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Continuing versus tapering low-dose glucocorticoids in patients with rheumatoid arthritis and systemic lupus erythematosus in states of low disease activity or remission: A systematic review and meta-analysis of randomised trials

Andriko Palmowski [a,b,*], Anne Pankow [a], Kalina Terziyska [a], Sabrina M Nielsen [b,c], Robin Christensen [b,c], Henning Bliddal [b], Zhivana Boyadzhieva [a,1], Frank Buttgereit [a,1]

[a] Department of Rheumatology and Clinical Immunology, Charité – Universitätsmedizin Berlin, Germany
[b] Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Denmark
[c] Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark

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ABSTRACT

Objectives: To study the benefit and harm associated with continuing versus tapering low-dose glucocorticoids (GCs) in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) who have achieved low disease activity/remission.

Methods: A protocolised (PROSPERO—CRD42022325175) systematic review and meta-analysis of randomised trials was performed. Trials compared, in patients with low disease activity/remission and GCs at baseline, continued low-dose GCs (≤7.5 mg/d prednisone equivalent) with a taper. Co-primary outcomes were time to flare and adverse events (AEs), accompanied by secondary benefit and harm outcomes. We performed meta-analyses and evaluated risk of bias and quality of evidence (QoE). Subgroup analyses were conducted for patients with RA.

Results: Four trials (three: RA; one: SLE; study duration 24–104 weeks) with 472 participants were included. Tapering GCs resulted in a shorter time to flare (hazard ratio 3.41 [95 %-CI 1.96–5.93]; $p<0.01$; *very low* QoE). The risks of AEs, serious AEs, and withdrawal due to AEs were similar in both groups (*very low* to *low* QoE). There were more withdrawals due to lack of efficacy with tapered GCs (risk ratio 3.02 [1.56–5.87]; *low* QoE). In RA, the disease activity score-28 was lower with continued GCs (mean difference 0.49 [0.07–0.91]; *low* QoE). One of 238 patients in the tapering groups experienced adrenal insufficiency. Subgroup analyses yielded consistent results.

Conclusion: In RA and SLE with low disease activity, continuing low-dose GCs may provide better sustained disease control, but QoE is insufficient. Adrenal insufficiency is very rare when tapering low-dose GCs. Longer-term safety concerns for GCs remain.

Introduction

Glucocorticoids (GCs) are widely used anti-inflammatory and immunosuppressive drugs. Despite well-known adverse events (AEs), their use, in varying ways, is advised in current European Alliance of Associations for Rheumatology (EULAR) recommendations for the treatment of inflammatory rheumatic diseases such as rheumatoid arthritis (RA) [1] or systemic lupus erythematosus (SLE) [2] because of their efficacy.

Recommendations on the duration and dosing of GC therapy are, however, to this day contradictory, in part because the real extent of AEs during treatment and therefore the ultimate benefit:risk ratio is not completely objectified [3]. For example, current American College of Rheumatology (ACR) RA guidelines conditionally advise against using GCs while the 2022 EULAR recommendations for RA suggest considering GCs as a bridging therapy [1,4]. In SLE, current guidelines and recommendations advise minimization of the daily GC dose to ≤7.5 mg/d prednisone equivalent, highlighting that there are concerns for

* Corresponding author at: Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
E-mail address: andriko.palmowski@charite.de (A. Palmowski).
[1] Both last authors contributed equally.

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AEs with long-term use even at a low dose.

One way or another, some patients require GCs at low dosages for longer periods because they do not respond sufficiently to other treatment options. When patients with inflammatory rheumatic diseases such as RA or SLE reach low disease activity or remission with low-dose GCs, benefit and harm of tapering these low-dose GCs are not clear. Individual trials have been performed, but their statistical power is often low when events such as flares are assessed. The frequency of adrenal insufficiency when tapering GCs varied greatly in prior studies [5]. Grading of the quality of evidence has not yet been done.

The aim of this systematic review and meta-analysis was to investigate the benefit and harm associated with continuing low-dose GC compared with a GC taper ending with withdrawal in patients with inflammatory rheumatic diseases in which GCs are regularly used (RA and SLE) who have achieved a state of low disease activity or remission.

Methods

This systemic literature review was conducted and reported according to the PRISMA 2020 statement [6]. A protocol was preregistered with PROSPERO (CRD42022325175). No patients were involved in the planning and conduct of this study. GC dose is presented as prednisone equivalent without further notes from this point on.

