

Medical therapy of steroid-resistant Crohn's disease

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BE Sands. Medical therapy of steroid-resistant Crohn's disease. Can J Gastroenterol 2000;14(Suppl C):33C-37C. Glucocorticosteroids are commonly used in the treatment of moderate to severe Crohn's disease and are effective for the short term amelioration of symptoms. However, not all patients respond to corticosteroid therapy. Approximately 20% of patients fail to respond to initial treatment with steroids, while 36% of patients may be considered steroid dependent. Sharp distinctions between steroid-dependent and steroid-resistant populations are difficult to draw because steroid responsiveness is often dose dependent. Clearer distinctions may be drawn between those who fail to respond to initial treatment with corticosteroids and those who have secondary failure later in the course of their disease on repeated treatment. Effective therapies for steroid-resistant Crohn's disease include azathioprine and 6-mercaptopurine, methotrexate, cyclosporine and infliximab. Limited data are available on the use of tacrolimus, mycophenolate mofetil and thalidomide. Steroid-resistant Crohn's disease, while involving a small minority of patients, continues to present a difficult therapeutic challenge.

Key Words: *Corticosteroids; Crohn's disease; Infliximab; Steroid resistance*

Traitement médicamenteux de la maladie de Crohn réfractaire à la corticothérapie

RÉSUMÉ : Les corticostéroïdes sont couramment utilisés dans le traitement de la maladie de Crohn d'intensité modérée à grave et ils sont efficaces dans l'amélioration à court terme des symptômes. Par contre, les patients n'y répondent pas tous. Environ 20 % des patients ne répondent pas à la corticothérapie initiale, alors que 36 % des patients sont jugés stéroïdodépendants. Il est difficile d'établir des distinctions claires entre les populations stéroïdodépendantes et stéroïdorésistantes parce que la réponse aux corticostéroïdes est souvent liée à la dose. On peut tirer des distinctions plus nettes entre les sujets qui ne répondent pas à la corticothérapie initiale et ceux qui présentent un échec secondaire, plus tard durant l'évolution de la maladie, après l'administration de traitements répétés. Les traitements efficaces pour la maladie de Crohn stéroïdorésistante sont, entre autres, l'azathioprine et la 6-mercaptopurine, le méthotrexate, la cyclosporine et l'infliximab. On dispose de données limitées sur l'utilisation du tacrolimus, du mucophénolate mofetil et de la thalidomide. La maladie de Crohn stéroïdorésistante, quoiqu'affectant une faible minorité de patients, continue de poser un défi thérapeutique de taille.

Initial descriptions of the use of corticosteroids for active, symptomatic Crohn's disease date to the 1950s (1). In 1979, The National Cooperative Crohn's Disease Study showed that remission, defined as a Crohn's Disease Activity Index (CDAI) score of less than 150, occurred at eight weeks in 76% of patients treated with oral prednisone 40 mg/day compared with 15% of patients treated with placebo (2). Similarly, the European Cooperative Crohn's Disease Study showed a tapering regimen of prednisolone to be effective in

the short term treatment of active disease (3). The populations in these studies comprised patients with an established diagnosis of Crohn's disease as well as patients not previously treated. Therefore, it is unclear how many patients failed to respond to corticosteroids upon first exposure rather than to subsequent trials of corticosteroid. Indeed, much of the literature fails to distinguish between these two groups, which may be fundamentally different and may differ with regard to the mechanisms of resistance.

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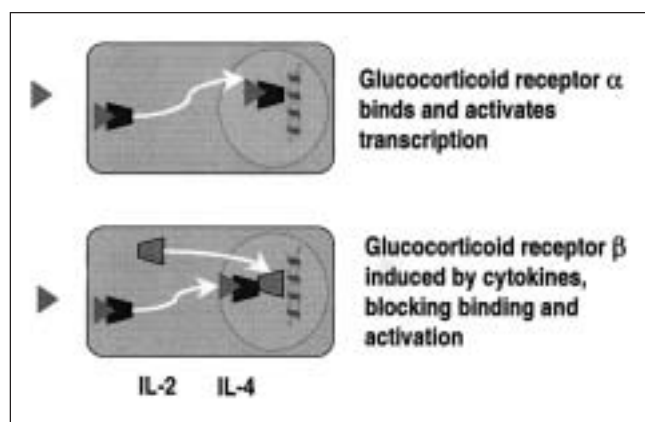


