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ABSTRACT

Objective To investigate the success rate of glucocorticoid (GC) discontinuation during follow-up in observational cohorts and clinical trials using temporary GC as part of initial therapy ('bridging') in newly diagnosed patients with rheumatoid arthritis (RA).

Methods Systematic literature searches were conducted to identify observational cohorts and clinical trials including patients with RA treated with initial GC bridging therapy, defined as discontinuation of GC within 1 year. Patient percentages still using GC were considered the reverse of successful discontinuation. Random effects meta-analyses were performed stratified by time point.

Results The scoping literature search for observational cohort studies could not identify studies answering the research question. The literature search for clinical trials identified 7160 abstracts, resulting in 10 included studies, with varying type and dose of GC and varying tapering schedules, of which 4 reported sufficient data on GC discontinuation or use after the bridging phase. The pooled proportion of patients who were still or again using GC was 22% (95% CI 8% to 37%, based on four trials) at 12 months and 10% at 24 months (95% CI −1 to 22, based on two trials). Heterogeneity was substantial ($I^2 \geq 65\%$).

Conclusion The success rate of GC discontinuation after bridging as part of initial treatment of RA has been described in a limited number of studies. Reports on observational cohorts did not answer the research question. In clinical trials, protocolised discontinuation was mostly successful, although 22% of the patients who started GC bridging therapy still or again used GC at 12 months, and 10% at 24 months.

INTRODUCTION

Glucocorticoids (GC) are widely used for the initial treatment of rheumatoid arthritis (RA), to induce rapid suppression of inflammation and clinical symptoms, thereby limiting radiographic damage progression.[1–3] It has been repeatedly shown in clinical trials that in newly diagnosed patients with RA, adding GC to initial treatment with conventional synthetic (cs)DMARD(s) is more effective than csDMARD treatment alone.[4–9] Due to the fast acting mechanism of GC, treatment with GC leads to rapid clinical improvement, before DMARD treatment is fully effective.[4 10] However, there are concerns that GC use in the long term is associated with a dose and duration dependent risk of serious side effects, including among others cardiovascular disease, infections and increased mortality.[11–17] Therefore, international guidelines have recommended to start GC when initiating a csDMARD, but to discontinue treatment with GC as rapidly as clinically feasible, preferably within 3 months.[18] This is often called 'bridging therapy'. Data from current daily practice cohorts show that in accordance with these recommendations, GC are indeed started in the majority of patients.[19 20] Recently, concerns have been expressed that in many patients it may be difficult to discontinue GC.[21] This could lead to longer-term use of GC than is generally recommended, and thereby to an increased risk of serious side effects. However, it is still uncertain to what extent this continued use occurs, in routine practice or in clinical trials that assign GC unbiased and include protocolised GC tapering. We systematically reviewed the literature to investigate in how many patients the intended GC discontinuation was successful (success rate), in both observational cohorts reflecting real-world data and in clinical trials with selected patients where GC were used as (part of) the initial therapy in newly diagnosed patients with RA.

METHODS

This systematic literature review (SLR) and meta-analysis consists of two parts (observational cohorts and clinical trials) and was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22] While the cohort part was designed to provide an overview of real-world data in a scoping way, the trial part was designed as an in-depth systematic review. Neither patients nor public representatives were involved in design, conduct, reporting or dissemination of this project.

SLR of observational cohorts

A scoping systematic literature search was conducted by AP and FB in MEDLINE to find

articles published from 2005 onwards investigating observational cohorts reporting on early or methotrexate (MTX)-naive patients with RA starting or using GC at baseline. The objective of this scoping literature search was to evaluate how many people use GC in observational cohorts and at which dose and to see how this proportion and dose changes over time. The year 2005 was chosen as the lower bound of publication year because we did not want to confound our analysis by including older studies with fewer treatment options than today. Since observational cohorts in general have a higher generalisability, we aimed for a specific search strategy. Cohort studies could be included if the proportion of patients who started GC at baseline and were still taking GC over time were reported. Also, to be eligible for inclusion, these outcomes had to be reported at, at least two prespecified time points (baseline, 3, 6, 9, 12 and/or 24 months). For the complete search strategy, see online supplemental appendix I. Articles were screened by one experienced researcher (AP).

