August 10th, 2023

Confounding by Indication in Observational Studies Investigating Glucocorticoid-Associated Adverse Events in Rheumatoid Arthritis: A Protocol for a Systematic Review

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Competing Interests

FB has received consultancy fees, honoraria and travel expenses from AbbVie, Pfizer, Gruenenthal, and Horizon Therapeutics, all unrelated to this manuscript. The other authors report that they have no relevant competing interests to disclose.

Funding

None.

SUMMARY

Background Glucocorticoids (GCs) are regularly used drugs in rheumatoid arthritis (RA), but they can cause adverse events (AEs). Observational studies provide important real-world evidence but can be biased. Observational studies investigating the association between AEs and GCs in RA are particularly susceptible to confounding by indication as patients with higher disease activity are more likely to suffer from AEs and more likely to receive GCs.

Objective To assess how often observational studies in RA which investigate the association between GCs and certain AEs adjust for disease activity (such as the disease activity score-28 joints) and/or systemic inflammation (such as serum C-reactive protein levels).

Methods A systemic literature review will be conducted and reported in compliance with the 2020 PRISMA statement.

BACKGROUD AND RATIONALE

Glucocorticoids (GCs) are commonly used drugs in the treatment of rheumatoid arthritis (RA) due to their rapid onset of action and their disease-modifying properties. Despite the considerable benefits of GCs,[1] there is widespread controversy regarding the overall benefit-risk ratio as GCs can cause adverse events (AEs). However, much evidence on GC-related AEs is observational, and observational studies are subject to confounding. Regarding GCs, observational studies are particularly vulnerable to confounding by indication: Patients with more active disease are more likely to receive GCs, and these patients also have a higher likelihood of developing AEs such as osteoporosis or cardiovascular events.[2 3] If disease activity is not appropriately adjusted for, a false link between GCs and AEs can be established. Observational studies investigating the association between GCs and AEs must adjust for disease activity and/or inflammation (in addition to other confounders) in order to provide the dearly needed real-world information.

Our objective is to determine how many observational studies investigating the association between GCs and certain AEs in RA adjust their analyses for disease activity and/or inflammation.

METHODS

This systematic literature review will be conducted and reported in compliance with the 2020 update of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[4] This research protocol will be preregistered with the open-access online platform PROSPERO.

Eligibility Observational studies (cross-sectional, case-control, and cohort studies) investigating the association between GCs and certain AEs (see below; we chose AEs feared by patients and rheumatologists[5]) in patients with RA will be included. Of note, the primary objective of each study may have been to assess the association not only between GCs and AEs, but maybe also between other risk factors (e.g., age) and AEs. However, we require that GCs be mentioned in the study abstract. Studies must have been published in English since 2008 (i.e., we will include studies published within the last 15 years). No restrictions will be made concerning dosage and duration of GC therapy. In the published analyses, GCs may be analysed in any form, e.g., as a dichotomous variable (e.g., yes/no), as a multinomial variable (e.g., in groups such as 0mg/d, >0mg/d to <7.5mg/d, ≥7.5mg/d), or as a continuous variable. Different GC-related measures such as current dose, cumulative dose, average daily dose, or duration of use are allowed.

Data Sources MEDLINE (via PubMed) will be searched. We may miss some studies not indexed in MEDLINE. However, we deem it unnecessary to search other databases for completeness as we want to paint a picture of the overall RA research landscape and do not need every single study published in the field.

Search Strings The search strings, which can be found in the **Appendix**, were crafted using the PECOS[6] criteria (**Table 1**).

Table 1. Eligibility criteria

Eligibility criteria	
Population	Patients with rheumatoid arthritis
Exposure	Glucocorticoids OR higher dose/duration of glucocorticoids
Comparator	No glucocorticoids OR lower dose/duration of glucocorticoids
Outcome	Adverse events which were found to be especially worrisome in a survey among rheumatologists and patients[5]: Death Bone-related: Bone mineral density, fractures, osteoporosis Cardiovascular: Overall cardiovascular events, stroke, myocardial infarction, hypertension Endocrinological: Diabetes mellitus, weight gain Infectious diseases: Infections Psychiatric: Depression Ophthalmological: Cataract, glaucoma
Study Design	Observational studies

Study Selection Retrieved articles will be imported into EndNote software (Clarivate Analytics, Philadelphia, PA, USA). First, duplicates will be identified and removed using EndNote software. Two independent reviewers (JO and APalmowski) will then assess the articles for inclusion or exclusion based on the title and abstract. The remaining articles will go through a full text assessment. In case of disagreement, a third reviewer (APankow) will be consulted to reach a consensus on study inclusion through discussion.