Figure 1) Glucocorticoid resistance may be related to the expression of an alternate glucocorticoid receptor in inflammatory states. Data from reference 7

Seminal work by Munkholm et al (4) indicated the scope of the problem. Of patients with Crohn's disease receiving their first course of corticosteroids by mouth, 20% failed to respond to four weeks of therapy. These patients might be said to display primary resistance to corticosteroids. Of the remaining 80% of patients who fully or partially responded to corticosteroids, 36% were unable to completely taper off steroids at one year. Traditionally, these patients would have been characterized as being steroid dependent. Mechanistically, however, the line dividing dependence and resistance to corticosteroids appears to be largely a matter of dose response. For example, the patient whose symptoms reappear at doses of prednisone less than 15 mg may well respond to doses higher than 20 mg.

Two other lines of evidence suggest that so-called steroid-dependent and steroid-resistant populations are not fundamentally distinct. First, carefully conducted studies demonstrate that clinical remission induced by oral corticosteroids is associated with mucosal healing in only 29% of patients (5). Second, extending the duration of steroid induction to the point of inducing endoscopic resolution of inflammation does not affect the long term likelihood of maintaining clinical remission (6).

In contrast to the lack of long term therapeutic benefits of corticosteroid therapy in Crohn's disease, most of the well known toxicities associated with corticosteroids correlate well with dose and duration of therapy. Accordingly, the guiding principle of corticosteroid therapy has become to employ the lowest effective doses for the briefest possible time.

MECHANISMS OF STEROID RESISTANCE

The mechanisms by which patients fail to respond to corticosteroid therapy are poorly understood and are likely to be multiple. Given the anti-inflammatory and immunosuppressive properties of corticosteroids, patients experiencing symptoms of noninflammatory or pyogenic complications of Crohn's disease are not likely to benefit from treatment. Examples are patients with irritable bowel-like symptoms complicating their disease, patients with symptomatic stricture and

TABLE 1
Therapies commonly used in the treatment of steroid-resistant Crohn's disease

Agent	Dosage	Time to onset of response
6-mercaptopurine	1.5 mg/kg/day po	8 to 16 weeks
Azathioprine	2 to 3 mg/kg/day po	8 to 16 weeks
Methotrexate	25 mg IM weekly	8 weeks
Cyclosporine	5 to 7.5 mg//day po 4 mg/kg/day IV	2 weeks
Infliximab	5 mg/kg IV	2 weeks

IM Intramuscularly; IV Intravenously; po Orally

patients with intra-abdominal abscess. In addition, many experienced clinicians have observed exacerbation of fistulas in patients with Crohn's disease after the introduction of corticosteroids.

When inflammatory changes are evident, corticosteroid responsiveness may be complex and dynamic. In asthma, for example, certain proinflammatory cytokines may induce the expression of an alternate glucocorticoid receptor (7). Expression of this alternate receptor and binding to the glucocorticoid may inhibit the usual anti-inflammatory effects of steroids at the level of gene expression (Figure 1). Very rarely, individuals may be genetically deficient in glucocorticoid receptors. These processes and perhaps many others may account for the roughly 20% of patients who fail to respond to steroids on first use.

Additional evidence suggests that the expression of P-glycoprotein 170, a multidrug resistance channel, may be associated with resistance to corticosteroids in individuals with inflammatory bowel disease (8). Although levels of expression of the multidrug resistance gene did not correlate directly with the use of corticosteroids, it seems likely that the adaptive pressure of repeated exposure to corticosteroids over time might nevertheless induce expression of this channel and lead to an evolving steroid-resistant state.

For these reasons, the widely used nomenclature of steroid dependence and steroid resistance should be revised. It seems reasonable to describe some patients as having primary steroid resistance (ie, failure to respond to corticosteroids upon first exposure) and others as having secondary steroid resistance (ie, not responding to subsequent courses of corticosteroid therapy). In addition, one might describe the set point of resistance, ie, the threshold dose capable of maintaining symptomatic remission.

