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A systematic literature review into the success rate of discontinuation glucocorticoids after their use as bridging therapy in clinical trials and observational cohorts

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ABSTRACT

Objective: To investigate the success rate of GC discontinuation during at least 12 months of follow-up in clinical trials using GC as bridging therapy in newly diagnosed rheumatoid arthritis (RA) patients.
Methods: A systematic literature searches will be conducted to identify clinical trials including RA patients treated with initial GC bridging with at least 12 months follow-up. Bridging therapy will be defined as tapering within the first 6 months after start of GC and complete discontinuation within one year. After assessment of heterogeneity, a separate meta-analysis will be performed in case at least three studies have the outcome of interest available.
Data source: A systematic literature search will be conducted in MEDLINE, Embase, Web of Science, COCHRANE library, Emcare and Academic Search Premier

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Objective

1 To investigate the success rate of glucocorticoids (GC) discontinuation during at least 12 months of follow-up in clinical trials using GC as bridging therapy in newly diagnosed rheumatoid arthritis (RA) patients.

Methods

2 ***Review strategy***

The program Rayyan will be used to keep track of the reviewing process:
M. Ouzzani, H.Hammady, Z. Fedorowicz, A. Elmagarmid. Rayyan — a web and mobile app for systematic reviews. Systematic Reviews (2016) 5:210, DOI: 10.1186/s13643-016-0384-4.

Search results will first be screened by title and abstract, and subsequently based on full text reading based on the following exclusion criteria (in this order):
- No randomized clinical trial
- No rheumatoid arthritis patients
- Patients are not MTX or DMARD naïve
- Patients do not receive GC bridging therapy or a single dose of GCs as part of the initial treatment
- Not at least 12 months of follow-up

Two reviewers will first review 100 abstract to test whether these exclusion criteria are sufficient to identify all relevant abstracts and to reach agreement on the abstracts to include for full text reading (training set). In case of considerable changes to the exclusion criteria, they will review another 100 abstracts (second training set). Next, one reviewer will review all abstracts. The second reviewer will review 10% of the abstracts to calculate an inter rater agreement.
One reviewer will perform full-text reading. In case of doubt, the second reviewer will also perform full-text reading.
Risk of bias at the study level will be assessed using the Cochrane Collaborations Risk of Bias tool for randomised controlled trials.

Another option, in case of a high number of search results, would be to independently read 200 abstracts after the training set, calculate an inter-rater agreement and divide the abstracts afterwards.

Meta-analysis

Also heterogeneity in reported results is expected. All available outcomes as mentioned in the PICOS will be listed for each of the identified articles. Outcomes that are reported at least three times will be included in a random effects meta-analysis. The between study standard deviation and the I-squared will be used as measures of heterogeneity between studies.

3 *Data source*

A systematic literature search was conducted in MEDLINE, Embase, Web of Science, COCHRANE library, Emcare and Academic Search Premier to find clinical trials about newly diagnosed DMARD naïve RA patients treated with initial GC bridging with at least 12 months follow-up.

4 *Search strategy*

(("Arthritis, Rheumatoid"[Mesh:noexp] OR "rheumatoid arthritis"[tw] OR "early rheumatoid arthritis"[tw] OR "early rheum*"[tw] OR "early arthritis"[tw] OR "early arthri*"[tw] OR "early RA"[tw] OR "recent onset rheum*"[tw] OR "recent onset arthri*"[tw] OR "recent onset RA"[tw]) AND ("Glucocorticoids"[mesh] OR "Glucocorticoids"[Pharmacological Action] OR "Glucocorticoids"[tw] OR "Glucocorticoid"[tw] OR "glucocorticoid*"[tw] OR "alclometasone dipropionate" [Supplementary Concept] OR "amcinonide"[Supplementary Concept] OR "Beclomethasone"[mesh] OR "Betamethasone" [mesh] OR "betamethasone acetate"[Supplementary Concept] OR "betamethasone benzoate"[Supplementary Concept] OR "betamethasone dipropionate, betamethasone sodium phosphate drug combination"[Supplementary Concept] OR "betamethasone sodium phosphate"[Supplementary Concept] OR "Betamethasone Valerate"[mesh] OR "Budesonide" [mesh] OR "ciclesonide"[Supplementary Concept] OR "Clobetasol"[mesh] OR "clobetasone butyrate"[Supplementary Concept] OR "clocortolone"[Supplementary Concept] OR "clocortolone pivalate"[Supplementary Concept] OR "Desoximetasone"[mesh] OR "Dexamethasone"[mesh] OR "dexamethasone 21-phosphate"[Supplementary Concept] OR "Dexamethasone Isonicotinate"[mesh] OR "dichlorisone acetate"[Supplementary Concept] OR "diflorasone" [Supplementary Concept] OR "Diflucortolone"[mesh] OR "difluprednate"[Supplementary Concept] OR "drocinonide phosphate potassium"[Supplementary Concept] OR "Flumethasone"[mesh] OR "flumethasone pivalate"[Supplementary Concept] OR "Fluocinolone Acetonide"[mesh] OR "Fluocinonide"[mesh] OR "fluocortin butyl ester"[Supplementary Concept] OR "Fluocortolone"[mesh] OR "Fluorometholone"[mesh] OR "fluperolone acetate"[Supplementary Concept] OR "fluprednidene acetate"[Supplementary Concept] OR "Fluprednisolone"[mesh] OR "Flurandrenolone"[mesh] OR

