Steroid-dependent Crohn's disease

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WJ Sandborn. Steroid-dependent Crohn's disease. Can J Gastroenterol 2000;14(Suppl C):17C-22C. Placebo controlled trials have demonstrated that a tapering course of corticosteroids is an effective therapy for active Crohn's disease. A population-based study of 109 patients with Crohn's disease undergoing their first course of corticosteroids showed that, at the end of one year, 44% of patients were steroid responsive, 36% were steroid dependent and 20% were steroid refractory. Side effects occur frequently during a four-month tapering course of corticosteroids, including moon face, acne, infection, ecchymoses, hypertension, hirsutism, petechial bleeding and striae. More serious side effects occur with long term use, including hypertension, diabetes, infection, osteonecrosis, osteoporosis, myopathy, cataracts, glaucoma and psychosis. Low dose corticosteroids, alternate-day corticosteroids and mesalamine (5-aminosalicylate) are not effective steroid-sparing agents in patients with Crohn's disease. Controlled ileal release budesonide, 6 mg/day, is an effective steroid-sparing agent, but it does result in some decrease in adrenal function. Azathioprine, 6-mercaptopurine and methotrexate are all effective steroid-sparing agents, as is the humanized, anti-tumour necrosis factor monoclonal antibody, CDP571. A preliminary, uncontrolled study has suggested that the mouse/human chimeric monoclonal antibody infliximab may also be steroid sparing. Surgical resection is an effective strategy to reduce steroid use in the short to intermediate term, but postoperative reoccurrence of Crohn's disease occurs frequently. Given the morbidity associated with prolonged corticosteroid use, medical and surgical treatment strategies to reduce steroid use should be employed routinely.

Key Words: Corticosteroids; Crohn's disease; Infliximab; Steroid-dependent patients; Steroid-sparing medications

Maladie de Crohn et dépendance aux stéroïdes

RÉSUMÉ : Des essais contrôlés contre placebo montrent que la corticothérapie dégressive constitue un traitement efficace de la maladie de Crohn en évolution. Cent neuf patients atteints de la maladie de Crohn et soumis pour la première fois à un traitement aux corticostéroïdes ont participé à une étude fondée sur la population : au bout d'un an, 44 % d'entre eux étaient sensibles aux stéroïdes, 36 % y étaient dépendants et 20 % y étaient réfractaires. La corticothérapie dégressive d'une durée de quatre mois s'est accompagnée, dans bien des cas, d'effets indésirables comme le faciès lunaire, l'acné, les infections, les ecchymoses, l'hypertension, l'hirsutisme, les pétéchies et les vergetures. Des effets indésirables plus sérieux ont été observés au cours de traitements prolongés, notamment l'hypertension, le diabète, les infections, l'ostéonécrose, l'ostéoporose, les myopathies, les cataractes, le glaucome et la psychose. Les corticostéroïdes à faible dose, pris aux deux jours, et la mésalamine (5-aminosalicylate) ne sont pas des épargneurs de stéroïdes efficaces chez les patients atteints de la maladie de Crohn. Le budésônide à libération lente dans l'iléon, administré à raison de 6 mg/jour, s'avère un épargneur de stéroïdes efficace, mais il entraîne une diminution du fonctionnement surrénalien. L'azathioprine, la 6-mercaptopurine et le méthotrexate sont tous des épargneurs de stéroïdes efficaces, de même que l'anticorps monoclonal humanisé anti-facteur de nécrose des tumeurs, le CDP571. Selon une étude préliminaire non contrôlée, l'infliximab, un anticorps monoclonal chimérique souris-humain, aurait des propriétés d'épargne des stéroïdes. La résection chirurgicale offre une stratégie efficace pour diminuer l'utilisation des stéroïdes à court et à moyen terme, mais les récurrences de la maladie de Crohn ne sont pas rares après les opérations. Compte tenu de la morbidité associée à l'usage prolongé des corticostéroïdes, il serait approprié d'avoir recours autant aux stratégies de traitement médical qu'aux stratégies de traitement chirurgical pour diminuer l'utilisation des stéroïdes.

Corticosteroids are effective for inducing remission in patients with Crohn's disease, but they are not safe at high doses for maintaining remission and they are not effective at low doses for maintaining remission. Because of the lack of effective alternative medical therapies and the mor-

bidity associated with surgery, many patients, in the past, have been maintained for prolonged periods of time on corticosteroids at moderate to high doses. This treatment approach is no longer appropriate given the availability of a variety of other medications with steroid-sparing properties.