SLR of clinical trials

A systematic literature search was conducted in MEDLINE, Embase, Web of Science, the Cochrane Library, Emcare and Academic Search Premier to identify clinical trials investigating newly diagnosed DMARD naïve patients with RA treated with initial GC bridging with at least 12 months follow-up. It was required that initial bridging therapy was tapered within the first 6 months after start of GC and discontinued within 1 year after initiation. The search included three components: "rheumatoid arthritis", "glucocorticoids" and "randomized controlled trial" (for the complete search strategy, see online supplemental appendix I). We aimed for a sensitive search including meeting abstracts, to ensure the inclusion of all available trials. Studies were excluded if GC were given only as intra-articular injections, or if no full text was available. From the included abstracts, the full text was analysed, and the same decision rule was used to exclude articles. For this in- and exclusion process of articles the programme Rayyan was used.[23]

Heterogeneity of the finally included studies was assessed based on predefined items. These items describe patient characteristics and details about treatment protocols (online supplemental table 1). Studies were furthermore assessed to extract the following information (if available): proportion of GC use and/or rates of GC discontinuation at 1, 3, 6, 12, 18 and 24 months, number of episodes of GC use (intra-articular and intramuscular included) after the induction scheme, number of cumulative GC injections at 4, 12 and 24 months, maintenance dose (before tapering) of GC after induction scheme, proportion of flares after discontinuation of GC, mean or median duration of GC use after restart, Disease Activity Score (DAS) (28) at 12 and 24 months in patients who stopped GC and in patients who did not stop GC, proportion of patients with DMARD adaptation after GC discontinuation and DMARD dose in patients who stopped GC and in patients who did not stop GC. Studies that did not report an outcome of interest were not included in the analyses for that outcome. Data collection was conducted by three researchers (LvO, ISN and SAB) for four included articles as a training set, the remaining articles were assessed separately. In case of at least three available studies per outcome, a meta-analysis with random effects using a restricted maximum-likelihood estimation for proportions was performed using R V.4.1.0 software with package metafor. To stabilise variances in case of proportions close to or at the 0 or 100 margins, the Double Arcsine transformation was used.[24] We used I^2 as an effect estimate to describe the proportion of variability caused by heterogeneity (and not random error) between the included trials. Standard errors were obtained from proportions using the recommendations provided by the Cochrane Handbook.[25]

The Cochrane risk of bias (RoB) tool 2 was used to assess the quality of the included studies.[26] The RoB assessment was conducted by two researchers (LvO and ISN) for four included articles as a training set, the remaining articles were assessed separately and discussed afterwards with an adjudicator (SAB) in case of doubt.

RESULTS

Observational cohorts

Eleven cohorts were identified that evaluated GC use over time. However, none of them were included in this SLR as not all patients in the cohorts started GC at baseline and no separate results were reported for the patients who did (online supplemental figure 1). One study that was published in 2021 did fit our research question regarding the use of GC as bridging therapy, but only reported cumulative probabilities over time. In the early DMARD naïve patients with RA, the cumulative probability of GC discontinuation was 29.9% at 12 months and 53.5% at 24 months.[27]

Clinical trials: study selection

The literature search for clinical trials identified 7160 abstracts (online supplemental figure 2) on the 9th of February 2021. Based on reviewing the first 100 abstracts which were randomly selected, we found a 97% interobserver agreement (IOA) between the three researchers (LvO, ISN and SAB). The remaining abstracts were screened separately by the researchers. A total of 350 abstracts were included for full text analysis, of which first a random selection of 10 full texts were reviewed together by two researchers (ISN and LvO), whereby an IOA of 70% was obtained. After a final meeting to resolve any remaining disagreements the remaining full texts were reviewed separately by the researchers, resulting in inclusion of 10 unique studies (table 1). During all stages of the review, weekly meetings were scheduled to discuss any uncertainties. One additional clinical trial partly met the inclusion criteria, since it included patients with 'very early arthritis', of which a substantial part fulfilled the ACR/EULAR 2010 classification criteria for RA.[28 29] Unfortunately, despite repeated attempts we did not obtain specific data for the patient group fulfilling the inclusion criteria of our review, and therefore, the study was omitted from final inclusion.

RoB assessment

The overall RoB was high in 9/10 included studies, mostly because of not having complete blinding (online supplemental tables 2 and 3 for complete RoB assessment results). Out of 10, 7 trials did have a blinded outcome assessor for the assessment of joint involvement. However, the DAS, which was an important outcome measure in most studies, also includes a patient reported component. In 3/7 trials with a blinded assessor, patients were not blinded to the intervention while they were part of the outcome assessment. This might have influenced the results.