GOALS OF THERAPY

Two primary goals of therapy for the patient with steroid-resistant Crohn's disease are a successful intervention before the onset of deleterious consequences of disease or steroid use, and the rapid alleviation of the signs and symptoms of inflam-

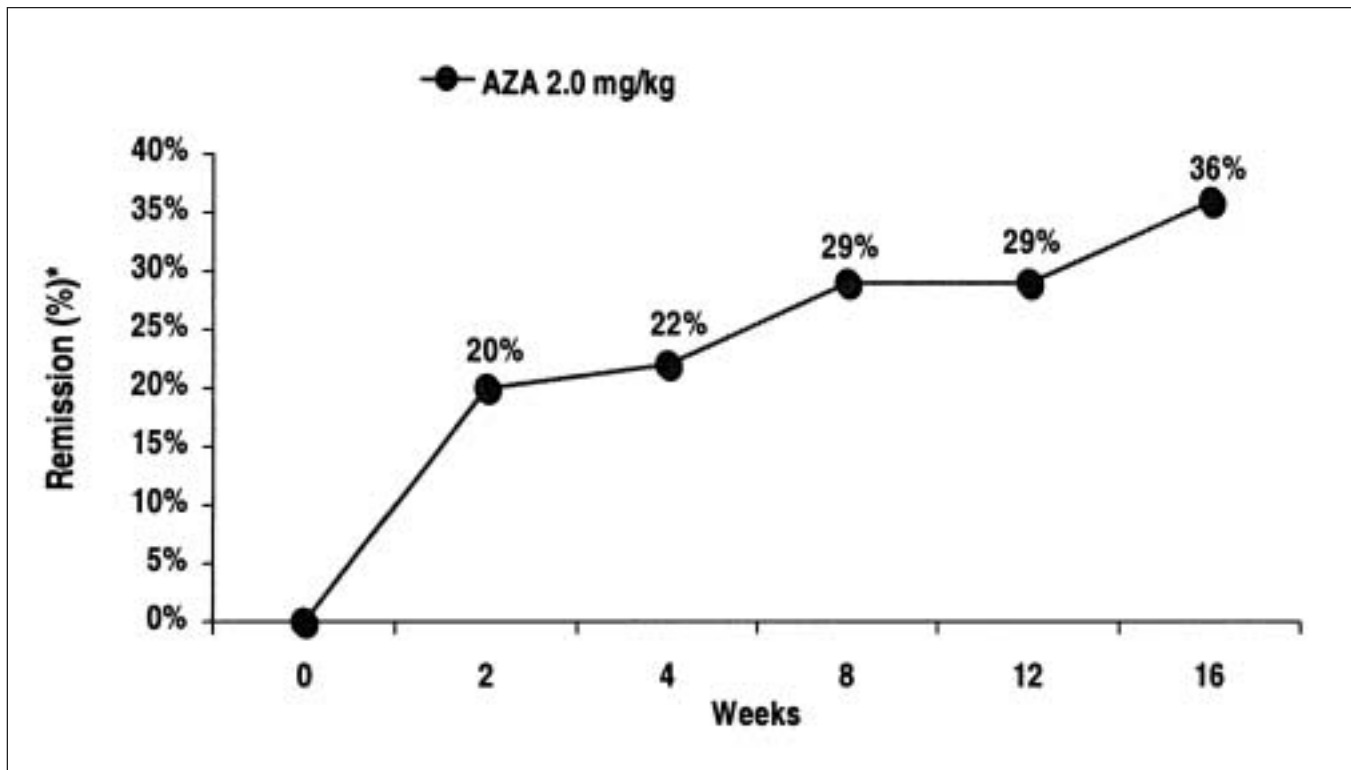


Figure 2) Time course of response to oral azathioprine (AZA) 2 mg/kg in the treatment of steroid-resistant Crohn's disease. *Crohn's Disease Activity Index less than 150. Data from reference 11

mation. Patients resistant to corticosteroids are generally not expected to respond to 5-aminosalicylates or antibiotics, which may be beneficial for patients with mild to moderate disease (9). Immune modulators and, increasingly, biological response modifiers have found a role in the treatment of steroid-resistant disease (Table 1). Although many trials have included patients with active symptoms despite corticosteroid therapy, few have specifically targeted steroid-resistant patients.