Eligibility

We included double-blind randomised controlled trials (RCTs) if they enrolled patients with RA or SLE and compared continued low-dose (≤7.5 mg/d) treatment to any GC tapering regimen ending with withdrawal. GCs could be accompanied by any other treatment (e.g., standard of care). Studies had to enroll patients aged 18 years or older, and these patients had to be in a state of low disease activity or (partial) remission (any criteria) at baseline. They had to have received GCs for at least 4 weeks before the start of the randomised trial period. No restrictions concerning publication dates were applied. Studies had to be published in English, German, Spanish, or Russian. Of note, originally, we planned to include polymyalgia rheumatica and giant cell arteritis as well, but no studies meeting the eligibility criteria were found.

Data sources and search strings

MEDLINE via PubMed, EMBASE via Ovid, and the Cochrane Central Register of Controlled Trials via Cochrane Library were searched to satisfy the recommendations provided by the Cochrane Handbook [7]. A hand search was conducted to identify further articles. References of included publications were screened for further inclusions. The PICOS framework [8] was used to construct search strings – Details can be found in the **Appendix** (**Table S1**) alongside the search strings. The search was conducted on April 24th, 2022.

Study selection

Search results were imported into EndNote X8 Software, where duplicates were eliminated. Two reviewers (ZB and KT) independently screened the retrieved records for inclusion and exclusion: First through an assessment of title and abstract, then by assessing the remaining articles in full text. In case of discrepancies, a third reviewer acted as an arbiter (APalmowski).

Data management, items and collection

For data extraction (performed by APalmowski) and management, we used Microsoft Excel for Microsoft 365 (Microsoft Corporation, Redmond, WA, USA). A standardised data extraction form was designed and used for extracting study characteristics and outcome data.

Outcomes

Several benefit and harm outcomes were evaluated. Time to first flare and AEs (any) were defined as co-primary outcomes. Several secondary outcomes were investigated: disease activity (e.g., disease activity score-28 joints [DAS28], Safety of Estrogen in Lupus National Assessment - Systemic Lupus Erythematosus Disease Activity Index [SELENA-SLEDAI]), disability (health assessment questionnaire disability index [HAQ-DI]), serious AEs (as defined by each eligible study), adrenal insufficiency, and withdrawals (separate investigations: due to AEs and due to lack of efficacy). Except for disease-specific outcomes measures, outcome measures were pooled across diseases (i.e., combining in meta-analyses data from different diseases).

Risk of bias assessment

The risk of bias (RoB) in individual studies was assessed by two independent reviewers (APankow and ZB) using the Cochrane tool for assessing the RoB in RCTs [9]. In case of discrepancies, APalmowski was consulted.

Summary measures and data synthesis

Mean difference (MD) was used for continuous outcomes (e.g., disease activity scores), risk ratio (RR) for dichotomous outcomes (e.g., AEs) and hazard ratio (HR) for time-to-event outcomes (e.g., time to first flare). For statistical analyses, the two-sided significance level α was set at 0.05. Tests for statistical significance were only conducted for our co-primary outcomes to reduce the probability for false-positive results.

Restricted maximum likelihood random effects meta-analyses pooled results for each outcome. If multiple intervention groups were present in one study, we combined groups as recommended by the Cochrane Handbook [10]. For each random effects meta-analysis, heterogeneity across included studies was evaluated with Cochran's Q-statistic and interpreted based on the I^2 statistic; I^2 measures the total percentage of variance across studies due to clinical heterogeneity rather than statistical error [11,12] . R software (R Foundation for Statistical Computing, Vienna, Austria) with package *meta* was used for analyses [13].

Subgroup analyses were performed within trials enrolling patients with RA.

Quality of evidence

One reviewer (APalmowski) applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to make an overall judgement about the quality of evidence (QoE) [14]. The GRADE system was used to summarise the QoE on an outcome-by-outcome basis as *high, moderate, low*, or *very low*.

Results

We identified 1700 articles, of which five articles (reporting on four RCTs) satisfied the eligibility criteria (Fig. 1; three RCTs in RA and one in SLE) [15–19]. Trial characteristics can be found in Table 1. All trials allowed or even requested concomitant DMARD therapy. RoB assessments are reported in the **Appendix** (**Table S2**). Study duration varied between 24 and 104 weeks.