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Figure 1 Immediate outcome (after one month) of the first steroid treatment course in 109 patients with Crohn's disease. Reprinted with permission from reference 4

This article reviews the efficacy and toxicity associated with conventional corticosteroid therapy; defines steroid dependency; describes the natural history of steroid therapy in Crohn's disease; outlines ineffective and effective steroid-sparing strategies; and gives the natural history of the postoperative reoccurrence of Crohn's disease.

EFFICACY AND TOXICITY OF CONVENTIONAL CORTICOSTEROIDS

In the National Cooperative Crohn's Disease Study (NCCDS), prednisone at a dosage of 0.25 to 0.75 mg/kg/day induced remission in 78% of patients with active Crohn's disease compared with only 49% of placebo-treated patients (1). Similarly, in the European Cooperative Crohn's Disease Study (ECCDS), 6-methyl-prednisolone at a dose of 48 mg/day induced remission in 83% of patients with active Crohn's disease compared with only 38% of placebo-treated patients (2). These two studies clearly demonstrated that a tapering course of conventional corticosteroids, beginning at a high dose, is an effective therapy for active Crohn's disease. Unfortunately, corticosteroid toxicity occurred frequently over 17 weeks of therapy. Toxicities observed included a moon face in 47% of patients, acne in 30%, infection in 27%, ecchymoses in 17%, hypertension in 15%, hirsutism in 7%, petechial bleeding in 6% and striae in 6% (3). Thus, high dose corticosteroids are effective, but the side effects preclude prolonged treatment.

Low dose corticosteroids cause fewer side effects, and thus maintenance studies with low dose corticosteroids in pa-

tients with Crohn's disease in remission were undertaken. In the NCCDS, maintenance therapy with prednisone at a dosage of 0.25 mg/kg/day (20 mg/day) was not effective compared with placebo for maintaining remission (1). Similarly, in the ECCDS, 6-methylprednisolone at a dose of 8 mg/day was not effective compared with placebo for maintaining remission (2). The two studies showed that low dose, conventional corticosteroids are not effective in maintaining remission in patients with Crohn's disease. Nevertheless, clinical experience has demonstrated that some patients have an improved clinical course while taking low to intermediate doses of corticosteroids (prednisone dose equivalent of 15 to 30 mg/day). Such patients have been deemed to be steroid dependent.

NATURAL HISTORY OF STEROID THERAPY IN PATIENTS WITH CROHN'S DISEASE

Munkholm and colleagues (4) reported on the clinical course of a population-based cohort of 109 patients with Crohn's disease who received an initial course of corticosteroid therapy. They defined a steroid-responsive state as a complete or partial clinical response to 40 to 60 mg/day of prednisone and no regression of clinical symptoms 30 days after prednisone treatment was completed. A steroid-dependent state was defined as a partial or complete clinical response to treatment with prednisone 40 to 60 mg/day and a relapse within 30 days after prednisone treatment was completed or relapse with a dose reduction of prednisone resulting in the use of prednisone at doses greater than or equal to 15 mg/day for at least six

Figure 2) Prolonged outcome (one year) after steroid treatment had finished in patients initially obtaining complete and partial remission (n=87). Reprinted with permission from reference 4

months. A steroid-refractory state was defined as no response to prednisone at doses of 40 to 60 mg/day. Using these definitions, the outcomes at one month and one year are shown in Figures 1 and 2. Overall, at one year, 44% of patients were steroid responsive, 36% were steroid dependent, and 20% were steroid refractory.

TOXICITY ASSOCIATED WITH PROLONGED STEROID THERAPY

Prolonged corticosteroid therapy at low to intermediate doses (doses frequently used in steroid-dependent patients) is associated with the potential for multiple serious side effects (5). Hypertension occurs in up to 20% of patients (6). New-onset diabetes mellitus, requiring initiation of hypoglycemic therapy, occurs at a frequency of 2.33 times greater than in the general population (7). Infection occurs at a frequency of 13% to 20% (8). Osteonecrosis occurs at a frequency of approximately 5% (9). The frequency of steroid-associated osteoporosis may be as high as 50% (10). Neurological side effects occur often and can include myopathy at a frequency of 7% and psychosis at a frequency of 3% to 5% (11). Ophthalmological side effects also occur, including cataracts at a frequency of 22% (dose-dependent) and glaucoma (frequency unclear, response genetically determined) (12,13).