Assessment of heterogeneity

A complete overview of the patient and study characteristics is given in online supplemental table 1. The majority of included studies were about patients who fulfilled the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) 2010 criteria (6/10 studies) or the ACR

Table 1 Overview of included clinical trials

Study (publication year)	Type of GC	Initial GC dose	Tapering schedule	Included in meta-analysis
COBRA (1997)[5]	Prednisolone	60 mg/day	In 7 weeks to 7.5 mg/day. Stop after 28 weeks*	No
BeSt (2005)[35]	Prednisone	60 mg/day	In 7 weeks to 7.5 mg/day. Stop in 8 weeks after week 28 if DAS persistently ≤2.4	Yes
IDEA (2014)[34]	Methylprednisolone	250 mg iv once	N.A.	No
COBRA-light (2015)[36]	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	Yes
IMPROVED (2014)[33]	Prednisone	60 mg/day	In 7 weeks to 7.5 mg/day. Stop after 20 weeks if DAS <1.6 at 4 months	Yes
ARCTIC (2016)[32]	Prednisolone	15 mg/day	In 7 weeks to 0 mg/day if DAS <1.6 and no swollen joints present	No
tREACH (2013)[30]	Arm 1: methylprednisolone or kenacort arm 2 and 3: prednisone	arm 1: 120 mg or 80 mg im once (single dose) arm 2 and3: 15 mg/day	In 10 weeks to 0 mg/day*	No
CareRA (2017) ► *COBRA Classic* ► *COBRA Slim* ► *COBRA Avant garde*[37]	Prednisone	 ► 60 mg/day ► 30 mg/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.	Yes
Hua *et al* (2020)[31]	Prednisone	10 mg/day	Tapering after 4 months to 5 mg/day, stop after 6 months*	No
NORD-STAR (2020) *- arm 1 A (oral prednisolone)*[38]	Prednisolone	20 mg/day	In 9 weeks to 5 mg/day. Stop after 9 months*	No

*GC tapered and stopped according to protocol, not depending on DAS.
CRP, C-reactive protein ; DAS, Disease Activity Score; GC, glucocorticoid; im, intramuscular; iv, intravenous; mg, milligram; N.A, not applicable.

1987 criteria (3/10 studies). One study included patients based on a clinical diagnosis only.[30] Mean or median symptom duration was reported in 9/10 studies and was in all studies less than 1 year. One study did not report symptom duration at baseline but only mean RA duration at baseline which was 4.7 months in the prednisone group.[31] At baseline, a mean DAS was reported in all trials: 4/10 reported a DAS (based on Erythrocyte Sedimentation Rate (ESR) or C-reactive protein (CRP)), 4/10 a DAS28 (based on ESR or CRP) and 2/10 reported both a DAS and a DAS28. The reported mean DAS28 at baseline ranged from 5.2 to 6.2. The reported mean baseline DAS ranged from 3.3 to 4.4.

All trials started with MTX at baseline next to GC, which in 4/10 trials was combined with sulfasalazine (SSZ), in 2/10 trials with SSZ and hydroxychloroquine (HCQ) and in 1/10 trials with leflunomide. In all trials except two, all patients were randomised to different treatment arms at baseline.[32] The ARCTIC trial was conducted to evaluate if including ultrasound information was beneficial in treatment decisions. This was done in two treatment arms, both treated equally with MTX and prednisone, but one arm was tightly controlled using ultrasound, while the other was controlled with a conventional treat to target approach based on clinical assessment of disease activity.[32] In the IMPROVED study, all patients first received MTX and prednisolone bridging. Patients were subsequently randomised into two different treatment arms if they were not in remission at 4 months, or tapered treatment if they were in remission.[33] In one study GC were given as a single intravenous injection at baseline.[34] In the other nine studies GC treatment consisted of oral or intramuscular (im) 'bridging therapy', with an initial dose ranging between 10 and 60 mg/day (oral)[5 30–33 35–38] and 80 or 120 mg once (im).[30] If the initial oral dose was high, 30 or 60 mg/day, this was followed by rapid tapering to 5 or 7.5 mg/day as maintenance dose, (table 1). In 4/10 studies, the initial dose was lower, and GC were tapered to 2.5 mg/day (1/4 studies), to 5 mg/day (2/4) or directly to 0 (1/4).