With regard to RA, the doses in the continued GC groups were 5–7.5 mg/d [16], 5 mg/d [15], and 1–4 mg/d [18,19]. The tapering pace was slow, ranging from −2.5 mg of the total weekly dose per week to −1 mg/d per month. All patients were on the same GC dose for at least 4 weeks before the intervention.

In SLE, we found only one trial. This trial employed a continued GC dose of 5 mg/d [17]. In this study, tapering was rapid with a sudden stop of 5 mg/d oral prednisone and a one-month bridging of 20 mg/d hydrocortisone (which would convert to 5 mg/d prednisone) to prevent

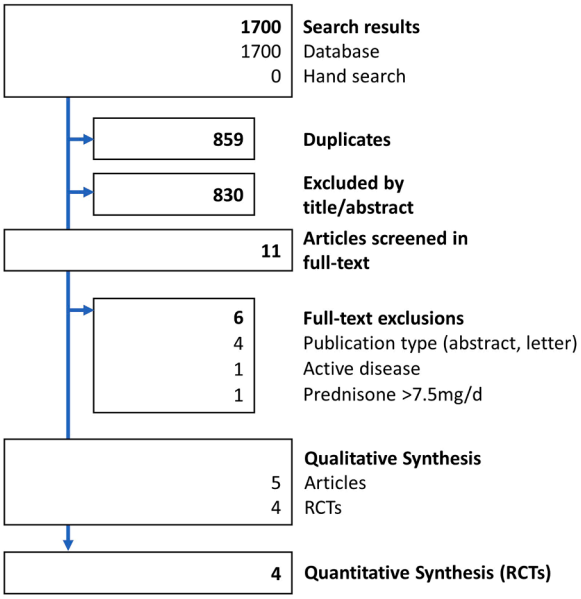

Fig. 1. Search flow. RCTs, randomised controlled trials.

adrenal failure. Patients were required to be taking 5 mg/d GCs for one year before inclusion.

Time to first flare

As illustrated in Fig. 2 (upper panel), two trials investigated the time to first flare (one in RA[15] and one in SLE[17]). Both individual trials, and the meta-analysis estimate (HR 3.41; 95 %-CI 1.96 to 5.93; I^2 10 %; $p < 0.01$), found a statistically significantly shorter time to flare with tapering GCs compared with continuing GCs. This was rated to be *very low* QoE because of the following: First, GCs were suddenly stopped in the tapering group of the SLE trial instead of a gradual taper (downgrade for indirectness) and all patients received background tocilizumab in the RA trial (another downgrade for indirectness). Second, the SLE trial was an open-label trial with potential bias because participants knew if they continued GCs or not (downgrade for RoB).

Most flares in the SEMIRA trial occurred late in the tapering process at 1 mg or 0 mg/d, indicating a potentially 'flare-safe' threshold dose below 5 mg/d but above 0 mg/d. Other trials did not provide data in this regard.

Adverse events

All four included trials were pooled in the meta-analysis of AEs (Fig. 2). There was no statistically significant difference in the risk of AEs, although there was a tendency towards more AEs with tapering GCs (RR 1.22; 0.98 to 1.52; I^2 36 %; $p = 0.07$). QoE was seen as *very low* because of RoB (one open-label trial, one trial with incomplete outcome data), inconsistency (different directions of effect estimates of some trials), and indirectness. Concerns for indirectness arose from the large weight of the SEMIRA trial in this analysis, which included only patients on stable tocilizumab therapy.

Secondary outcomes

The meta-analysis results of secondary outcomes are summarized in Table 2. Forest plots of all meta-analyzed outcomes are presented in the **Appendix** (**Figures S1-S4**). There were no substantial differences in serious AEs, withdrawal due to AEs, and cases of adrenal insufficiency when comparing GC continuation versus tapering. Overall, there was only one case of cinically manifest adrenal insufficiency (tapering group; denominator: 238 patients randomised to tapering). However, this case occured in the only trial employing a sudden GC stop instead of a gradual taper. No trial employed a standardized screening method to test for adrenal insufficiency. Interestingly, there was an increased risk of withdrawal due to lack of efficacy with tapering GCs (*low* QoE). QoE was *very low* for all adverse event outcomes.

The DAS28 was available from two RA trials [15,16]. The tapering group had higher pooled DAS28 scores (mean difference 0.49; 0.07 to 0.91; I^2 35 %]; forest plot in **Appendix** [**Figure S5**]). QoE was rated *low* because of RoB and indirectness. (SELENA-)SLEDAI and HAQ could not be assessed because of a lack of reported data.

