INTRODUCTION

Corticosteroids are the “Dr. Jekyll and Mr. Hyde” of inflammatory bowel disease (IBD) therapy. On the one hand, no other medication produces such consistent and rapid clinical benefit in both ulcerative colitis (UC) and Crohn’s disease (CD), however, no other commonly used therapy causes so many difficult and damaging treatment related side effects. Despite the well recognized potential dangers associated with their use, especially with prolonged use, corticosteroids remain one of the most effective therapies in the medical treatment of IBD (1–3). When judiciously and wisely employed, corticosteroids can produce rapid symptomatic improvement in IBD and drug toxicity can be minimized.

CORTICOSTEROID PREPARATIONS

Available corticosteroid preparations differ in their potency and, to a lesser degree, in their side effects.
Prednisone is a synthetic glucocorticoid, which undergoes hepatic hydrolysis to prednisolone, thereby increasing its glucocorticoid activity. Newer synthetic glucocorticoids, such as dexamethasone, are even more potent (Table 1). Corticosteroids may be administered topically, as suppositories, foams or enemas, orally, or intravenously. In the United States, most physicians use hydrocortisone for topical administration, prednisone for oral administration, and hydrocortisone or methylprednisolone for intravenous administration. Compared to many medications used for the treatment of IBD, corticosteroids are cheap and affordable therapy.

Budesonide is a novel synthetic corticosteroid structurally related to prednisolone. Budesonide has a very strong affinity for the glucocorticoid receptor, giving it potent local anti-inflammatory activity. However, the systemic effects of budesonide are significantly less than conventional corticosteroids due to rapid, near complete first-pass hepatic conversion to metabolites with limited activity. Budesonide capsules are designed to delay the release of budesonide until reaching the ileum and ascending colon. The capsules start releasing their content at a pH of over 5.5 and systemic availability is approximately 10%.

### MECHANISM OF ACTION

The actions of glucocorticoids, both natural and synthetic, are mediated by specific intracytoplasmic glucocorticoid receptors. Since most cells express glucocorticoid receptors, glucocorticoids affect the function of a large number of different cell types. The beneficial, as well as deleterious, effects of glucocorticoid administration result from this widespread, multifactorial effect and cannot be explained by any one particular action. Glucocorticoids impair specific and non-specific immune reactions, affecting both early and late inflammatory events. They inhibit early events, such as vasodilation, leukocyte infiltration, increased vascular permeability, and the release of inflammatory cytokines, and also act to suppress later processes including fibroblast activations and vascular proliferation (Figure 1). The combination of glucocorticoid effects on the recruitment and proliferation of immune cells at sites of inflammation, along with effects on the production of soluble inflammatory mediators, such as cytokines, leukotrienes, and prostaglandins, explains the potent anti-inflammatory effects of these compounds.

### TREATING ULCERATIVE COLITIS WITH STEROIDS

Despite advances in the management of UC, systemic corticosteroids remain a mainstay of medical therapy for acute attacks of moderate to severe disease (Table 2). Response rates of 70%–80% can be expected with the use of intravenous corticosteroids for hospitalized patients with severe attacks of UC. Similar response rates are seen with the use of oral preparations for

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Table 2
Indications for corticosteroid use in ulcerative colitis

- Acute treatment of moderate disease (oral steroids)
- Acute treatment of severe disease (intravenous steroids)
- Acute treatment of proctitis and proctosigmoiditis (topical steroids)
- No role for maintenance steroid therapy

more moderate flares. In mild to moderate UC there is a documented dose response between 20 and 60 mg of prednisone per day, with no obvious benefit from higher oral doses. Outpatients with a moderately severe flare of UC should receive prednisone 40 mg daily, with the higher dose of 60 mg daily reserved for more severe flares. Most clinicians use once a day dosing, however, “split-dosing” two to four times a day may be helpful in patients who remain symptomatic after a trial of once daily dosing, particularly if they are bothered by nocturnal bowel movements. Split dosing may also be useful for hospitalized patients transitioning from parenteral steroids to oral therapy. Once the decision has been made to initiate oral steroid therapy for the treatment of UC, no rationale exists for starting at lower doses in an attempt to prevent steroid side effects. This approach leads to inadequate clinical response and typically results in a longer duration of steroid therapy. Likewise, premature tapering of steroids before a complete response is obtained is likely to lead to rapid symptom relapse (4). Corticosteroids should be continued at full dose until clinical remission has been obtained, typically within two weeks, but occasionally longer, followed by gradual dose tapering. Oral corticosteroids are neither effective nor indicated in preventing relapse of UC. Doses of prednisone up to 15 mg/day have failed to maintain remission, and continuation of corticosteroids beyond several months risks short- and long-term complications. Patients unable to taper off of corticosteroids need to be evaluated for alternative medical therapy or surgical intervention.

