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Changes in Bone Mineral Density and Incidence of Fractures during Two Years of Low Dose Glucocorticoid Treatment for Rheumatoid Arthritis: Protocol for a Systematic Review and Individual Participant Data Meta-Analysis

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SUMMARY

Background Glucocorticoids (GCs) are regularly used drugs in the treatment of rheumatoid arthritis (RA), and lower bone mineral density and fractures are common adverse effects of the treatment with higher GC dosages. However, the effects of low dose (i.e., ≤7.5mg/day) and very low dose (i.e., ≤5mg/day) treatment over longer periods of time (i.e., ≥ 24 months), as often seen in RA, have not been fully elucidated yet.

Objective To conduct a systematic review and meta-analysis of individual patient data from long-term randomized controlled trials (RCTs) in RA, which compared low dose GCs to a control treatment, in order to investigate the effects on bone mineral density and incidence of fractures (clinical/symptomatic).

Methods We will search the literature to identify published trials which collected data on bone mineral density and/or the incidence of fractures. This will be followed by the acquisition of individual participant data. Included RCTs will be combined to compare bone mineral density and fractures in GC and control groups. To underpin our findings, we will perform additional analyses to identify potential effect modifiers and a sensitivity analysis related to missing data.

BACKGROUND

Glucocorticoids (GCs) are commonly used drugs in the management of rheumatoid arthritis (RA) due to their rapid onset of action and their disease-modifying and damage-impeding properties.[1] While GCs remain an important adjunct treatment, especially when initiating or changing csDMARDs or in refractory and/or highly active disease despite treatment with disease-modifying anti-rheumatic drugs (DMARDs), the current EULAR recommendation advises that GCs be tapered and discontinued as rapidly as clinically feasible due to adverse events.[2] One of these adverse events is osteoporosis. Even low doses of GCs have been associated with fractures in observational research.[3] This poses a problem as patients with RA have an elevated risk of osteoporosis and fractures in general.[4]

RATIONALE

Observational studies on GCs can provide important real-world information. However, since GC therapy and disease activity are associated, observational studies on the role of GCs in fractures and osteoporosis can be biased. Randomized controlled trials (RCTs) offer protection against various sorts of confounding as patients are selected by chance whether or not to receive GCs. Consequently, only inference from randomized trials can answer the causal question of whether (and to what extent) GCs induce a decrease in bone mineral density (BMD) and amplify the risk of fractures in RA. It should be noted, however, that RCTs often have limited statistical power due to lower sample sizes. We will combine data from several RCTs to overcome this hurdle. The aim is to investigate the effects of long-term low-dose glucocorticoids in RA on bone mineral density and the incidence of clinical/symptomatic fractures by conducting a systematic literature review and meta-analysis of individual participant data from RCTs. The use of individual participant data will allow additional analyses related to GC dosages, missing data, and interactions.

METHODS

This research protocol for a systematic review and meta-analysis of individual patient data will be preregistered with the open-access online platform protocols.io. The final manuscript will adhere to the PRISMA-IPD statement [5].

Identifying Studies and Study Selection

In accordance with current recommendations outlined in the Cochrane Handbook [6], we will search for studies in three electronic international literature databases: MEDLINE (via PubMed), Embase (via Ovid) and the Cochrane Central Register of Controlled Trials (via Cochrane Library). The search strings and eligibility criteria were formulated using the PICOTS framework and can be found in the **Appendix** and **Table 1**, respectively.

The two reviewers (JO and AP) will independently screen the identified studies, first by title and abstract, then in full text, using EndNote X8 software (Clarivate Analytics, Philadelphia, PA, USA) or similar. Duplicates will be eliminated beforehand using EndNote X8 software. In case of disagreements, a third reviewer (FB) will be consulted to reach a consensus on study inclusion.

Table 1. PICOTS and eligibility criteria

PICOTS and eligibility criteria	
Population	Rheumatoid arthritis
Intervention	Low dose systemic glucocorticoid (GC) treatment (≤7.5mg/d prednisone equivalent) [7]
Comparator	Any (placebo or any other non-GC control)
Outcome	*No restrictions in search strategy*
Time	At least two years
Study Design	Randomized controlled trials
Other	Any language

Risk of Bias within Trials

The outcomes we will assess have, to our knowledge, sometimes not been published with the main trial articles. This makes it difficult to assess some domains of the widely acknowledged updated Cochrane RoB 2 tool [8]. Furthermore, principal investigators of trials we will include are co-authors of the present protocol. Consequently, a risk-of-bias assessment might itself be seen as biased. These reasons are why we decided not to perform assessments for the risk of bias within trials.