MEDICAL THERAPY STRATEGIES FOR STEROID SPARING

A variety of medical therapies have been evaluated as potential steroid-sparing agents for patients with steroid-dependent Crohn's disease. As discussed above, low dose corticosteroids

are not effective for maintaining remission in patients in whom remission was induced with high dose corticosteroids (1,2). Other potential steroid-sparing strategies include alternate-day corticosteroids, controlled ileal release (CIR) budesonide, mesalamine (5-amino salicylate), 6-mercaptopurine and its prodrug azathioprine, methotrexate, the humanized, antitumour necrosis factor (TNF) monoclonal antibody CDP571 and infliximab.

Alternate-day corticosteroids: The rationale for alternate-day corticosteroid therapy is that this dosing schedule does not interfere with the normal ACTH-cortisol cycle and does not expose tissues to sustained concentrations of corticosteroids throughout the day (14-18). Alternate-day corticosteroid therapy appears to be as effective as daily steroid dosing in some but not all immunological diseases. Uncontrolled data have suggested that alternate-day corticosteroid therapy may be beneficial in patients with Crohn's disease and may be associated with fewer side effects than standard corticosteroid therapy (19). However, the evidence supporting this approach to therapy for Crohn's disease is minimal, and given the availability of nonsteroid alternatives, it is not recommended by most experts in the field.

CIR budesonide: CIR budesonide is effective in patients with active Crohn's disease at doses of 9 and 15 mg/day, but not 3 or 6 mg/day, compared with placebo (20). CIR budesonide is equivalent in efficacy to prednisolone 40 mg/day (21,22). In patients with a medically induced remission, maintenance therapy with CIR budesonide at doses of 3 or 6 mg/day was not effective compared with placebo (23,24). Thus, when considering the broad population of patients with Crohn's

TABLE 1
Safety and efficacy of various treatment options for steroid-dependent Crohn's disease

Therapy	Efficacy	Safety
Low dose corticosteroids	No	No*
Alternate-day corticosteroids	No*	No*
Controlled ileal release budesonide	Yes	Yes*
Mesalamine	No	Yes
Azathioprine/ 6-mercaptopurine	Yes	Yes
Methotrexate	Yes	Yes
CDP571	Yes	Yes
Infliximab	Yes*	Yes*
Surgery	Yes	Variable

*Efficacy and/or safety data unclear

disease who have achieved a medically induced remission, CIR budesonide at a dose of 6 mg/day is not effective as a maintenance therapy. Furthermore, while CIR budesonide 6 mg/day is reasonably well tolerated from a side effect standpoint, there is some decrease in adrenal function (23).

In contrast, in patients who are steroid-dependent at prednisone doses of 10 to 30 mg/day, CIR budesonide 6 mg/day is effective in maintaining remission and allowing a total withdrawal of prednisone in 68% of patients compared with only 35% of placebo-treated patients (25). The side effect profiles are similar in both groups. Based on these data, CIR budesonide 6 mg/day can be considered a steroid-sparing therapy. The safety of long term therapy with CIR budesonide at the 6 mg/day dose remains to be determined.

Mesalamine: Many clinicians assume that mesalamine has steroid-sparing properties. It is common in clinical practice to prescribe high dose mesalamine (4 to 4.8 g) in combination with a tapering course of corticosteroids. This approach was evaluated in a placebo controlled trial by Modigliani et al (26), who reported that the oral mesalamine formulation Pentasa (Ferring Inc) at a 4 g/day dose was not effective for steroid sparing in patients with active Crohn's disease who required a tapering course of corticosteroids (26). This negative result is in accord with the evolving evidence that mesalamine is not effective for maintaining remission in patients with Crohn's disease (27).

Azathioprine and 6-mercaptopurine: 6-mercaptopurine and its prodrug, azathioprine, are used in patients with Crohn's disease for induction of remission, closure of fistulae, maintenance of remission and steroid sparing. The steroid-sparing properties of these medications are best illustrated by studies showing that 42% of patients treated with azathioprine 2.5 mg/kg/day were able to discontinue steroids compared with only 7% of placebo-treated patients (28), and that 85% of patients treated with 6-mercaptopurine 1.5 mg/kg/day were able to discontinue steroids compared with only 54% of placebo-treated patients (29). These medications are now the most

widely used agents for steroid sparing in patients with Crohn's disease.

