

Seymour Katz, M.D., Series Editor

Steroids and Crohn's Disease: Use and Abuse

by Peter M. Irving, Peter R. Gibson

Steroids were first used to treat Crohn's disease over 50 years ago. Since that time it has become evident that steroids rapidly improve the symptoms of active disease but are both ineffective and inappropriate for the maintenance of remission. However, although steroids are associated with an array of side-effects, it must also be remembered that many of these side effects may also be caused by active disease. Furthermore, while there are newer drugs available for the treatment of Crohn's disease, many gastroenterologists still feel more comfortable using a drug with which they are familiar. For this reason, it is important that efforts continue to optimize the use of corticosteroids in Crohn's disease.

INTRODUCTION

The advent of the "biologic era" in the management of Crohn's disease has focused attention on how we use some of the older treatments for this condition. Corticosteroids, in particular, have come in for their fair share of criticism. In this article we shall review how much of this criticism is justified, and whether the use of corticosteroids has become an anachronism or is still an accepted part of the management of Crohn's disease

REMISSION INDUCTION

Corticosteroids are potent anti-inflammatory agents capable of promptly improving the symptoms of active Crohn's disease in the majority of patients. Two large scale randomized placebo controlled trials (the National (1) (NCCDS), and European (2) (ECCDS)

Peter M. Irving and Peter R. Gibson, Monash University Department of Medicine, Department of Gastroenterology, Box Hill Hospital, Melbourne, Australia.

Cooperative Crohn's Disease Studies), along with several excellent natural history studies (3,4) clearly demonstrate that oral prednisolone given at doses of 40–60 mg or 0.5–1 mg/kg will induce remission in up to about 80% of patients with active Crohn's disease. The remainder of patients are termed steroid-resistant. This magnitude of response is unrivaled by any other drug used to treat Crohn's disease and it is, at least in part, for this reason that corticosteroids remain popular with both patients and doctors alike. However, induction of remission is only part of the battle: where do we go from there?

NATURAL HISTORY

The steroid natural history studies universally described excellent remission and response rates. Importantly, however, they also gave information about what happened over the ensuing months whilst steroids were withdrawn. It quickly became apparent

(continued on page 40)

(continued from page 38)

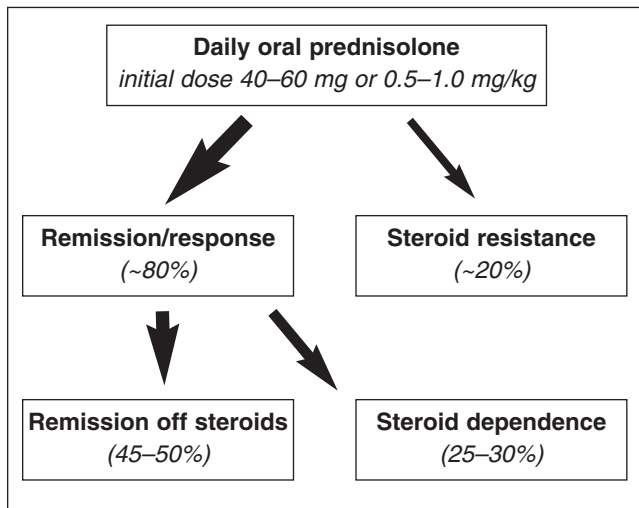


Figure 1. Natural history of steroid usage in moderate to severely active Crohn's disease.

that a significant proportion of patients, between a quarter and a third, were either unable to withdraw steroids without relapsing, or relapsed quickly after they had been withdrawn. The term steroid-dependence has been used to characterize this group of patients (Figure 1). Why should this be the case? It seems likely that mucosal healing, or in the case of corticosteroids, a lack of it, is of some importance in this regard. Mucosal healing has become the watchword of many Crohn's disease opinion leaders and corticosteroids appear to under-perform in this respect resulting in mucosal healing in about a third of cases. This compares with 50%–75% of people treated with thiopurines, nutritional therapy or biologics (5). When one considers, therefore, that in many patients corticosteroids improve symptoms without healing the mucosa, it is perhaps unsurprising that a proportion require ongoing steroid use to keep their symptoms under control; that is, they become steroid-dependent. Clinical characteristics predictive of steroid-dependency include the presence of fistulizing disease, early age of disease onset, smoking, and a persistently raised C-reactive protein despite symptomatic remission after weaning of steroids (6,7). Steroid resistance is associated with a high Crohn's Disease Activity Index, previous surgery and perianal disease (8). It is to be hoped that advances in the areas of genetics, pharmacogenetics and serological testing will improve predictive

identification of individuals at high risk of steroid-resistance and steroid-dependence.