Subgroup analyses

Subgroup analyses of AEs, serious AEs, and withdrawal due to lack of efficacy including only trials in RA led to similar results compared with the pooled meta-analyses of RA and SLE (forest plots in **Appendix** [**Figures S6-S8**]). No subgroup analyses were performed regarding adrenal insufficiency and withdrawal due to AEs as only one RA trial had cases. Subgroup analyses were also omitted for time to first flare as there was only one trial in each disease.

Discussion

In this systematic review and meta-analysis of RCTs comparing tapering with continuing low-dose GCs in patients with low disease activity/remission, we found *very low* quality evidence of a reduced time to first flare with tapering GCs in RA and SLE. With tapered GCs, there were more withdrawals due to lack of efficacy (*low* quality evidence). *Very low* quality evidence showed no difference in the number of AEs. There was *low* quality evidence for better sustained low disease activity in RA with continued low-dose GCs.

Rheumatology seems divided when it comes to GCs: E.g., the ACR conditionally advises against using GCs for RA [4], and the EULAR recommends to use GCs for no longer than three months in RA [1]. A EULAR task force, on the other hand, concluded that there is low risk of harm for a majority of patients with inflammatory rheumatic diseases at

Table 1
Characteristics of included trials.

Author and year	Disease	Region	Type of continued GC	Dosage of continued GC[1]	Tapering speed	Disease duration (months)	Sample size (randomised)	Trial duration (weeks)[2]
Burmester & Buttgereit 2020	RA	Multiple	Prednisone	5	−1 mg/d per month	> 6	259	24
Tengstrand 2007	RA	Europe	Prednisolone	5–7.5	−2.5 mg of total weekly dose per week	> 24	58	104
Pincus 2008/2011	RA	USA	Prednisone	1–4	−1 mg/d per month	> 3	31	36
Mathian 2020	SLE	Europe	Prednisone	5	Sudden stop with a 4-week hydrocortisone bridging	> 12	124	52

[1] In mg/d prednisone equivalent.
[2] Time from the beginning of GC tapering/continuation to end of observation. GC, glucocorticoid, RA, rheumatoid arthritis, SLE, systemic lupus erythematosus.

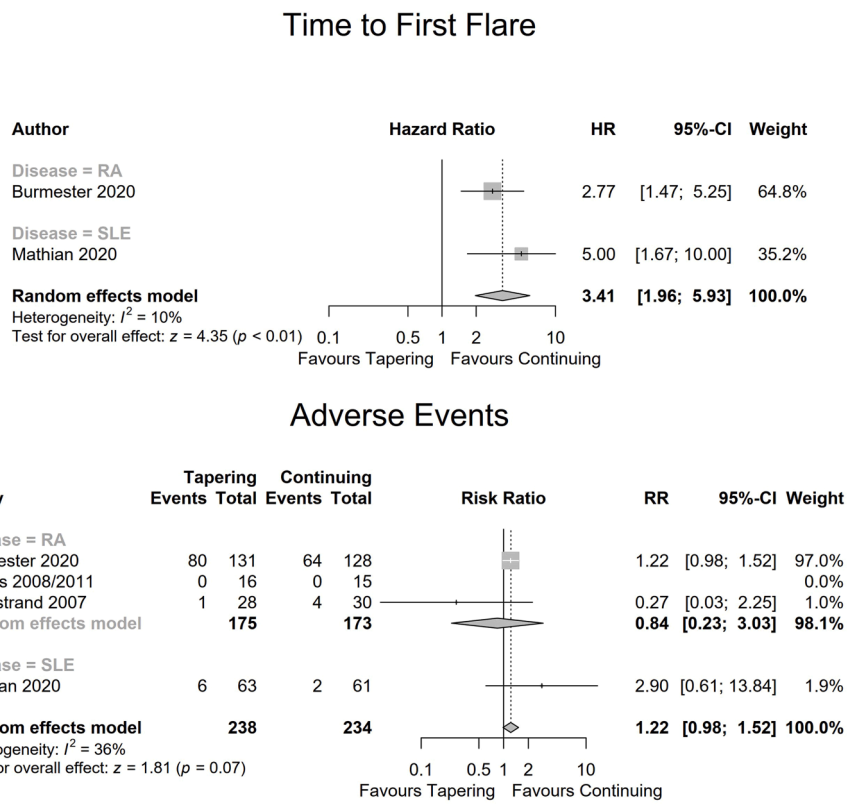

Fig. 2. Meta-analysis of co-primary outcomes: time to first flare (upper panel) and adverse events (lower panel). RR, risk ratio; HR, hazard ratio; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; 95 %-CI, 95 % confidence interval.

