Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis

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CRD summary
The authors concluded that longer courses of glucocorticoids in antibody-associated vasculitis were associated with fewer relapses. The conclusions appeared reliable, but poor-quality included studies and potential error and bias in the review processes suggest a need for caution.

Authors’ objectives
To assess if glucocorticoids target doses influence relapses of antibody-associated vasculitis.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched from January 1995 to December 2008. Search terms were reported. Reference lists of relevant articles were handsearched. Experts in the field were contacted. Abstract-only publications were considered. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) and observation studies with treatment regimens that included glucocorticoids or where glucocorticoid treatments were protocol driven were eligible for inclusion. Studies had to enrol patients with antibody-associated vasculitis (Wegener’s granulomatosis, microscopic polyangiitis and/or renal-limited vasculitis, but not Churg-Strauss syndrome) and report relapses as an outcome. Studies with less than 18 months follow-up were excluded. Studies that did not report outcomes for patients with antibody-associated vasculitis separately from those without antibody-associated vasculitis were excluded.

Included studies enrolled patients with Wegener’s granulomatosis alone (eight studies) and with both Wegener’s granulomatosis and microscopic polyangiitis (five studies). All included studies enrolled patients with at least some renal involvement. The proportion of women ranged from 36% to 54%. The proportion of patients with Wegener’s granulomatosis and microscopic polyangiitis ranged from zero to 100%. The proportion of patients with renal involvement (where reported) ranged from 28% to 100%. Mean age of patients ranged from 35 to 62 years. Serum creatine levels were varied (range 106 to 255m/L). None of the included studies directly compared glucocorticoids regimens. Induction and maintenance treatments included methotrexate, cyclophosphamide, azathioprine, mycophenolate mofetil and leflunomide. Oral glucocorticoids therapy consisted of either prednisone or prednisolone.

One reviewer initially assessed abstracts of identified articles for eligibility; further evaluation of preselected articles against inclusion and exclusion criteria was performed by two reviewers.

Assessment of study quality
The quality of included RCTs was assessed using the Jadad scale of randomisation, blinding and withdrawals; scores ranged from zero to 5.

The quality of cohort studies was assessed using four items from the Downs and Black checklist: by whom and when groups were accrued, description of withdrawals/dropouts and adjustment for confounding variables.

The authors stated that disagreements were resolved by consensus. They did not specify how many reviewers performed quality assessment.

Data extraction
Data on outcomes (proportion of patients with a relapse) were abstracted using standardised forms; disagreements were resolved by consensus. Authors of primary studies were contacted if data were incomplete and where uncertainties
The authors stated that disagreements were resolved by consensus, but did not specify how many reviewers performed data extraction.

**Methods of synthesis**
Studies that attempted to fully withdraw glucocorticoids at any point in the study were classed as zero glucocorticoids target dose; those that did not attempt to withdraw glucocorticoids during the study period were classed as non-zero glucocorticoids target dose.

The pooled proportion of patients with a relapse was calculated using random-effects meta-analysis (DerSimonian and Laird methods). Heterogeneity was assessed using Q and I^2. Meta-regression was used to explore factors (such as classification of glucocorticoids target dose, inclusion of newly diagnosed patients only, withdrawal of immunosuppressive medications) that potentially contributed to between-study variations.

**Results of the review**
Thirteen studies were included (n=983 participants, range 30 to 164): eight RCTs (n=776) and five observational studies (n=205). Study quality was mixed. One RCT scored 3 and all others scored 2. All observational cohort studies selected patients from the same population and adequately accounted for patient dropouts, but one recruited patients from different time periods.

The pooled proportion of patients with a relapse was 36% (95% CI 25% to 47%, I^2=93.4%). Glucocorticoid regimen was the most significant variable explaining variability between the proportions of patients with relapses.

The proportion of patients with a relapse was 14% (95% CI 10% to 19%) in non-zero glucocorticoids target dose studies (n=288 patients) and 43% (95% CI 33% to 52%) in zero glucocorticoids target dose studies (n=695 patients).

**Authors’ conclusions**
Longer courses of glucocorticoids in antibody-associated vasculitis were associated with fewer relapses.

**CRD commentary**
The review addressed a well-defined question. Three databases were searched without any language restrictions and efforts were made to search for unpublished literature. Steps were taken to minimise potential reviewer error and bias during study selection; it was unclear whether similar steps were applied in data extraction and quality assessment. Study quality was assessed using the Jadad scale (considered inadequate) and a quality checklist; results were reported to be mixed. Statistical methods used to combine study results appeared adequate. The authors acknowledged a number of weaknesses in the review (inability to assess for all potential confounders, limited statistical power in some analyses and differences in definitions of relapses).

The authors’ conclusions appeared reliable, but poor-quality included studies and potential for error and bias in the review processes suggest a need for caution.

**Implications of the review for practice and research**
**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that additional adequately powered RCTs that compared protocols that utilised longer durations of low-dose glucocorticoids and protocols with early discontinuation were needed. Future studies must take into account the impact of glucocorticoids tapering regimens on relapse rates since they may substantially alter sample size estimations.

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