APPROPRIATE USE OF CORTICOSTEROIDS

Guidelines from various organizations agree that corticosteroids are an appropriate first-line agent for the management of moderately-severely active Crohn's disease and for mild-moderate Crohn's disease unresponsive to 5-ASA or budesonide (9,10). Intravenous steroids are appropriate for severe or fulminant disease, or for patients who fail to respond to adequate doses of oral corticosteroids.

INAPPROPRIATE USE OF CORTICOSTEROIDS

There are various circumstances in which use of corticosteroids is either inappropriate or dangerous. Most practitioners agree that fistulizing disease does not respond to, and may even be exacerbated by corticosteroids. Furthermore, patients with an abdominal mass resulting from an abscess are at increased risk of death if given steroids (2).

One argument used to counter the increasing body of evidence that steroids (both systemic and topical) are ineffective at maintaining remission (11,12) is that steroid-dependent patients are, in effect maintained in remission above a critical dose of steroid. However, one fact is unarguable, and that is that steroids can not *safely* maintain remission.

SIDE EFFECTS OF CORTICOSTEROIDS

There is a plethora of side effects, both long and short-term, associated with the use of corticosteroids. These are summarized in Table 1. While many of these, such as suppression of the hypothalamic-pituitary-adrenal (HPA) axis, are indisputably solely related to steroid usage, it is less clear with others whether steroids are entirely to blame. Indeed, one of the arguments for using biological agents to induce remission is their relative lack of side effects in comparison to steroids. This, however, deserves closer examination.

Osteopenia and osteoporosis are well-recognized side-effects of long term steroid usage. However, both malabsorption of calcium and vitamin D, and active

Table 1
Side Effects of Corticosteroids

<i>System</i>	<i>Side effect</i>
Cosmetic	Cushingoid facies Acne
Ocular	Glaucoma Cataracts
Musculoskeletal	Osteomalacia Osteopenia Osteoporosis Osteonecrosis
Psychological	Mood disturbance Insomnia Psychosis
Infective	Exacerbation of infective complications of Crohn's disease Increased risk of opportunistic infections Possible increased perioperative risk
Growth retardation	Possible increased risk in children
Metabolic	Hypothalamic-pituitary-adrenal axis suppression Hypertension Hyperglycaemia

inflammation may contribute to bone loss (13). Indeed, in patients with Crohn's disease low bone mineral density is frequently detected at diagnosis (i.e. in steroid-naïve patients). Although a two month course of steroids for active Crohn's is associated with significant bone loss, the relative contributions of inflammation and steroids to this loss remains unclear (14).

The infective risks of steroids are also not without controversy. While evidence from the ECCDS showed clearly that the use of steroids in patients with an abscess is associated with an increased risk of mortality (2), the risk of perioperative steroids is unclear; if there is a risk of using steroids in patients undergoing abdominal surgery, it likely relates to high doses for extended periods (5). Similarly, while a meta-analysis of 71 controlled trials using steroids demonstrated that the relative risk for infection was 1.6 (95% confidence intervals 1.3–1.9), the risk for the subgroup of patients with gastrointestinal disease was less (15). Further-

more, as with perioperative risk, cumulative dose seems to be important, the increased risk being associated only with total doses greater than 700 mg of prednisone. What of the alternatives? While the TREAT registry suggests that infliximab may be safer than steroids (16), at least with regard to infectious risk, methodological issues remain. What is clear is that combinations of steroids, immunosuppressants and biologics confer a greatly increased risk of infection; the differences in infectious risk between individual drugs are dwarfed by the increased risk associated with using more than one immunosuppressive agent (17).

Pediatricians often try to avoid using steroids in their patients although, when they do use them, it is sometimes at a relatively higher dose than that used in adults (18). The fear of inducing growth retardation undoubtedly plays some part in the avoidance of steroids in the pediatric population and trials have shown that enteral nutrition is superior to steroids in improving linear growth. However, other factors, such as active disease, inflammatory cytokines, nutrition and alteration in hormones and sex steroids may also contribute to growth retardation (19).

In summary, while it is evident that steroids have protean adverse effects it is important to consider the balance between controlling inflammation and putting the patient at risk of side effects.