Table 2
Secondary outcomes. [1]Only one trial with cases. [2]Risk ratio in favor of continuing glucocorticoids (higher risk for withdrawal due to lack of efficacy with tapering glucocorticoids). [3]Mean difference in favor of continuing glucocorticoids (higher DAS28 with tapering glucocorticoids). *k*, number of trials; RoB, risk of bias, NA, not available, RR, risk ratio, MD, mean difference.

Outcome	*k*	Effect Size	I^2	Quality of evidence		Downgrading due to
Serious adverse events	4	RR: 1.41 (0.50 to 3.95)	38 %	⨁	Very low	RoB, inconsistency, indirectness, precision
Adrenal insufficiency	4	RR: 2.91 (0.12 to 69.96)	NA [1]	⨁	Very low	RoB, indirectness, precision
Withdrawals due to adverse events	4	RR: 0.73 (0.17 to 3.21)	NA [1]	⨁	Very low	RoB, indirectness, precision
Withdrawals due to lack of efficacy	4	RR: 3.02 (1.56 to 5.87)[2]	0 %	⨁⨁	Low	RoB, indirectness
DAS28	2	MD: 0.49 (0.07 to 0.91)[3]	35 %	⨁⨁	Low	RoB, indirectness

long-term (3–6 months or longer) dosages of ≤5 mg/d prednisone equivalent [3]. In SLE, the EULAR recommends to "minimize daily dose to ≤7.5 mg/d prednisone equivalent or to discontinue them," also highlighting that some studies suggest lower doses might be harmful in SLE as well [2].

Anyway, real-world data from around the world shows that GCs are used as a long-term treatment in a substantial proportion of patients with inflammatory rheumatic diseases (ca. 30–50 %) around the world [20–27]. Yet, a systematic review and meta-analysis of trials investigating benefit and harm of continuing versus tapering low-dose GCs in patients who have achieved low disease activity or remission with GCs is lacking.

At this point, we want to underline our argumentation for including only RCTs: Patients with inflammatory rheumatic diseases who have higher disease activity and/or higher levels of inflammation usually receive higher doses of GCs and are more likely to receive GCs in general. Both disease activity and inflammation can lead to AEs such as cardiovascular events or osteoporosis. In observational studies, the use of GCs may be associated with such AEs, even though disease activity could – at least in part – be the 'true' culprit. This type of confounding is known as 'confounding by indication'. While b/tsDMARDs are also used in patients with more severe disease, research on GCs is more likely to suffer from confounding by indication because guidelines (in short) recommend using GCs only for disease flares and to discontinue them as fast as clinically feasible, while b/tsDMARDs may be continued for a longer time, even if flares have resolved. While well-designed observational studies try to adjust for disease activity or inflammation, residual confounding cannot be completely ruled out, which is why colleagues from oncology called confounding by indication "a most stubborn bias" [28].

With regard to RA, we recently performed a systematic literature review of two-year RCTs enrolling patients with background DMARDs that compared low-dose GCs with placebo[29] and found reduced disease activity (*high* quality evidence), disability (*moderate* quality evidence), and radiographic progression (*very low* to *moderate* depending on the scoring method) with low-dose GCs. *Low* quality evidence suggested no increased risk of AEs over two years. The results of the study at hand are very similar and support this evidence. The DAS28 with continued low-dose GCs in our study was lower and the time to flare longer compared with a GC taper. In the SEMIRA trial, which we included in our meta-analysis, the number needed to treat to avoid a flare or loss of low disease activity at 6 months was 8. For RA, we summarize that continued low-dose GCs may provide better sustained

disease control.

There is one prior systematic literature review investigating tapering versus continuing GCs in SLE – looking at both observational studies and RCTs –, which included 17 publications [30]. In their study, GC discontinuation was associated with an increased risk of flare compared with GC continuation (RR 1.38 [95 %-CI 1.01 to 1.89]) as well. The risk of 'major' flares was increased, but without statistical significance and with very wide confidence intervals (RR 1.77 [95 %-CI 0.40 to 7.83]). The only published SLE trial investigating this question found a five-fold increase in the risk of flare when stopping low-dose GCs in patients with SLE with low disease activity, corresponding to a number needed to treat to avoid a flare of approximately only 5 patients at 12 months [17]. Regrettably, GCs were not slowly tapered as most rheumatologists would recommend, but they were suddenly stopped (with a one-month bridging of 20 mg/d hydrocortisone), and we worry that this procedure produced an artificially high risk of flare. Also, neither patients nor caregivers were blinded to treatment. This is why we rated the overall QoE of evidence for time to first flare as *very low*. Further double-blind RCTs should be performed with a slower tapering course.