Parenteral corticosteroids are the treatment of choice for hospitalized patients with severe UC. The optimal dose response for parenteral steroids in the treatment of severe UC has not been clarified. Most treatment regimens use methylprednisolone 60 mg per day or its equivalent delivered as intravenous bolus 3-4 times daily (5) and there is little evidence to support the use of higher doses. Compared to equivalent doses of intravenous hydrocortisone, methylprednisolone results in less renal potassium loss. Some debate remains as to how long to continue intensive intravenous steroid therapy in patients with severe UC before deciding it has failed to bring about remission. The majority of patients respond within five days. Recently, it has been reported that after only three days of intensive treatment most (85%) patients with persistent frequent stools (>8/day) or a raised c-reactive protein (>45 mg/L) will eventually need colectomy (6). Most practitioners will treat severe colitis with seven to 10 days of intravenous corticosteroid before moving to other medical treatments or surgery.

The rectal administration of corticosteroids is an important component of UC treatment, with topical steroids having a primary role in the treatment of distal UC . Although studies of rectally administered steroids have reported fewer systemic side effects than with oral steroids, plasma concentrations of prednisolone are similar with identical oral and rectal doses and suppression of the pituitary-adrenal-hypothalamic axis does occur. A variety of topical steroid formulations, including hydrocortisone, prednisolone, and betamethasone are available as suppositories, foams, and enemas. In general, suppositories are useful for the treatment of proctitis, while enemas and foams are useful for more extensive left-sided disease, with documented spread to the splenic flexure. Many patients prefer foam preparations to enemas due to ease of administration and retention. Despite their utility in the treatment of UC, topical glucocorticoids are less effective than topical aminosalicylates (7).

The role of budesonide in the treatment of UC remains uncertain. Pilot studies have suggested less overall clinical benefit from budesonide compared to prednisolone for mild to moderate UC (8). Importantly, patients with UC treated with budesonide have not shown suppression of plasma cortisol, though this is seen in CD treated with oral budesonide. Budesonide has also been used successfully in corticosteroid-dependent UC patients as a means discontinu-
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ing conventional steroids. Although the results of these studies are encouraging, obtaining sufficient spread through the colon and preventing bacterial metabolism and inactivation of non-systemic steroids continue to be practical obstacles in the widespread use of these medications as oral therapy for UC.

Although corticosteroids are effective for the acute therapy of UC, not all patients respond to corticosteroid treatment (steroid resistant), and some patients who respond are either unable to taper off medication or relapse shortly after discontinuing corticosteroids (steroid dependent). Natural history studies suggest that less than 50% of patients will ever require steroid therapy for their UC. Among UC patients treated with steroids, short-term responses are remission in 54%, partial response in 30%, and no response in 16%. At one year, prolonged response can be expected in 49%, corticosteroid dependence in 22%, and colectomy in 29% (9).

CORTICOSTEROID THERAPY OF CROHN’S DISEASE

Several large, randomized, placebo-controlled trials have shown clinical remission rates of 60%-70% in steroid treated CD (10,11) (Table 3). Doses range between 0.25–1 mg/kg/day of prednisolone or its equivalent. As in UC, most physicians in the United States use between 40–60 mg of prednisone for the outpatient treatment of moderate Crohn’s disease. Although no large studies have evaluated the use of intravenous corticosteroids in the treatment of hospitalized patients with more severe CD, they are routinely used with good results. Doses tend to be the same as in severe UC, namely methylprednisolone 60 mg daily or its equivalent. As with UC, however, steroids do not prevent relapse for patients with quiescent disease. Patients with CD unable to discontinue corticosteroids after several months should be considered for alternative therapies, such as azathioprine, 6-mercaptopurine, methotrexate, or infliximab.

The targeted delivery of budesonide to the distal ileum and ascending colon make it an ideal therapy for CD. Budesonide 9 mg once daily has been found to be superior to mesalamine at inducing remission in active CD. Studies have also shown that budesonide is almost as efficacious as prednisolone for the treatment of active CD (12). Although slightly less effective than conventional steroids at induction of remission, budesonide treated patients are less likely to have steroid related side effects. Budesonide does cause a dose related reduction cortisol concentrations, however, compared to prednisolone, budesonide causes less moon facies, weight gain, acne, and mood change. The combination of clinical efficacy with fewer side effects makes it clear, that budesonide in a controlled-release, targeted formulation at 9 mg per day for eight to 10 weeks offers an effective and attractive alternative to traditional systemic corticosteroids for the treatment of active CD involving the ileum, ileocolic region, and ascending colon. Similar to conventional corticosteroids, budesonide does not prevent relapse in patients with quiescent CD.