OPTIMAL USE OF STEROIDS (TABLE 2)

Dose

While it is axiomatic that steroids should be used at the lowest effective dose for the shortest period of time possible, it is impossible to know what the effective

Table 2
Steroid Use in Crohn's Disease: Rules of Engagement

1. Use appropriate dose to induce remission
2. Have a prospective "exit strategy"
3. Use a standard weaning regimen to allow prompt recognition of patients who are likely to become steroid-dependent
4. Protect the bones with concomitant calcium and vitamin D

dose of steroids will be for an individual prior to treatment. Furthermore, there is little to guide us as to who will fail to respond to steroids and who will become dependent upon them. Accordingly, for moderate to severe Crohn's disease, or non-responsive mild-to-moderate disease, daily doses of prednisone of 40–60 mg or 0.5–1 mg/kg are supported by high quality trials. There is no evidence that giving oral steroids at doses higher than these leads to increased efficacy and this practice is, therefore, not encouraged. For severe or fulminant Crohn's disease, doses of intravenous hydrocortisone (300–400 mg/day) or methylprednisolone (60 mg/day) are probably not worth exceeding. While oral budesonide (9 mg/day) may be associated with fewer side effects than oral prednisone and is an effective treatment for active ileal Crohn's disease, prednisone is probably slightly more effective.

Route of Administration

As mentioned above, topically acting steroids, such as budesonide, are less effective than systemic steroids but, due to high first pass metabolism, are associated with lesser side-effects. The same cannot necessarily be said, however, for topical prednisone and hydrocortisone. For example, rectal therapy with these drugs has been reported to cause HPA axis suppression, Cushing's syndrome and avascular necrosis (5). Indeed, because the venous drainage of the lower rectum is systemic rather than portal, steroid absorbed from this part of the lower bowel avoids first pass metabolism. Finally, although rectal steroids are sometimes used as adjunctive therapy to induce remission in distal Crohn's disease, this practice lacks an evidence base.

Similarly, the use of intravenous steroids for severe or fulminant Crohn's disease is based more on experience than evidence, although the ethical implications of a trial designed to answer this question mean that it is unlikely to happen. Furthermore, infusions of steroid are probably no more effective regular than regular intravenous boluses (20).

Weaning Regimen

Evidence on how to wean steroids is, by contrast, almost non-existent. The issue of HPA suppression

requires that steroids are withdrawn over a number of weeks. In addition, the received wisdom is that overly rapid steroid withdrawal results in an increased chance of relapse in patients with Crohn's disease. The only trial to examine this issue, however, suggests that there is no difference in relapse rate if steroids are weaned over four weeks or 12 weeks (21). Overall, it is probably wise to have a standardized weaning regimen to allow prompt identification of patients who are likely to become steroid-dependent and are, therefore, likely to benefit from a steroid-sparing agent.

Protecting the Bones

Bone loss can be minimized by encouraging conservative measures, such as discontinuing smoking, limiting alcohol intake, taking weight-bearing exercise, ensuring adequate dietary intake of calcium (1,000–1,500 mg/day), and prescribing supplemental calcium if required (500–1,000 mg) and vitamin D (for example, cholecalciferol, 800 units) (13).

Prospective Exit Strategy

Clinicians should define an "exit strategy" when initiating steroids to induce remission. It might be considered too late (biologically and by the patient) to act, for example, after three episodes of dose escalation by which time steroid adverse effects are well established. A good prospective plan might comprise the concomitant introduction of an immunomodulator (such as a thiopurine) in patients with a high chance of relapse, chronically active disease or steroid dependence (such as a smoker with moderately severe disease). Such a philosophy has the potential to reduce the likelihood of steroid dependence with severe side effects.

Alternatives to Corticosteroids

Whilst it is important to continue to outline the dangers of the misuse of steroids, their continued judicious use in Crohn's disease is entirely acceptable. This view is supported by their inclusion as an important part of the management of Crohn's disease in recently published guidelines (9,10). This will remain the case until a drug

(continued on page 45)

(continued from page 42)

that is not only safer but is similarly effective is discovered. Many would argue that this has already occurred with the advent of the biologic agents, in particular the anti-TNF α monoclonal antibodies. However, the biologics are unlikely to completely usurp steroids, at least in the near future. There are three reasons for this:

