Glucocorticoid withdrawal schemes in chronic medical disorders: a systematic review

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Authors' objectives
To determine the effects of different glucocorticoid withdrawal schemes on the risk of treatment failure and adverse events.

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched to 2001; the search strategies were provided. The Science Citation Index was also searched and the reference lists of eligible studies were checked for further references.

Study selection

Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies comparing different forms of glucocorticoid withdrawal, following their use in the stabilisation of an acute exacerbation of a chronic disease, were eligible for inclusion. The included studies were of prednisone, prednisolone and methylprednisolone, with intravenous or intramuscular administration, and a stabilisation period ranging from 3 days to 3 weeks. The programme of withdrawal ranged from zero to 21 weeks. The total glucocorticoid dose during withdrawal ranged from zero mg to 6,300 mg/m2.

Participants included in the review
Participants with any chronic medical disorder (definition provided) who were undergoing glucocorticoid withdrawal were eligible for inclusion. The participants in the included studies were aged from 28 to 68 years; some studies only included men. The participants had Crohn's disease, acute asthma, moderate to severe acute graft-versus-host disease (GVHD) in association with bone marrow transplant, and chronic obstructive pulmonary disease (COPD).

Outcomes assessed in the review
Studies reporting data on safety and efficacy were eligible for inclusion. The main outcome measures of interest were treatment failures (i.e. exacerbation or relapse of the disease or biological indicators of worsening of the disease), the adverse effects of glucocorticoid administration and withdrawal, and the change of morbidity indicators and effects on mortality.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the identified articles and any disagreements were resolved by consensus.

Assessment of study quality
The studies were assessed for randomisation, allocation concealment, blinding, description of withdrawals and drop-outs, and intention-to-treat analysis. Two reviewers independently assessed each study for quality and any disagreements were resolved by consensus.

Data extraction
The data were extracted in duplicate using a data extraction form. Data were extracted for the primary outcome in each study in addition to other outcomes and adverse effects.

Methods of synthesis
How were the studies combined?
A narrative synthesis of the trials was undertaken. Where more than one study was available, common conditions were grouped together.

How were differences between studies investigated?
Differences between the trials were reported in the tables and discussed in the text.

Results of the review
Nine RCTs (n=556) were included.

Two trials mentioned allocation concealment; three trials blinded patients and health care staff; most trials reported drop-outs in detail; one trial reported an intention-to-treat analysis; and two trials measured patient compliance with therapy. The number of trial participants ranged from 20 to 271.

Crohn's disease (1 trial): there was no significant difference in disease remission rate after 6 months between a 7-week and 15-week glucocorticoid withdrawal programme.

Bone marrow transplant GVHD (1 trial): there was a quicker (P<0.05) but not more frequent resolution of GVHD in a 21-week versus a 12-week withdrawal programme. The other outcomes did not differ significantly.

Acute asthma attacks (5 trials): three of the trials used abrupt withdrawal (two of which used placebo tapering). There were no significant differences between different glucocorticoid withdrawal programmes for the following: lung function, relapses, hospital admissions, severe exacerbations, median length of stay in hospital, and symptom scores. In all of the trials, patients were receiving medium to high doses of inhaled glucocorticoids during the withdrawal programmes.

COPD (2 trials): in one trial, a 3-day stabilisation course of glucocorticoids followed by a 7-day withdrawal programme was related to statistically significant improved outcomes in lung function, arterial oxygenation and dyspnea on exertion, compared with a 7-day placebo withdrawal. There was no significant difference in acute exacerbation within 6 months. In another study there was no statistically significant difference in treatment failure between an 8-week glucocorticoid, 2-week glucocorticoid and a placebo withdrawal programme.

Authors' conclusions
The authors stated that there was no clear relation between the rapidity of glucocorticoid withdrawal and the risk of treatment failure, and there were no clinically significant differences in adverse effects between the various glucocorticoid withdrawal programmes. In patients with asthma and COPD who were receiving concomitant inhaled glucocorticoid therapy, the rapid withdrawal of corticoids did not result in an increase in exacerbations compared with longer withdrawal programmes.

CRD commentary
The review question was clearly stated, although the inclusion criteria for the participants was very broad. A number of relevant databases were searched and there did not appear to have been any language restrictions. However, attempts could have been made to identify unpublished studies and studies may have been missed. The study selection, data extraction and quality assessment processes were carried out in duplicate, which helps to reduce errors and any bias. Adequate details on the individual studies were provided. A narrative synthesis was appropriate given the presence of clinical heterogeneity. A quality assessment was reported but the discussion of the findings, in the context of study quality, was limited. The authors' conclusions appear to follow from the evidence presented though, as they pointed out, the findings are not applicable to all chronic conditions.

Implications of the review for practice and research
Practice: The authors stated that the evidence suggests that the termination of glucocorticoid therapy can be achieved after one to two weeks in patients with bronchial asthma and COPD, but the evidence for other chronic conditions is
Research: The authors stated that high-quality studies are required in relation to the safety and efficacy of glucocorticoid withdrawal in chronic conditions. The outcomes where evidence is particularly sparse are quality of life, well-being, and symptoms and socioeconomic consequences.

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