Data Collection, Items, and Management

After identifying eligible studies, we will contact the authors (primarily the first and/or last author) to obtain individual patient data (IPD). Trials that do not provide IPD will not be included in quantitative synthesis as we plan to conduct several additional analyses to identify potential effect modifies (especially subgroup analyses for at-risk patients). Subgroup analyses are not possible with aggregate data. For each trial, the data will be sent to the primary investigator (AP) and the senior researcher (FB) separately in an Excel or in a similar compatible file format. In case the data cannot be fully extracted, but are available on individual patient sheets, a doctoral candidate (JO) will extract the data, which is then reviewed by the primary investigator. The preferred time points of BMD assessments are baseline and 24 months. The outcome, fractures, includes clinical/symptomatic fractures during the 24-month study period. Missing data will be indicated with *NA*. The following data will, if available, be collected for each included trial:

Variable name	***Description***	***Timepoint***
Study_name	Name of clinical trial	Baseline
GC_dose	Dosage of GC in mg/d prednisone equivalent (presumably 0, 5, or 7.5)	Baseline
Patient_ID	Patient identification number	All visits
Contextual Factors and Patient Characteristics		
Age	Age	Baseline
Male Sex	1 = male, 0 = female	Baseline
Trial_arm	G = GC, P = Placebo	Baseline
ACPA positive	0 = negative, 1 = positive	Baseline
RF positive	Rheumatoid factor: 0 = negative, 1 = positive	Baseline
Smoking	0 = never smoked, 1 = previous smoker, 2 = current smoker	Baseline
BMI	Body mass index (kg/m^2)	Baseline

DAS28	Disease activity score based on 28 joints	Baseline
Disease duration	Years	Baseline
Pain	Pain numerical or visual analogue scale (0-10)	Baseline
ESR	ESR mm/h	Baseline
CRP	CRP mg/L	Baseline
HAQ-DI	Health Assessment Questionnaire	Baseline
Outcomes:		
BMD	Bone Mineral Density, g/cm^2 or T-Score (reported separately for each measurement site)	Baseline and FU
Fractures	Number of clinical (symptomatic) fractures during study	FU

Abbreviations: ACPA, anti-citrullinated protein antibodies; RF, rheumatoid factor; BMI, body mass index; DAS, disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HAQ, health assessment questionnaire; FU, follow-up.

For data extraction, harmonization, and management, we will use Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) as well as the statistical software SPSS (IBM, Armonk, NY, USA) or similar.

Risk of Bias Across Trials

If a meaningful number of studies can be included, we will assess publication bias in our co-primary outcomes by visual inspection of funnel plots.

Data Integrity

Supplied data will be checked for consistency with published data by assessing patient numbers and baseline values in each group of each trial.

Statistical Analysis

We will report both P values and 95% confidence intervals for our statistical analyses with a two-sided interpretation. Instead of applying explicit adjustments for multiple testing, we will limit the number of statistical tests performed. Tests will be conducted for our two co-primary outcomes: Fractures during the study (clinical or symptomatic) and changes in BMD from baseline until two years (in g/cm²). If several measurement sites are available for the analysis of BMD, we will use the lowest T-score available for each patient of the following: total hip, femoral neck, or lumbar spine. We will consider a P value of < 0.05 as statistically significant. To handle missing outcome data, we will use multiple imputation by chained equations. Missing baseline characteristics will be replaced by the grand mean across all data sets. Statistical analysis will be performed using R or a similar software. Descriptive data will be presented stratified by group (GC versus control).

For our primary analysis, we will use a one-stage analysis. For change in BMD, we will use an analysis of covariance (ANCOVA) model, including treatment (two levels), baseline value of the outcome (one for each participant), and trial ID as terms. Trial ID will be treated as a random effect and accounts for clustering of patients within trials. For fractures, we will use a logistic regression including similar terms. Least squares means will be obtained from these models and contrasts (with 95% confidence intervals) will be estimated at follow-up. I^2 will be estimated from standard random effects meta-analysis models (by performing a two-stage analysis).

Subsequently, we will conduct the following interaction/subgroup analyses – only with change in BMD as the outcome as we expect fractures to be too rare to allow for adequate statistical power –

to assess potential effect modifiers. Continuous variables without commonly used cut-off values will be converted to binary by using medians to define subgroups (median and above versus below median).