GC use as indication of unsuccessful protocolised GC discontinuation

Only 4/10 studies reported rates of patients who still or again used GC after the GC induction phase, either only at 12 months (4/4) or also at 24 (2/4) months follow-up (table 2). The data reported in table 2 are proportions of active participants still or again on GC (either at 12 or at 24 months). The proportion of patients still using GC ranged from 0% to 60% at 12 months and from 0% to 28% at 24 months. The 0% use of GC at 12 and 24 months was reported in arm 2 of the IMPROVED study. After 4 months open-label treatment with MTX and prednisone, patients in the IMPROVED study who were not in remission were randomised into arm 1 (MTX, HCQ, SSZ and prednisone) or arm 2 (MTX and adalimumab). This switch to adalimumab appeared to prevent further prednisone use. In other trials in which biological (b) DMARDs were part of the treatment protocol, bDMARDs were either prescribed at a later stage and in addition to GC,[32 34 36] or the difference in GC use between patients who remained on GC and patients who switched to a bDMARD were not reported.[30] Other outcome measures (eg, cumulative or average GC dose, number of GC episodes) were reported in <3 studies and were therefore not pooled (online supplemental table 4). Hence, a meta-analysis was only performed on proportions of patients with GC use at 12 and 24 months. The I^2 for these studies was 99% at 12 months and 98% at 24 months. The pooled proportion of GC use was 22% (95% CI 8% to 37%) at 12 months and 10% (95% CI −1 to 22) at 24 months (figure 1A,B).

DISCUSSION

This SLR and meta-analysis included clinical trials about patients with early RA, in which GC were used as part of the initial treatment and tapering (within 6 months) and discontinuation (within year 1) were protocolised. The proportion of patients still using

Table 2 Glucocorticoid use after the induction phase in clinical trials*

	N (at baseline)†	% GC use 12 months	% GC use 24 months
COBRA light arm COBRA light	81	60‡	–
COBRA light arm COBRA classic	81	60‡	–
IMPROVED early remission	387	24.8	10.2
IMPROVED arm 1	83	17.3	4.0
IMPROVED arm 2	78	0	0
BeSt arm 3	131	43.2	27.6
CareRA arm COBRA classic	98	7.8	–
CareRA arm COBRA slim	98	4.5	–
CareRA arm COBRA avant garde	93	4.7	–
CareRA arm COBRA slim (low risk)	43	5.3	–

*Data reported per treatment arm of the four included clinical trials which have data on GC use after the induction phase published. Reported here: percentages use over time (no discontinuation rates were reported, except for COBRA light at 12 months). For tapering protocols see table 1.
†number of patients shown at baseline, at which treatment was initiated.
‡COBRA light only reported an approximation of the percentage of patients who could taper prednisone to zero in week 26 and 39, which we recalculated to a percentage of patients still using GC for comparison with the other trials.
GC, glucocorticoids; N, number.

GC were analysed and interpreted as the opposite of the proportion of patients who successfully discontinued GC, as (successful) discontinuation rates were mostly lacking. Our meta-analysis results of the clinical trials showed that at 12 months, 22% of the patients still or again used GC and after 24 months 10%. In the included clinical trials few data was available on GC dose over time. No useful data could be extracted from the observational cohorts, since in all of the identified cohorts it either remained unclear which proportion of the patients that used GC during follow-up, also used GC from baseline as bridging therapy or the desired outcome measure was not reported. We could therefore not perform a meta-analysis of the observational cohorts.