Data Management, Items and Collection We will use Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA) and R (R Foundation for Statistical Computing, Vienna, Austria) software for data extraction and management.

Outcomes Our co-primary outcomes are adjustment for disease activity (dichotomous: yes or no) and systemic inflammation (dichotomous: yes/no) in the study's main (adjusted) analysis (analysis of primary outcome).

Disease activity must have been assessed with a validated disease activity composite score such as disease activity score-28 joints (DAS28; with either serum C-reactive protein or erythrocyte sedimentation rate) or similar (e.g., clinical disease activity index [CDAI], simplified disease activity index [SDAI], routine assessment of patient index data 3 [RAPID3], patient activity scale [PAS] II).[7] Inflammation must have been measured by serum C-reactive protein levels or erythrocyte sedimentation rate (or similar).

In case of longitudinal studies, we will investigate if disease activity and inflammation were adjusted for by using them as time-varying covariates or if only baseline values were used.

Risk of Bias Three reviewers (JO, APankow, and AB) will critically appraise study quality with tools supplied by the Joanna Briggs Institute (https://jbi.global/critical-appraisal-tools). If more than 50 studies are included, critical appraisal will be performed in a sample.

Statistical Analyses We will descriptively present study characteristics including our outcomes. Subgroup analyses will be conducted (see below).

Subgroup Analyses To explore potential sources of heterogeneity, we will perform subgroup analyses (e.g., comparing studies by year of publication, Journal Impact Factor, type of AE, type of study [longitudinal vs. cross-sectional], critical appraisal checklist score, etc.).

Data Synthesis Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria) will be used for analyses. For statistical analyses, the two-sided significance level α is set at .05.

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APPENDIX

Search String for MEDLINE (PubMed)

("Rheumatoid"[Title] OR "arthritis, rheumatoid"[MeSH:noexp])

AND

("cortison*"[Title/Abstract] OR "hydrocortison*"[Title/Abstract] OR "methylprednisolon*"[Title/Abstract] OR "predniso*"[Title/Abstract] OR "cortico*"[Title/Abstract] OR "glucocort*"[Title/Abstract] OR "steroid*"[Title/Abstract] OR "glucocorticoids"[MeSH:noexp])

AND

(("Fractures, Bone"[Mesh:NoExp] OR "Bone Density"[Mesh:NoExp] OR "Osteoporosis"[Mesh:NoExp] OR "Bone"[Title] OR "fracture*"[Title] OR “osteoporo*”[Title]) OR

("Stroke"[Mesh:NoExp] OR "Myocardial Infarction"[Mesh:NoExp] OR "Hypertension"[Mesh:NoExp] OR "Death"[Mesh:NoExp] OR "Cardiovascular"[Title] OR "stroke"[Title] OR "infarction"[Title] OR "hypertension"[Title] OR "death"[Title]) OR

("Diabetes Mellitus"[Mesh:NoExp] OR "Diabetes"[Title] OR "glucose"[Title]) OR

("Infections"[Mesh:NoExp] OR "infection*"[Title]) OR

(“depression”[Title] OR “mood”[Title] OR “Depression”[Mesh:NoExp] OR “Mood Disorders"[Mesh:NoExp]) OR

(“cataract”[Title] OR “Cataract”[Mesh:NoExp] OR “lens opacity”[Title]) OR

(“glaucoma”[Title] OR “Glaucoma”[Mesh:NoExp]))

NOT ("Review"[Title] OR "meta"[Title] OR "randomized"[Title] OR "randomised"[Title] OR "trial"[Title] OR review[pt])

AND (2008:2023[pdat])