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"Fluticasone-Salmeterol Drug Combination"[mesh] OR "FX006"[Supplementary Concept] OR "halometasone" [Supplementary Concept] OR "medrysone"[Supplementary Concept] OR "Melengestrol Acetate"[mesh] OR "Methylprednisolone"[mesh] OR "Methylprednisolone Hemisuccinate"[mesh] OR "Paramethasone"[mesh] OR "prednicarbate"[Supplementary Concept] OR "Prednisolone"[mesh] OR "prednisolone hemisuccinate"[Supplementary Concept] OR "prednisolone phosphate"[Supplementary Concept] OR "Prednisone"[mesh] OR "rimexolone" [Supplementary Concept] OR "terofenamate"[Supplementary Concept] OR "Tobramycin, Dexamethasone Drug Combination"[mesh] OR "Triamcinolone"[mesh] OR "Triamcinolone Acetonide"[mesh] OR "triamcinolone benetonide" [Supplementary Concept] OR "alclometasone dipropionate"[tw] OR "amcinonide"[tw] OR "Beclomethasone"[tw] OR "Betamethasone"[tw] OR "betamethasone acetate"[tw] OR "betamethasone benzoate"[tw] OR "betamethasone dipropionate, betamethasone sodium phosphate drug combination"[tw] OR "betamethasone sodium phosphate"[tw] OR "Betamethasone Valerate"[tw] OR "Budesonide"[tw] OR "ciclesonide"[tw] OR "Clobetasol"[tw] OR "clobetasone butyrate"[tw] OR "clocortolone"[tw] OR "clocortolone pivalate"[tw] OR "Desoximetasone"[tw] OR "Dexamethasone"[tw] OR "dexamethasone 21-phosphate"[tw] OR "Dexamethasone Isonicotinate"[tw] OR "dichlorisone acetate"[tw] OR "diflorasone"[tw] OR "Diflucortolone"[tw] OR "difluprednate"[tw] OR "drocinonide phosphate potassium"[tw] OR "Flumethasone"[tw] OR "flumethasone pivalate"[tw] OR "Fluocinolone Acetonide"[tw] OR "Fluocinonide"[tw] OR "fluocortin butyl ester"[tw] OR "Fluocortolone"[tw] OR "Fluorometholone"[tw] OR "fluperolone acetate"[tw] OR "fluprednidene acetate"[tw] OR "Fluprednisolone"[tw] OR "Flurandrenolone"[tw] OR "Fluticasone-Salmeterol Drug Combination"[tw] OR "FX006"[tw] OR "halometasone"[tw] OR "medrysone"[tw] OR "Melengestrol Acetate"[tw] OR "Methylprednisolone"[tw] OR "Methylprednisolone Hemisuccinate"[tw] OR "Paramethasone"[tw] OR "prednicarbate"[tw] OR "Prednisolone"[tw] OR "prednisolone hemisuccinate"[tw] OR "prednisolone phosphate"[tw] OR "Prednisone"[tw] OR "rimexolone"[tw] OR "terofenamate"[tw] OR "Tobramycin, Dexamethasone Drug Combination"[tw] OR "Triamcinolone" [tw] OR "Triamcinolone Acetonide"[tw] OR "triamcinolone benetonide"[tw]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mesh] OR random allocation[mesh] OR double-blind method[mesh] OR single-blind method[mesh] OR clinical trial[pt] OR clinical trials[mesh] OR "clinical trial"[tw] OR ((singl* [tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR "latin square"[tw] OR placebos[mesh] OR placebo*[tw] OR random*[tw] OR research design[mesh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR follow-up studies[mesh] OR prospective studies[mesh] OR cross-over studies[mesh] OR control[tw] OR controll*[tw] OR prospectiv*[tw] OR volunteer*[tw] OR "rct"[tw] OR "trial"[tw]))

5 *Outcomes*

- Proportion of patients on GCs
- 1, 3, 6, 12 and 18 months after the induction scheme.
- at 12 and 24 months follow-up
- longer follow-up?

-Cumulative GC dose at 6, 12 and 18 months follow-up.
-Proportion of patients with at least 3 months of continuous GC use within 12 and within 24 months (and longer?) of follow-up outside of the induction scheme.
-Number of GC episodes within 12 and within 24 months (and longer?) outside of the induction scheme.
-Mean or median GC dose in patients still using GCs 1, 3, 6 and 12 months (and longer?) after the induction scheme.
-Proportion of patients that flare after stopping their GC
-Mean or median GC dose in patients who stopped.
-Cumulative GC dose in patients who stopped.
-Mean/median duration of GC therapy when stopping.
-Disease activity at 12 and 24 months of follow-up in patients who continued and in patients who stopped GCs.
-Proportion of patients that change their DMARD after they flare after stopping GC treatment.
DMARD dose in patients who stopped vs. patients who continued GC at 12 and 24 months of follow-up. Cumulative dose might not be the best measure to report GC dosing over longer follow-up periods (e.g. 24 months). A high initial dose that is subsequently tapered may have the same cumulative dose as a lower dose that remains stable, but the risk profile may not be similar.

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