MEDICAL THERAPY OF STEROID-RESISTANT CROHN'S DISEASE

Azathioprine and 6-mercaptopurine: Azathioprine and 6-mercaptopurine are commonly used in the treatment of patients who are unable to discontinue corticosteroids without exacerbation of symptoms, as well as in the treatment of patients with continued symptoms despite corticosteroid therapy. Present et al (10) described the long term use of 6-mercaptopurine in patients with chronically active Crohn's disease. Of the 83 patients studied, 60 were also being treated with steroids at enrolment. Three-quarters were able to discontinue or reduce the dose of steroids. The recent study by Sandborn et al (11) provided the only blinded, randomized, controlled data available regarding the efficacy of azathioprine in steroid-resistant Crohn's disease (Figure 2). Patients with active disease despite at least four weeks of treatment with prednisone (20 mg daily) were assigned to oral azathioprine 2 mg/kg and intravenous loading with azathioprine or placebo infusion. Intravenous loading did not reduce the

time to remission, largely because of an unexpectedly rapid time to response among patients receiving oral azathioprine alone. Approximately one-quarter of patients were able to discontinue prednisone and achieve clinical remission by week 8. Overall, 29% of patients were able to discontinue steroids and achieve a CDAI less than 150 by week 16, indicating little additional response beyond eight weeks of therapy. Slightly higher dosages of azathioprine (2.5 to 3 mg/kg) might have improved the rate of response.

Methotrexate: Feagan et al (12) clearly demonstrated the utility of methotrexate in facilitating the discontinuation of corticosteroids (Figure 3). All patients had chronically active disease despite having received prednisone 12.5 mg/day for three months or more. The mean CDAI was 184. The response rate (CDAI less than 150 and off prednisone at week 16) of 39% in treated patients versus 19% in placebo patients indicates the efficacy of methotrexate in steroid-resistant disease.

Cyclosporine: The use of cyclosporine to treat steroid-resistant Crohn's disease remains controversial. Careful scrutiny of the available data reveals that high dose cyclosporine (ie, to achieve whole blood levels between 400 and 800 ng/mL) is effective in patients who do not show a satisfactory response to corticosteroids (13). However, the risk of severe toxicity associated with high doses of cyclosporine and the lack of efficacy of lower doses (14,15) restrict the utility of this agent.

Infliximab: Infliximab is a new alternative in the treatment of patients with steroid-refractory Crohn's disease. Targan