At this point, we want to note that we originally also planned to investigate polymyalgia rheumatica and giant cell arteritis. However, we did not find a single RCT comparing continuing with tapering low-dose GCs in patients with low disease activity.

The risk for adrenal insufficiency when tapering GCs varied greatly in a prior systematic review and meta-analysis that included studies which used rigorous tests for adrenal insufficiency [5]. In patients with rheumatic disorders, the 95 % confidence interval of the absolute risk was 27.5 % to 52.6 %, and included studies showed substantial weaknesses in the risk of bias assessments. In our meta-analysis, only one of 238 patients (0.4 %) randomized to GC withdrawal suffered from clinically apparent adrenal insufficiency, and this was in the only trial with a relatively sudden GC stop. Unfortunately, there was no standardized screening for adrenal insufficiency in the included trials.

Recent research has raised the question whether there might be 'flare-safe' threshold doses below 5 mg/d but above 0 mg/d. Indeed, in the SEMIRA trial, most flares occurred late in the tapering process at 1 mg or 0 mg/d, indicating either a delayed effect on the risk of flare during tapering or a 'very low' potentially 'flare-safe' threshold dose. This second hypothesis is supported by a recent observational study [31]. Adami et al. performed a case-crossover study of 508 patients with RA. In short, GC doses in the six-month period preceding a flare (DAS28CRP increase of >1.2 and current DAS28CRP of ≥ 3.2) were compared to GC doses in six-month periods that were not followed by a flare. Tapering to doses >2.5 mg/d was not associated with an increased risk of flare, suggesting that there might indeed be a 'flare-safe' threshold dose below 5 mg/d. More research in independent cohorts is needed to support this claim; in addition, it is unclear whether such a 'very low' dose would be safe in terms of GC-related AEs (most of which were found at higher dosages only).

Strengths of this study are rigorous execution according to a pre-registered research protocol, the assessment of randomised evidence, which is shielded from confounding by indication, a comprehensive search for literature – performed in three large databases by two independent reviewers –, and confirmation of results in subgroup analyses. This study also has some limitations. No conclusions can be drawn for GCA and PMR because of a lack of trials. Furthermore, trial duration was not long enough to address concerns for adverse events with long-term (i.e., >1–2 years) use of low-dose GCs. In addition, only one reviewer performed data extraction and rated the QoE because of personnel constraints connected to the Coronavirus pandemic. Moreover, the SEMIRA trial (Burmester & Buttgereit et al., 2020) with its 259 randomized participants had a particularly large weight in our meta-analyses compared to the other trials. Finally, the trials were conducted at different timepoints, possibly leading to different results because of a rapidly changing treatment landscape.

In conclusion, this systematic review and meta-analysis found that continuing low-dose GCs in RA and SLE may provide better sustained disease control, but QoE is insufficient. Adrenal insufficiency is very rare when tapering low-dose GCs. Longer-term safety concerns for GCs remain. High-quality trials are needed to guide GC tapering and to assess whether there is a 'safe' GC dose when considering long-term treatment, especially in SLE, giant cell arteritis and polymyalgia rheumatica.

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CRediT authorship contribution statement

Andriko Palmowski: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing. **Anne Pankow:** Data curation, Writing – review & editing. **Kalina Terziyska:** Data curation. **Sabrina M Nielsen:** Conceptualization, Methodology, Writing – review & editing. **Robin Christensen:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Henning Bliddal:** Conceptualization, Supervision, Writing – review & editing. **Zhivana Boyadzhieva:** Data curation, Investigation, Writing – review & editing. **Frank Buttgereit:** Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

AP has received honoraria from Novartis for participating in advisory boards (unrelated to this manuscript). FB has received consultancy fees, honoraria and travel expenses from Abbvie, Pfizer, Gruenenthal, and Horizon Therapeutics, all unrelated to this manuscript. The other authors declare no conflicts of interest

Data availability

APalmowski and FB are willing to examine all requests for the gathered data and statistical code during a period of 5 years from the date of this publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152349.

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