Corticosteroid therapy does not reduce the rate of relapse in Crohn disease


Questions
Is conventional systemic corticosteroid therapy effective and safe for maintenance of clinical remission in Crohn disease? What is the long-term toxicity of corticosteroid therapy?

Data sources
Studies were identified with MEDLINE (1966 to May 1998) by using the index terms Crohn disease, inflammatory bowel disease, and glucocorticoid and synthetic glucocorticoid (exploded). Lists of conference proceedings for 1985 to 1997, bibliographies of relevant studies, and trial registers from the Cochrane Library and the Inflammatory Bowel Disease Review Group were scanned.

Study selection
Randomized, double-blind, placebo-controlled trials were selected if patients of any age with Crohn disease in clinical remission at baseline (Crohn Disease Activity Index score < 150, absence of symptoms, or mild symptoms) were studied; if oral systemic corticosteroid therapy was evaluated; and if outcome data were provided for relapse, adverse effects, withdrawals caused by side effects, and drug interactions. Studies that evaluated topically active corticosteroid agents, such as budesonide and fluticasone, were excluded. Studies published in English, French, Spanish, Italian, and German were reviewed for possible inclusion.

Data extraction
Data were extracted on methodologic quality; patient and disease characteristics; interventions; outcomes at 6, 12, and 24 months; and adverse effects. A fixed-effects model was used to combine the data.

Main results
Of 8 studies identified, 3 met the inclusion criteria (368 patients in each of the active drug and placebo groups). Regimens studied were prednisolone, 7.5 mg/d for 3 years; prednisone, 0.25 mg/kg of body weight per day for 2 years; and 6-methylprednisolone, 8 mg/d for 2 years. No study, individually or in combination, showed a reduction in the relapse rate of Crohn disease overall or at 6, 12, or 24 months. Overall odds ratio for relapse was 0.75 (95% CI 0.54 to 1.06); odds ratio for relapse at 24 mo was 0.72 (CI 0.38 to 1.35); odds ratio for relapse at 12 mo was 0.82 (CI 0.47 to 1.43); and odds ratio for relapse at 6 mo was 0.71 (CI 0.38 to 1.31). Data on adverse effects were not adequate for analysis.

Conclusion
Oral systemic corticosteroid therapy does not reduce the relapse rate for Crohn disease at 6, 12, or 24 months. Source of funding: No external funding.


Commentary
Although the landmark National Cooperative Crohn's Disease Study (NCCDS) (1) and European Cooperative Crohn's Disease Study (ECCDS) (2) failed to show a benefit of low-dose (5 to 20 mg/d) glucocorticoid maintenance therapy, some clinicians believe that this strategy is effective in some patients. Limited data are available to support this viewpoint. In the ECCDS, a subgroup of patients who received glucocorticoid therapy for induction of remission before receiving glucocorticoid maintenance therapy appeared to have a lower risk for relapse than those who received placebo. In the NCCDS, patients with colonic disease appeared to benefit.

Although the methodologically rigorous meta-analysis by Steinhart and colleagues failed to identify a statistically significant benefit of glucocorticoid maintenance therapy, the pooled estimates of the treatment effect consistently showed a trend favoring the intervention over placebo. As the wide confidence intervals around the estimates suggest, insufficient numbers of patients were studied in the 3 trials for any meaningful subgroup analyses to be done. An overall evaluation of the frequency of adverse drug reactions was also not possible because of differences among the trials in the definition of these outcomes.

These findings are unlikely to change the opinions of the antagonists in the maintenance therapy debate. Those who adhere to the orthodox viewpoint, that glucocorticoid maintenance therapy is ineffective, can point to the lack of a statistically significant treatment effect confirmed by the current study. True believers, however, can take solace in a "trend" toward a benefit and invoke the possibility of a type II statistical error (power failure) and the inability of the current study to examine the effects of treatment in those ethereal subgroups who may benefit. Nevertheless, most clinicians have already accepted the bottom-line message of this overview, which is that the therapeutic index of glucocorticoid maintenance therapy is unacceptably low.

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References