In the 2021 ACR RA treatment guidelines for DMARD naïve patients with with moderate-to-high disease activity, concerns are expressed about the risk of side effects of GC that outweigh their benefits. Due to these concerns, a conditional recommendation based on expert opinion was included against the use of short-term GC therapy next to a csDMARD.[21] Since these potential side effects of GC are related to duration of GC use, the success rate of tapering and discontinuing GC after their use as bridging therapy is important. Each of the included clinical trials that used GC as bridging therapy included tapering and discontinuation of GC in their treatment protocols, although at different time points and after different GC dosages. In our meta-analysis of clinical trial data 22% of the patients were still or again using GC after 1 year, which would indicate that the vast majority had in fact discontinued GC before that time. However, no data were reported regarding the proportion of patients who were able to successfully discontinue their GC within the recommended 3 months after initiation, as the bridging scheme was longer than 3 months in almost all studies (9/10).[18 21] The study that did stop GC bridging within the recommended 3 months (tREACH study) did not report data about GC use in their publications.[30] Whether there were differences in safety outcomes, associated with the protocolised (or actual) duration and dose of bridging GC, was beyond the scope of this review. In general the safety risks are dependent on the duration of GC use and cumulative dose over time, but also on the baseline risk of the patients and the other factors (comorbidities, severity of disease and other DMARDs), which in clinical trials may be different than in 'real life' cohorts. However, despite the well-known dose-dependent risk associated with long-term GC exposure, less is known about the benefit–risk ratio of using a low dose of GC for 1 to 2 years. A meta-analysis of randomised trials investigating the safety of GC treatment (up to 10 mg/day) in RA over more than 1 year found only limited GC toxicity and argued that the benefit–risk ratio is favourable.[39] The EULAR task force concluded in their viewpoint on long-term GC treatment that for dosages between 5 mg and 10 mg a day, the harm depends on patient specific characteristics.[40] More recent observational data from the CorEvitas RA registry showed that initiating GC is associated with increased cardiovascular events at daily doses ≥5 mg and increased cumulative dose and duration.[41] Discontinuation may appear the safest option, but this presents the risk of a disease flare, by itself a risk for cardiovascular events.[42 43] So far we cannot predict who can discontinue GC and who cannot.

Numerous studies have shown the importance of early and adequate suppression of disease activity in early RA to achieve improved long-term outcomes.[44–47] Randomised clinical trials have shown that GC can be useful as bridging treatment until slower-acting csDMARDs such as MTX may exert their effect, to ensure early suppression of disease activity, improvement of physical functioning, prevention of irreversible damage and reducing chronic non-steroidal anti-inflammatory drugs (NSAID) and other analgesic use.[5 6 8 48] Therefore, withholding GC to early patients with RA and starting MTX as monotherapy could

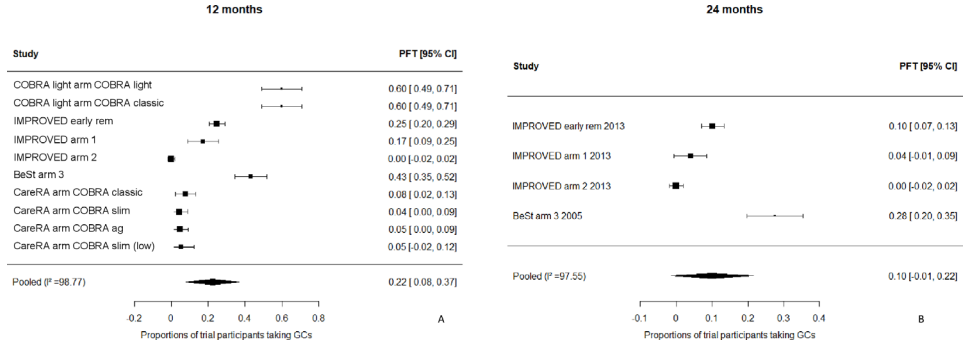

Figure 1 Proportions of trial participants using glucocorticoid (GC) at 12 months (A) and 24 months (B) after initial GC treatment in clinical trials. CareRA COBRA ag=CareRA COBRA avant garde; CareRA slim (low)=low-risk group; IMPROVED early rem=IMPROVED early remission.

result in missing the 'window of opportunity' to achieve long-term favourable treatment outcomes, including an unnecessary delay in preventing possible damage during the period MTX is not active.[49] As alternative to initial GC bridging therapy, rapidly acting bDMARDs can be equally effective. However, cost–utility analyses generally show a favourable picture for GC bridging, as the initial drug costs of bDMARDs are not compensated by the significantly higher retention of work productivity.[50] Nowadays, in most markets the costs of bDMARDs have decreased and they could reach a level in the near future where the costs do compensate the work productivity retention, making them more favourable. In patients without classical poor prognostic factors, the CareRA study showed cost-effectiveness for MTX plus GC bridging therapy compared with MTX monotherapy.[51]