1) Interaction between treatment and seropositivity (i.e., to assess the effect of GCs on the change in BMD in seropositive vs. seronegative patients)
2) Interaction between treatment and smoking status (i.e., to assess the effect of GCs on the change in BMD in smokers vs. prior smokers vs. never smokers)
3) Interaction between treatment and dose (i.e., to assess the effect of GCs on the change in BMD in 5mg/d vs. 7.5mg/d GCs)
4) Interaction between treatment and BMD (i.e., to assess the effects of GCs on the change in BMD depending on baseline BMD [cut-off: median])
5) Interaction between treatment and weight at baseline (i.e., to assess the effects of GCs on the change in BMD depending on baseline weight [cut-off: median])
6) Interaction between treatment and DAS28 at baseline (i.e., to assess the effects of GCs on the change in BMD in different levels of baseline DAS28 [remission, low, moderate, high disease activity])
7) Interaction between treatment and CRP at baseline (i.e., to assess the effects of GCs on the change in BMD depending on baseline CRP [cut-off: median])
8) Interaction between treatment and HAQ at baseline (i.e., to assess the effects of GCs on the change in BMD depending on baseline HAQ [mild to moderate, moderate to severe, very severe disability])
9) Interaction between treatment and age at baseline (i.e., to assess the effects of GCs on the change in BMD depending on baseline age [cut-off: median])

A sensitivity analysis will be conducted to assess whether the missing at random assumption is valid:

a) Replication of main analysis based on as-observed data instead of imputed data.

MANUSCRIPT OUTLINE

Figure 1: Flow Chart (Study Selection)

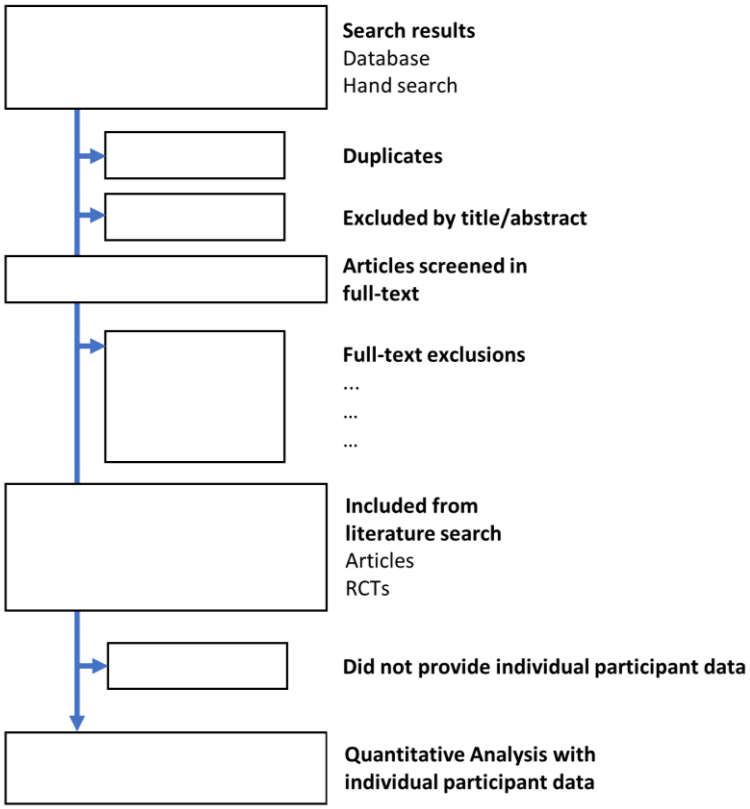

Table 1: Baseline Characteristics

	GC group n = xxx	***Control group n = xxx***
Age, years		
Female, n(%)		
ACPA positive, n(%)		
RF positive, n(%)		
Smoking status:		
Never smoked, n(%)		
Previous smoker, n(%)		
Current smoker, n(%)		
BMI, kg/m^2		
DAS28, score		
Disease duration, years		
Pain (NAS or VAS, 0-10)		
ESR, mm/h		
CRP, mg/l		
HAQ, score		
BMD, g/cm2		

Values are mean (SD), unless otherwise indicated. NAS, numerical analogue scale, VAS, visual analogue scale, ACPA, anti-citrullinated protein antibody, RF, rheumatoid factor, BMI, body mass index, DAS28, disease activity score 28 joints, ESR, erythrocyte sedimentation rate, CRP, C-reactive protein, HAQ, health assessment questionnaire, BMD, bone mineral density.