- Steroids are a fraction of the cost of biologics and are easy to administer.
- They may induce remission less frequently than steroids, although the studies on which these conclusions are drawn are not necessarily comparable.
- Although there is some evidence to suggest that the use of steroids is associated with a greater risk of infection than is seen with infliximab (16), while steroids can be used for a short period of time without fear of compromising their future efficacy, intermittent use of biologics is associated with antibody formation. Therefore, biologics, unlike steroids are often used for long periods of time thereby increasing the amount of time the recipient is exposed to an increased risk of infection. Furthermore, combination treatment with an immunomodulating agent is still the norm, at least initially, when prescribing a biologic. The concerning, but fortunately rare, cases of hepatosplenic T cell lymphoma seen in several patients treated with infliximab and azathioprine (22) may also discourage people from using biologics in preference to steroids.

Even if the biologics do turn out to be a reasonable alternative to steroids, it must be remembered that many gastroenterologists have far more experience with the latter than with the former. Particularly for those who practice outside specialist centers, this familiarity with "the devil they know" is likely to mean that steroids continue to be prescribed for Crohn's disease for some time to come. Rather than dismissing them, efforts to optimize the use and safety of steroids in Crohn's disease should, therefore, continue. ■

References

1. Summers RW, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology*, 1979; 77, 847-869.
2. Malchow H, et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology*, 1984;86, 249-266.
3. Munkholm P, Langholz E, Davidsen M, Binder V. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut*, 1994; 35, 360-362.
4. Faubion WA, Jr, Loftus EV, Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology*, 2001; 121, 255-260.
5. Irving PM, Geary RB, Sparrow MP, Gibson PR. Review article: appropriate use of corticosteroids in Crohn's disease. *Aliment Pharmacol Ther*, 2007; 26, 313-329.
6. Papi C, et al. Long-term outcome of Crohn's disease following corticosteroid-induced remission. *Am J Gastroenterol*, 2007; 102, 814-819.
7. Franchimont DP, Louis E, Croes F, Belaiche J. Clinical pattern of corticosteroid dependent Crohn's disease. *Eur J Gastroenterol Hepatol*, 1998; 10, 821-825.
8. Gelbmann CM, et al. Prior bowel resections, perianal disease, and a high initial Crohn's disease activity index are associated with corticosteroid resistance in active Crohn's disease. *Am J Gastroenterol*, 2002; 97, 1438-1445.
9. Travis SP, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut*, 2006; 55 Suppl 1, i16-i35.
10. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology*, 2006; 130, 940-987.
11. Steinhart AH, Ewe K, Griffiths AM, Modigliani R, Thomsen OO. Corticosteroids for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*, 2003; CD000301.
12. Otley A, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*, 2005; CD000296.
13. Makins R, Compston J. Prevention and treatment of osteoporosis. *Clinical Dilemmas in Inflammatory Bowel Disease*, 2006; 201-204 (Irving P, Rampton D, Shanahan F. (eds.), Blackwell Publishing, Oxford).
14. Tobias JH, Sasi MR, Greenwood R, Probert CS. Rapid hip bone loss in active Crohn's disease patients receiving short-term corticosteroid therapy. *Aliment Pharmacol Ther*, 2004; 20, 951-957.
15. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis*, 1989;11, 954-963.
16. Lichtenstein GR, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol*, 2006; 4, 621-630.
17. Toruner M, et al. Risk factors for opportunistic infections in inflammatory bowel diseases: A case-control study. *Gastroenterology*, 2006; 130(4, Suppl 2), 96.
18. Heuschkel RB, Menache CC, Megerian JT, Baird AE. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. *J Pediatr Gastroenterol Nutr*, 2001; 31, 8-15.
19. Koglmeyer J, Croft N. How to prevent growth failure in children. *Clinical Dilemmas in Inflammatory Bowel Disease*, 2007; 150-152 (Irving P, Rampton D, Shanahan F. (eds.), Blackwell Publishing, Oxford, UK).
20. Bossa F, et al. Continuous infusion versus bolus administration of steroids in severe attacks of ulcerative colitis: a randomized, double-blind trial. *Am J Gastroenterol*, 2007; 102, 601-608.
21. Brignola C, et al. Steroid treatment in active Crohn's disease: a comparison between two regimens of different duration. *Aliment Pharmacol Ther*, 1994; 8, 465-468.
22. Mackey AC, Green L, Liang LC, Dinndorf P, Avigan M. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr*, 2007; 44, 265-267.