Despite the study protocols aimed at GC discontinuation, our results do show that still 20% of the patients had either never stopped or restarted these GC before the end of year 1. Only in arm 2 of the IMPROVED study 100% of patients successfully discontinued GC. This suggests that GC discontinuation is at least partly dependent on a planned order in treatment steps, as only in IMPROVED arm 2 it was stipulated that in case of lack or loss of DAS remission, a bDMARD had to be started and that continuation or restart of GC was not allowed. In the other IMPROVED arms, the protocol required GC discontinuation if remission was reached but allowed for reintroduction (once) if at any point disease activity increased again. It is noteworthy that most of the included trials in this SLR did not plan to discontinue GC within the internationally recommended 3 months. This may be based on clinical experience or the results of previous trials, in particular the COBRA study, which set a benchmark for rapid suppression of disease activity with a tapered high dose of prednisone continued for 28 weeks. Subsequent studies may have tried to establish if similar success may be achieved with less GC compared with the 'established' schemes but based on the currently available data it is impossible to say whether these studies have been too cautious, potentially delaying the implementation of more rapid GC discontinuation. Besides identifying a lack of randomised controlled studies specifically comparing various GC bridging strategies, our literature search also shows there is a need for a protocol for GC tapering and for data on discontinuation of initial GC bridging therapy in daily practice. Various cohort studies have reported on prolonged GC use,[19 20 52] although not always started as initial treatment. These reports suggest that many patients with RA use GC in the course of their illness and often long term. Why patients do not always discontinue GC within 3 months is unclear.

To our knowledge, this is the first systematic review including both observational cohorts and clinical trials regarding the ability to discontinue GC after initial GC bridging therapy in newly diagnosed patients with RA. Despite an extensive search, we found that few published data were available concerning the predefined outcomes of interest. However, figures about GC use over time in the 5 years follow-up papers of CareRA and IMPROVED suggest that almost all patients are able to discontinue their GC in the end,[46 47] although specific details are lacking. No observational studies identified by the scoping literature search directly answered our research question. Some studies might have been missed by the specific search strategy, but we don't expect a higher yield of a broader search. The only observational cohort study that did address GC discontinuation after initial bridging therapy reported cumulative probabilities over time instead of proportions, which makes it hard to compare to the clinical trial results. For pragmatic reasons, we decided to double screen a random selection of 100 abstracts by all researchers. This is less than the 10% from the total number of identified abstracts which is recommended by the WHO. This could have resulted in bias. However, since agreement was high (97%) and weekly meetings were organised to discuss any doubts with an adjudicator, we consider this risk to be limited. Among the included trials in this SLR, there was substantial variation in initial GC doses and tapering schedules and few direct comparisons therein. Due to the lack of available data and the heterogeneity in study designs and GC administration route, the random effects meta-analysis could not be performed for all studies and predetermined outcome measures. We were only able to analyse proportions of patients using GC at 12 and 24 months in the meta-analysis, and only based on 4 of the included studies. For instance, very little information was reported on the GC dose after initial bridging therapy. Only the CareRA trial reported a low average daily dose of 4.9 mg/day for the total population during the first year of follow-up including GC use in the protocolised induction phase.[53] In this study, we aimed to assess successful discontinuation of GC. However, most studies reported proportions of patients still using GC instead of rates of successful discontinuation. For our analysis, we assumed that the rate of successful discontinuation equals 100% minus the rate of patients still using GC. This lack of detail is due to the fact that none of the included trials were originally designed for the research question of this SLR. Although the reported clinical trials have the advantage of non-selective prescription of GC and a protocolised tapering and stopping schedule of GC, they do not have the same level of evidence as a randomised controlled trial on the comparison of various protocolised GC discontinuation schedules vs for example protocolised (very) low-dose GC continuation. Such a trial would also provide more reliable data on (long-term) safety aspects of different tapering schedules. Another limitation is the high risk of bias in almost all (9/10) clinical trials included in this review, which was mainly due to a lack of blinding of patients. But as GC discontinuation was not the primary outcome of any of the included studies, the influence of bias on the outcomes of interest of this review is likely to be low.

In conclusion, the currently available observational cohort studies provide very few data on the success of GC discontinuation after their use as initial bridging therapy. In clinical trials, where all patients started GC bridging therapy at baseline, discontinuation of GC was successful in the majority of patients with RA within 1 year, as, 22% after 1 year and 10% after 2 years were reported to still or again use GC. More data on GC discontinuation success rates and success factors from RCTs comparing GC (cumulative) dosages and daily practice cohorts are necessary to identify the optimal GC bridging scheme with the optimal benefit–risk ratio in clinical practice, potentially for various disease and patient profiles.

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of this SLR. LvO, SAB and CFA have written the manuscript. All authors revised the manuscript and approved the final version.

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