Methotrexate: Methotrexate is also used for steroid sparing in patients with Crohn's disease. Feagan et al (30) reported that 39% of patients treated with intramuscular methotrexate at a dose of 25 mg/week could successfully maintain remission and discontinue prednisone over 16 weeks compared with only 19% of placebo-treated patients. In a subsequent follow-up study, Feagan et al (31) demonstrated that maintenance therapy with intramuscular methotrexate 15 mg/week maintained remission for 40 weeks. Methotrexate is currently used for steroid sparing as a second-line immunosuppressive agent after azathioprine and 6-mercaptopurine have failed. However, the available efficacy data are robust, and the choice between azathioprine or 6-mercaptopurine, and methotrexate is now becoming one of patient and physician personal preference.

Anti-TNF antibody therapy: A recent study with the humanized, anti-TNF monoclonal antibody CDP571 showed a steroid-sparing effect, with 44% of CDP571-treated patients maintaining remission and discontinuing prednisone compared with only 22% of placebo-treated patients (32). The mouse/human chimeric monoclonal antibody to TNF, infliximab, is effective for patients with active Crohn's disease, for closing Crohn's disease fistulae and for maintaining remission in patients with Crohn's disease (33-35). To date, there are no placebo controlled data regarding the steroid-sparing potential of infliximab in patients with Crohn's disease. However, uncontrolled data from the Mayo Clinic, Rochester, Minnesota suggest that infliximab is steroid sparing. Of the first 100 consecutive patients treated with infliximab at the Mayo Clinic, 61 had inflammatory disease and 39 had fistulizing disease. Ninety-five patients were receiving azathioprine, 6-mercaptopurine or methotrexate. In addition, 44 of the patients were receiving concomitant corticosteroids. Corticosteroid tapering was attempted in 40 of 44 patients, and total steroid withdrawal was possible in 29 of 40 patients (73%) (36).

SURGICAL THERAPY STRATEGIES FOR STEROID SPARING

Surgery is an effective and durable intervention for patients with refractory Crohn's disease or complications from Crohn's disease. This is equally true for patients with steroid-dependent Crohn's disease. Nevertheless, the recurrence rates of Crohn's disease following surgical resection are high. McLeod et al (37) reported that the rate of endoscopic or radiographic recurrence was 77% three years following a surgical resection. Munkholm et al (38) reported that the frequency of one operation 15 years after the diagnosis of Crohn's disease was 34%, the frequency of two operations was 14%, the frequency of three operations or more was 22%, and the frequency of not having an operation at 15 years was only 30%. For patients with a previous operation, the likelihood of a repeat surgery in patients with ileitis and an ileocolonic anastomosis is 44%, the likelihood of a repeat surgery in patients with ileocolitis and an ileocolonic anasto-

mosis is 53%, and the likelihood of a repeat surgery in patients with Crohn's colitis and a segmental resection is 45% (39). For patients with isolated Crohn's colitis who undergo proctocolectomy with ileostomy, the likelihood of a repeat surgery is only 6%, whereas, in patients with ileocolitis who undergo proctocolectomy with ileostomy, the likelihood of requiring a repeat operation is 29% (40).

CONCLUSIONS

The safety and efficacy of various treatment options for steroid-dependent Crohn's disease are outlined in Table 1. Low dose corticosteroids and alternate-day corticosteroids are not effective and, thus, are inappropriate. CIR budesonide is effective, but the safety of long term therapy at a 6 mg/day dose is not clear. Mesalamine is not effective and thus is not appropriate. Azathioprine, 6-mercaptopurine and

methotrexate are effective and reasonably safe agents for the steroid-sparing indication, and can be recommended for widespread clinical practice. The humanized, anti-TNF monoclonal antibody CDP 571 is investigational at the present time. When it becomes available clinically, it could also be recommended as a steroid-sparing therapy. Uncontrolled evidence suggests that infliximab is steroid sparing; a controlled, clinical trial is needed to confirm this preliminary observation. Surgical resection is effective and durable for steroid-dependent Crohn's disease, but both short and long term postsurgical morbidity issues are important, and the rates of reoccurrence and reoperation after surgical resection are high. Given the morbidity associated with prolonged corticosteroid use, medical and surgical treatment strategies to accomplish steroid sparing should be employed routinely.

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