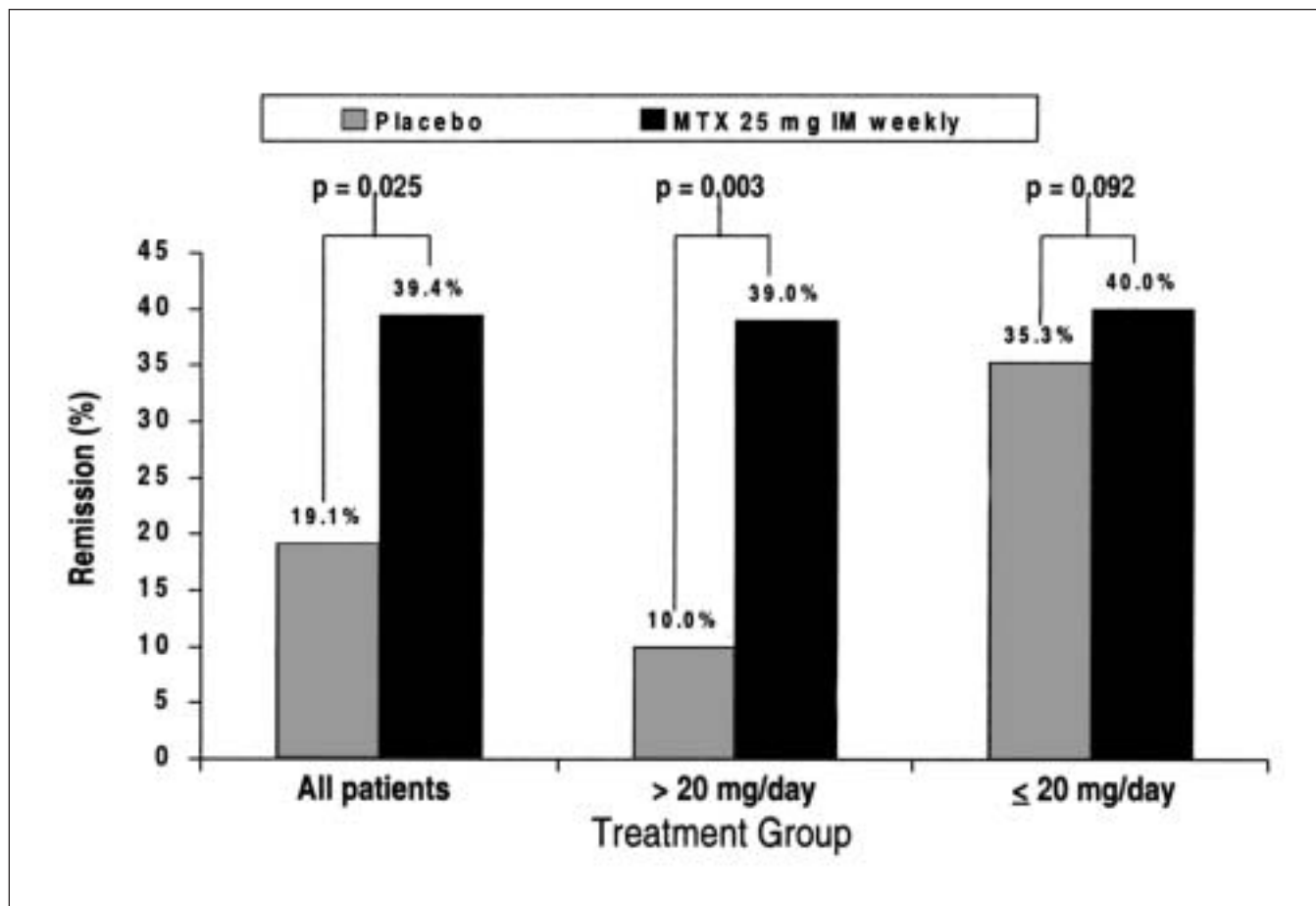


Figure 3 Methotrexate (MTX) in the treatment of steroid-resistant Crohn's disease. Remission was defined as ability to discontinue steroids while maintaining a Crohn's Disease Activity Index less than 150 at week 16. IM Intramuscularly. Reproduced with permission from reference 12

et al (16) reported the short term results of a mixed group of patients with active, symptomatic disease despite receiving a variety of therapies. Approximately 60% of the treated patients were receiving up to 40 mg/day prednisone. The time to response was rapid, with the majority of patients improving within two weeks of infusion. At week 4, 81% of patients treated with 5 mg/kg infliximab achieved a response compared with 17% with placebo. Post hoc analysis demonstrated the overwhelming effect of infliximab on the likelihood of response, regardless of concomitant therapy.

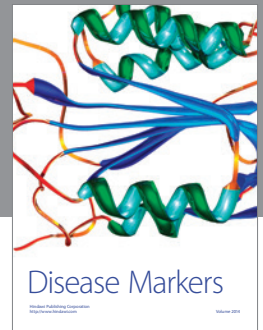
CONCLUSIONS

Research has been active in the treatment of steroid-resistant Crohn's disease. Azathioprine, 6-mercaptopurine, methotrexate and infliximab have all been shown to be effective. More limited studies have investigated the use of interleukin-10 (17), tacrolimus (18), mycophenolate mofetil (19) and thalidomide (20,21) with mixed results. Although patients with steroid-resistant Crohn's disease continue to present a considerable management challenge for the gastroenterologist, advances in drug therapy will continue to improve the outcomes for these patients.

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