Table 2: Main analysis

	GC group	***Control group***	***Contrast***	***P value***
Change in BMD from baseline until two years, g /cm²				
Fractures during the study period				

Figure 2: Forest plot of interaction/subgroup analyses.

APPENDIX

Search Strings: MEDLINE (via PubMed)

(Rheumatoid [Title] OR Arthritis, Rheumatoid [MESH:NoExp])

AND

(Alclometason*[TiAb] or Amcinonid*[TiAb] or Beclomethas*[TiAb] or Beclomethason*[TiAb] or Betamethason*[TiAb] or Budesonid*[TiAb] or Clobetaso*[TiAb] or Clocortolon*[TiAb] or Clopredno*[TiAb] or Cortison*[TiAb] or Cortivazo*[TiAb] or Deflazacor*[TiAb] or Desoximetason*[TiAb] or Dexamethason*[TiAb] or Dichlorison*[TiAb] or Diflorason*[TiAb] or Diflucortolon*[TiAb] or Difluprednat*[TiAb] or Flumethason*[TiAb] or Fluocinolon*[TiAb] or Fluocinonid*[TiAb] or Fluocorti*[TiAb] or Fluocortolon*[TiAb] or Fluorometholon*[TiAb] or Flupredniden*[TiAb] or Fluprednisolon*[TiAb] or Flurandrenolon*[TiAb] or Fluticason*[TiAb] or Hydrocortison*[TiAb] or Medryson*[TiAb] or Melengestro*[TiAb] or Meprednison*[TiAb] or Methylprednisolon*[TiAb] or Paramethason*[TiAb] or Prednicarbat*[TiAb] or Predniso*[TiAb] or Rimexolon*[TiAb] or Triamcinolon*[TiAb] or Cortico*[TiAb] or Glucocort*[TiAb] or Steroid*[TiAb] or Glucocorticoids[MeSh:NoExp])

AND

(Trial[Title] OR Randomi*[Title] OR Controlled[Title] OR Randomized Controlled Trial[Publication Type:NoExp])

Search String: EMBASE (via Ovid)

(Rheumatoid.ti or rheumatoid arthritis/)

AND

((Alclometason* or Amcinonid* or Beclomethas* or Beclomethason* or Betamethason* or Budesonid* or Clobetaso* or Clocortolon* or Clopredno* or Cortison* or Cortivazo* or Deflazacor* or Desoximetason* or Dexamethason* or Dichlorison* or Diflorason* or Diflucortolon* or Difluprednat* or Flumethason* or Fluocinolon* or Fluocinonid* or Fluocorti* or Fluocortolon* or Fluorometholon* or Flupredniden* or Fluprednisolon* or Flurandrenolon* or Fluticason* or Hydrocortison* or Medryson* or Melengestro* or Meprednison* or Methylprednisolon* or Paramethason* or Prednicarbat* or Predniso* or Rimexolon* or Triamcinolon* or Cortico* or Glucocort* or Steroid*).ti,ab OR glucocorticoid/)

AND

((Trial OR Randomi* OR Controlled).ti)

Search String: Cochrane CENTRAL

#1 MeSH descriptor: [Arthritis, Rheumatoid] this term only
#2 rheumatoid:ti
#3 #1 OR #2
#4 (Alclometason* or Amcinonid* or Beclomethas* or Beclomethason* or Betamethason* or Budesonid* or Clobetaso* or Clocortolon* or Clopredno* or Cortison* or Cortivazo* or Deflazacor* or Desoximetason* or Dexamethason* or Dichlorison* or Diflorason* or

Diflucortolon* or Difluprednat* or Flumethason* or Fluocinolon* or Fluocinonid* or Fluocorti* or Fluocortolon* or Fluorometholon* or Flupredniden* or Fluprednisolon* or Flurandrenolon* or Fluticason* or Hydrocortison* or Medryson* or Melengestro* or Meprednison* or Methylprednisolon* or Paramethason* or Prednicarbat* or Predniso* or Rimexolon* or Triamcinolon* or Cortico* or Glucocort* or Steroid*):ti,ab

#5 MeSH descriptor: [Glucocorticoids] this term only

#6 #4 OR #5

#7 (Trial OR Randomi* OR Controlled):ti

#8 ("randomized controlled trial"):pt

#9 #7 or #8

#10 #3 AND #6 AND #9

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