EDUCATION PRACTICE

Management of Steroid-Dependent Ulcerative Colitis: Immunomodulatory Agents, Biologics, or Surgery?

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Clinical Scenario

A 32-year-old woman with moderate pancolonic UC diagnosed 1 year ago makes an office appointment because she is unable to discontinue prednisone without experiencing a flare. At diagnosis, her symptoms improved within 2 weeks with 5-aminosalicylate therapy. Despite ongoing therapy with 5-aminosalicylates, she has experienced 2 moderate disease exacerbations requiring use of prednisone. Since her last flare 4 months ago, she has been unable to successfully reduce her prednisone below 10 mg per day without experiencing an increase in symptoms. On lower doses, she experiences abdominal cramping, an increase in bowel movements to 6 per day, urgency, and blood in the stool. Evaluation to date has consisted of a recent flexible sigmoidocopy showing mild to moderate mucosal inflammation to the descending colon, negative mucosal viral cultures for cytomegalovirus, and negative stool studies for bacteria, parasites, and *Clostridium difficile* toxin. Complete blood count and albumin are normal. She tells you that she is concerned about the cosmetic side effects of prednisone and the health effects of colitis impacting her upcoming wedding in 9 months. Since starting prednisone, she has experienced a 15-pound weight gain, as well as acne, insomnia, and fatigue. She requests a referral to a surgeon. She believes that "pouch surgery" is the only way she will be able to discontinue prednisone and be healthy for her wedding and married life.

What should be the next move in this patient with steroid-dependent UC: azathioprine, infliximab, or surgery?

The Problem

UC is a lifelong inflammatory condition of the colonic mucosa of unknown cause. Oral corticosteroids are among the most effective therapies for UC. Approximately 50%–80% of patients prescribed corticosteroids will experience resolution of symptoms or improvement at 1 month (Figure 1). Physicians commonly prescribe steroids with the intent of rapidly improving the disturbing and life-altering symptoms associated with UC. The expectation is that once improved, patients will be easily tapered off of steroids, transitioned to some other maintenance therapy with a better side-effect profile, and will experience few steroid-related side effects during this process.

One problem with corticosteroids is that steroid dependence is not an uncommon occurrence in patients with UC (Figure 1). A recently published hospital-based study from the United Kingdom reported that 17% of patients newly diagnosed with UC and treated with corticosteroids were steroid-dependent at 1 year. This finding is similar to a population-based study from the United States reporting that 22% of patients with UC treated with corticosteroids were steroid-dependent at 1 year. Furthermore, despite a physician's best intent and expectations, steroid-related side effects are also common. Steroid-induced side effects affect approximately 50% of patients on chronic corticosteroids. These side effects include acne, weight gain, insomnia, osteoporosis, cataracts, and infections, among others.

Besides the actual problem of steroid dependence, there is also a problem with the term *steroid dependence*. There is no standard definition in use in clinical practice or trials. A recently published position statement from the American Gastroenterological Association on the use of corticosteroids, immumodulators, and infliximab in IBD suggests a practical definition of steroid dependence: "the inability of a particular patient to taper below a certain dose of corticosteroid without flaring." This same position statement emphasizes the need to "lower or preferably eliminate [corticosteroid] use" in these patients. On the basis of this definition, this patient would qualify as steroid-dependent and needs to lower or preferably eliminate corticosteroid use. This review discusses the supporting evidence for 3 possible options to achieve this goal. Because all 3 strategies are effective and one might be preferred over the other depending on the clinical situation, we also address the long-term sequelae associated with each choice.

Management Strategies and Supporting Evidence

Option 1: Start an Immunomodulator (Azathioprine or 6-Mercaptopurine)

Azathioprine (AZA) and 6-mercaptopruine (6MP) are related thiopurine analogues that have been used to treat IBD for more than 30 years. Although the data supporting the use of immunomodulator therapy are more compelling in Crohn's disease than in UC, there are studies that suggest AZA is steroid-sparing in UC. Two randomized placebo-controlled trials published more than 20 years ago and one published in the past year have shown that AZA at a dose ranging between

Abbreviations used in this paper: ACT, Active Ulcerative Colitis Trial; AZA, azathioprine; FDA, Food and Drug Administration; IPAA, ileal pouch–anal anastomosis; 6MP, 6-mercaptopurine; QOL, quality of life; TPMT, thiopurine methyltransferase; UC, ulcerative colitis.

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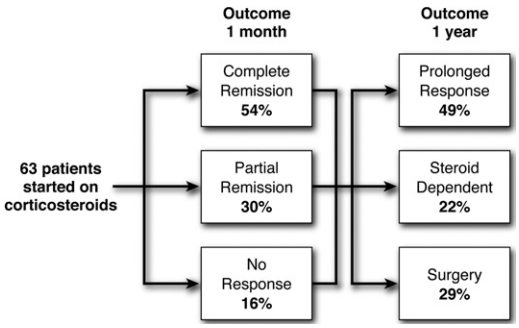

Figure 1. Efficacy of oral corticosteroids at 1 month and frequency of steroid dependence at 1 year among 63 newly diagnosed patients with UC started on corticosteroids (data from Faubion WA et al.[1] Gastroenterology 2001;121:255–260).

