years	No GC at baseline	descriptive	Cataract SAE	standard treatment + prednisolone standard treatment + placebo	0 2	
					Cataract AESI	standard treatment + prednisolone standard treatment + placebo	7 6	
Konijn 2017 Rheumatology[a]	2015	4 years	Yes	Descriptive	Cataract	MTX + SSZ + PRED 60 mg/d MTX + PRED 30 mg/d	5 3	

[a]Long-term extension of the COBRA light trial (see Den Uyl 2014 Ann Rheum Dis).

GC = glucocorticoid, PRED = prednisone, MTX = methotrexate, SSZ = sulfasalazine, SAE = serious adverse event, AESI = adverse event of special interest.

Dizziness

Table 6.33: Dizziness: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Bakker 2012 Ann Int Med	2008	2 years	yes	Descriptive	Dizziness	MTX + PRED MTX + placebo	19 15	
De Jong 2013 Ann Rheum Dis		3 months	Yes	Descriptive	Dizziness	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		1 7 1

MTX = methotrexate, PRED = prednisone, SSZ = sulfasalazine, HCQ = hydroxychloroquine, i.m. = intramuscular, GC = glucocorticoid

Headache

Table 6.34: Headache: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Bakker 2012 Ann Int Med	2008	2 years	yes	descriptive	Headache	MTX + PRED MTX + placebo	23 31	
Buttgereit 2013 Ann Rheum Dis	Feb 2009	12 weeks	No GC within 6 weeks from initiation	descriptive	Headache	standard treatment + MR prednisone standard treatment + placebo	99 58	
De Jong 2013 Ann Rheum Dis		3 months	Yes	descriptive	Headache	MTX + SSZ + HCQ + i.m. GCs MTX + SSZ + HCQ + oral GCs MTX + oral GCs		8 10 8
Sadra 2014 Int J Rheum Dis	Jul 2022	30 days		Descriptive	Headache	standard treatment + methylprednisolone standard treatment + dexamethasone	2 1	

MTX = methotrexate, PRED = prednisone, MR = modified release, SSZ = sulfasalazine, HCQ = hydroxychloroquine, i.m. = intramuscular, GC = glucocorticoid

Flushing

Table 6.35: Flushing: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Sadra 2014 Int J Rheum Dis	Jul 2022	30 days		Descriptive	Flushing	standard treatment + methylprednisolone standard treatment + dexamethasone	1 3	

Non-infectious pulmonary AEs

Table 6.36: Non-infectious pulmonary AEs: Outcome definition and outcomes of clinical trials

Study ID	End of follow-up	Follow-up time	GC naïve at baseline?	Type of analysis	Outcome definition	Exposure definition	N events	N pts with event
Nam 2014 Ann Rheum Dis	Jul 2009	78 weeks	No GC within 1 month before study start	Descriptive	Pain - pulmonary/upper respiratory SAE	MTX + infliximab MTX + i.v. methylprednisolone	1 0	1 0
					Pulmonary/upper respiratory SAE	MTX + infliximab MTX + i.v. methylprednisolone	4 0	4 0

GC = glucocorticoid, MTX = methotrexate, i.v. = inravenous, SAE = serious adverse event