CD patients treated with conventional corticosteroids for the first time can expect a complete remission between 48%–58%, a partial response between 26%–32%, and no response between 16%–20% of the time. At one year approximately 45% of steroid treated patients will be doing well, 35% will be steroid dependent, and 20% will be steroid resistant and/or require surgery (13). Recognizing that slightly less than half of all CD patients treated with steroids will be well and off steroids at one year, the need for steroid therapy must be considered a marker of poor prognosis in CD. With this in mind, the initiation of steroid therapy in CD justifies the consideration of alternative treatments, such as immunomodulators or infliximab, for long-term management.

COMPLICATIONS OF CORTICOSTEROID THERAPY

The adverse effects of corticosteroids relate directly to the dose and duration of therapy, and can be expected

Table 3

Indications for corticosteroid use in Crohn’s disease

- Acute treatment of moderate disease (oral steroids; budesonide)
- Acute treatment of severe disease (intravenous steroids)
- No role for maintenance steroid therapy
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Table 4
Side effects corticosteroid therapy

Metabolic
• Hyperglycemia, diabetes mellitus
• Hypertension
• Hypercholesterolemia
• Hypokalemia
• Adrenal suppression

Musculoskeletal
• Osteoporosis
• Aseptic necrosis of bone
• Proximal myopathy
• Growth retardation

Dermatologic
• Acne
• Plethora
• Striae

Ocular
• Cataracts
• Glaucoma

Neuro-psychiatric
• Neuropathy
• Insomnia
• Psychosis

Immunologic
• Increased risk of infection

Miscellaneous
• Moon face
• “Buffalo hump”
• Weight gain
• Ulcer disease

to impact on every organ system and metabolic process of the body. Corticosteroid side effects are the major factors limiting long-term use of glucocorticoids in IBD. The toxicities of corticosteroid therapy are listed in Table 4.

The metabolic effects of steroid therapy include hyperglycemia and an unmasking of a genetic predisposition to diabetes mellitus, hyperlipidemia, alteration of fat distribution with development of a cushingoid appearance, and hepatic steatosis. Glaucoma and cataracts have been described in both adults and children and correlate with the intensity and duration of treatment. Wound healing is impaired after steroid therapy, and corticosteroids are associated with increased post-operative infections. Steroid induced subcutaneous tissue atrophy causes striae, and predisposes to purpura and ecchymoses.

Corticosteroid-induced neuropsychiatric complications occur in approximately 25% of patients and are severe in up to 6% of patients, with symptoms including psychosis, depression, mania, and delirium. Milder more common side effects include irritability, anger, insomnia, and excessive talkativeness. At high corticosteroid doses cognitive impairment and hallucinations have been reported. A case report suggests that budesonide can be effective and well tolerated in patients with neuropsychiatric symptoms after treatment with conventional systemic steroids.

Most studies have implicated corticosteroids as a major risk factor for reduced bone mineral density (BMD) in IBD, although bone loss may be related to inflammation and occur independent of steroid therapy. Corticosteroids accelerate the rate of bone loss irrespective of other risk factors for osteoporosis, affecting men and women equally. Corticosteroids affect both bone resorption and formation, ultimately resulting in decreased bone mass and fractures (14). In IBD, the higher the total lifetime steroid dose, the lower the bone density. Despite the high prevalence of bone loss in steroid treated IBD patients, it remains uncertain whether these patients suffer an increased rate of osteoporotic fractures, with two population studies coming to opposite conclusions [Loftus, 2002 #3543]; (15).

All IBD patients treated with corticosteroids for greater than three months should have DEXA scanning. Osteopenia should be treated with calcium and vitamin D supplementation. Patients with osteoporosis should receive calcium and vitamin D supplementation and a bisphosphonate compound, such as alendronate or risedronate. Aggressive attempts should be made to discontinue steroid treatment and follow-up DEXA scanning should be yearly until stability or improvement of bone density is confirmed.

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Steroid-related osteonecrosis, particularly of the femoral head, is a less common musculoskeletal complication of IBD. This precise pathogenesis of this condition is uncertain and it can be difficult to anticipate and diagnose. This dreaded complication can lead to premature arthritis and joint collapse, leading to early prosthetic joint replacement.

**SUMMARY**

Corticosteroids are central to the acute management of UC and CD, showing clear benefit in the management of moderate to severe disease. No other class of medication acts as rapidly and with such consistent results to control disease activity, improve patient symptoms, and, in UC, promote endoscopic and histologic improvement. However, corticosteroids do not maintain remission in IBD, and no other class of medication produces such a wide variety of and difficult to manage side effects. A better understanding of the mechanism of steroid action has led to the development of potent new steroids with fewer side effects, such as budesonide. The promise of these less toxic steroids has yet to be fully realized, and the search continues for the optimal glucocorticoid with the best balance of efficacy and side effects. In the meantime, we can help our patients through the careful use of both conventional corticosteroids and budesonide. Attention to appropriate patient selection, dose, and duration of treatment can maximize benefit and minimize steroid related toxicity.

**References**