1.5–2.5 mg/day for 6 months significantly reduces steroid dependence. In the most recent of these 3 trials, the definition of steroid dependence closely resembles the situation for this patient: requiring ≥10 mg/day of steroids during the preceding 6 months with at least 2 attempts to discontinue the medication. In that trial, 53% of steroid-dependent patients randomized to AZA (2 mg × kg^{-1} × day^{-1}) were in remission and no longer on steroids at 6 months after study entry. This was statistically superior to the placebo arm, in which 21% of steroid-dependent patients who received 5-aminosalicylate therapy (3.2 g/day) were in remission and off steroids at the same time point.

Because chronic use of immunomodulators is advocated to reduce the risk of relapse, issues associated with long-term use, specifically infection, malignancy, and pregnancy, are particularly relevant for this patient. There is concern that AZA/6MP use increases the risk of developing lymphoma. A recent meta-analysis estimated a 4-fold increase of lymphoma in IBD patients treated with AZA/6MP. Despite this reported increased risk, the overall benefit of immunomodulator therapy is believed to outweigh the risk. Hence, AZA and 6MP are accepted therapies for the treatment of IBD. Use of AZA and 6MP can impart potential risks to the fetus. AZA and 6-MP are Food and Drug Administration (FDA) category D drugs for pregnancy (evidence of fetal risk but benefits to mother might outweigh potential risk). Despite this FDA category, these drugs are often maintained in pregnancy to keep the mother in remission. This rationale is based on the large experience in the use of these medications in transplant recipients who become pregnant, a growing body of evidence regarding their safety in IBD, and the importance of using these medications to keep the mother healthy and in remission during the pregnancy. To date, there is no significant evidence of an increase in the rate of congenital malformations in the children of mothers exposed to 6MP/AZA. Of note, methotrexate, an immunomodulator used to effectively treat active Crohn's disease, is contraindicated in pregnancy (category X) and has not been found to be efficacious to treat UC.

Option 2: Start Biologic Therapy (Infliximab)

Infliximab is a chimeric monoclonal antibody directed against the inflammatory cytokine tumor necrosis factor–alpha. Infliximab has been approved for the treatment of Crohn's disease since 1998 and for UC since 2005. The initial 5 (albeit small) controlled trial studies studying the efficacy of infliximab for the treatment of UC were conflicting. However, the 2 most recent large randomized controlled trials, Active Ulcerative Colitis Trials (ACT) I and II, demonstrated a consistent benefit of infliximab for the treatment of UC. Steroid-dependent patients were eligible in the inclusion criteria for ACT I/II (failing medical therapy with >20 mg/day steroids, AZA, or mesalamine (ACT II only) when they flared on a lower dose of prednisone. Although data for the steroid-dependent subgroup were not reported separately, 20%–25% of all patients randomized to an induction regimen of 5 mg/kg of infliximab at 0, 2, and 6 weeks followed by a maintenance dose every 8 weeks were in remission and not on corticosteroids at week 30 (7 months). This was statistically superior to the placebo arm, in which 3%–10% of patients were in remission and not on steroids at the same time point.

As with purine analogues, chronic use of infliximab is advocated to reduce the risk of relapse. Chronic use of infliximab is also advocated to minimize the development of drug-related antibodies, infusion reactions, and reduced medication efficacy. Infliximab has been associated with a risk of infection and malignancy when used for other disease states. Regarding the risk of malignancy associated with long-term use, there were no lymphomas reported at 1 year in the ACT I and II trials. However, long-term cohort studies and post-marketing surveillance on a larger population of UC patients will be required to completely assess this risk with long-term use. Regarding the risk of these drugs to the fetus, infliximab is an FDA-category B drug for pregnancy (either animal studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal studies have shown an adverse effect that was not confirmed in women in the first trimester). There is a small, but growing body of evidence that suggests that infliximab is low risk in pregnancy. The agent does cross the placenta and is detectable in the infant up to 6 months from birth.

Option 3: Proceed to Surgery (Proctocolectomy J Pouch Ileoanal Anastomosis)

Surgery is 100% effective for the treatment of UC and has historically been considered the definitive treatment of UC. As with medical therapy of UC, surgical therapy of UC has evolved with time. A proctocolectomy with ileal pouch–anal anastomosis (IPAA) is commonly offered to young patients as an alternative to the traditional permanent (Brooke) ileostomy. In experienced hands, total proctocolectomy with IPAA can result in low complication rates, good functional outcome, and improved quality of life (QOL), although the QOL improvement is highly dependent on QOL before surgery. Even so, IPAA is a technically demanding operation, with a 5%–18% risk of short-term pouch leakage and pelvic abscess.

If the rectum is completely removed along with the colon, then the long-term risk of malignancy after surgery is very low. There are rare reports of cancer in the remnant rectal cuff and the pouch itself. Therefore for most patients, more relevant longer-term sequelae to address when considering pouch surgery relate to the function of the pouch and to fertility. Chronic pouchitis is reported in 9%–20% of surgeries. The rate of pouch failure at 1 year is between 2%–10%. Patients on average have 6 daily bowel movements (1 nocturnal). Daytime and nighttime incontinence is approximately 7% and 12%, respectively. A recently published meta-analysis reported a 3-fold increase in