

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

Section Editor: Stephen B. Hanauer, MD

## The Role of Cyclosporine Therapy in Ulcerative Colitis Treatment

Simon Lichtiger, MD  
Assistant Clinical Professor of Gastroenterology  
Mount Sinai School of Medicine

**G&H** Can you describe the historic development of cyclosporine as a therapy for ulcerative colitis?

**SL** Cyclosporine was used uniquely in organ transplant patients in the 1970s and early 1980s. In the early 1980s it was noted that because cyclosporine blocks the effect of interleukin-2 on white blood cells, it could potentially be of use in the setting of ulcerative colitis (UC), as interleukin-2 plays a role in the propagation of inflammation.

The initial studies of cyclosporine in UC started in 1985 and continued through 1989. In these studies an 80% response rate to cyclosporine was observed in a population of patients who had failed steroid therapy, and who would otherwise be slated for colectomy. At this point it was decided to design a double-blind trial of cyclosporine versus placebo in patients with severe, steroid-refractory UC, which commenced in 1991. It was initially planned to enroll 40 patients. However, after 20 patients had completed treatment, the monitoring drug-safety committee halted the study. They cited the fact that nearly all patients receiving cyclosporine were showing response, whereas patients on placebo were not improving. In this light, continuation of the study was deemed unethical.

Since this time, there have been many others studies of cyclosporine as an adjunct to other therapies, as well as dose-ranging studies and studies of different forms of cyclosporine administration. However, there has only been one other study, conducted in Europe, that has examined patient response to cyclosporine versus placebo.

In regard to clinical practice, the use of cyclosporine has been at the initiative of individual doctors. There is no US Food and Drug Administration indication for the use of cyclosporine in UC. However, both the American Gastroenterologic Association and the American College of Gastroenterology guidelines for the treatment of severe UC include cyclosporine in their therapeutic regimens.

**G&H** Could you describe the dosing regimen for cyclosporine that has evolved over the years for use in severe UC?

**SL** The initial studies were in patients who had failed seven days of intravenous steroids. If, on the seventh day, there was no response, they were given intravenous cyclosporine at 4 mg/kg daily for a maximum of 14 days. After the patient finished the acute or intravenous phase of the drug, they would be sent home on a double dose of 8 mg/kg daily of cyclosporine taken orally. The initial intent was to keep them on oral cyclosporine in combination with oral steroids for 2 months and then to withdraw the cyclosporine gradually.

Over the years, it was learned that after 3 days of steroid nonresponse, cyclosporine could be infused. Further, patients not responding to cyclosporine after 10 days will most likely not respond at all. Eventually, it was also realized that cyclosporine was not a maintenance agent but an induction agent and in 1993 the approach changed, so that all patients who received oral cyclosporine also received oral 6-mercaptopurine (6-MP). 6-MP was started 2 weeks after discharge from the hospital. The 6-MP was used as the maintenance agent, with cyclosporine serving as the bridge to the maintenance phase.

**G&H** What safety and monitoring concerns are there regarding the use of cyclosporine?

**SL** I believe the initial concern was that cyclosporine had originally been used only in transplant patients and had been associated with a fair incidence of renal toxicity.

However, transplant patients and UC patients are very different. The likelihood of renal toxicity in a patient who has undergone a kidney transplantation is going to be much higher than in a patient with healthy kidneys.

Regardless, because of the concerns of nephrotoxicity, there was a perceived need to overmonitor patients receiving cyclosporine. In its initial use in UC, patients with a creatinine clearance rate less than 80 mL/min were not considered eligible for cyclosporine. It was thought that renal function needed to be monitored on a day-to-day basis and that serum cyclosporine levels needed to be measured daily.

Over the years our understanding has evolved with the realization that patients do not deteriorate quickly and that toxicities can be detected early and corrected by decreasing the dose of infused cyclosporine. Our long-term data regarding renal toxicity show that only 1 in approximately 250 patients have experienced permanent renal damage from cyclosporine. Blood pressure usually goes up several days before kidney function begins to deteriorate and by monitoring blood pressure, the dose can be corrected in a manner that reverses toxicity by 100%.

The other concern was simply that gastroenterologists were not familiar with cyclosporine as it was used in the transplant setting exclusively. Over the years, as gastroenterologists have gained familiarity with it, it has been used more freely in many community hospitals.

#### **G&H** How has the introduction of the anti-TNF- $\alpha$ agent infliximab affected the use of cyclosporine in clinical practice?

**SL** I believe that the two agents are used for different patients or, at least, studies show that they should be used for different patients. The data for infliximab have largely been based on treatment of patients with mild to moderately active UC. The investigators used a different gradation score than was utilized in the cyclosporine study and it did not include patients with genuinely severe UC. In both the ACT I and the ACT II infliximab trials, the patients studied were in the outpatient setting and had mild-to-moderate disease. The cyclosporine data were from patients with severe ulcerative colitis who were treated in-hospital.

However, most gastroenterologists feel more comfortable using infliximab because they've used it in Crohn's disease and have seen a clear, marked improvement. Even before the ACT studies were published, many clinicians used infliximab, assuming that if it improves Crohn's disease it will improve UC. That is not necessarily what has been observed in clinical practice.

In fact, studies that have looked at infliximab in severe UC have shown conflicting data. A study by Janerot and associates showed that it was effective but another by Probert and associates showed that it was not effective. There has never been a study directly comparing infliximab and cyclosporine in severe UC and I doubt that one will ever be done. With the introduction of more anti-tumor necrosis factor- $\alpha$  therapies for UC, I believe that, ultimately, patients who get cyclosporine will already have tried and failed a biologic agent. Cyclosporine will be used as a last line therapy in order to prevent colectomy.

The other issue that is coming into focus is that all of these immunosuppressive agents cannot be given concurrently. Beyond the concerns of possible infections, case reports of aggressive lymphomas indicate that there are both short- and long-term immunocompromising consequences when a biologic, 6-MP, cyclosporine, and prednisone or another steroid are all given in quick succession in an attempt to control disease progression.

#### **G&H** How long should a clinician wait after a patient fails a biologic or immunosuppressive agent to attempt therapy with cyclosporine?

**SL** If a patient does not respond to a biologic and the clinician is trying to avoid colectomy, the introduction of cyclosporine is going to be dependent on the patient's status. Though it may be better to wait, the patient's condition may not allow for more time before surgery becomes necessary. In short courses, I do not believe that overlapping therapies are a major concern. However, the clinician needs an exit strategy. In other words, regardless of whether a patient responds to a biologic or to cyclosporine, they cannot stay on them for maintenance. There must be a plan to move them to 6-MP or another maintenance medication in order to insure against permanent immunocompromise.

#### **G&H** What do clinicians need to know about cyclosporine in order to develop a greater level of comfort with its use?

**SL** First, the misconception that cyclosporine is a toxic agent should be dispelled. Clinicians need to learn that patients who have undergone transplantation and been treated with cyclosporine are different from UC patients with normal kidneys.

In addition, physicians need to understand that it is not necessary to get cyclosporine blood levels every day, particularly in patients receiving intravenous cyclosporine, where it has been found that the blood level remains

almost constant as long as the dose is maintained. Further, some papers suggest that instead of starting with 4 mg/kg, patients can be started on 2 mg/kg and achieve similar rates of remission.

Most important is the need to look at the long-term data. Thompson and colleagues studied UC patients who were 7 years postcyclosporine therapy and found the rate of colectomy to be almost 60%, which is a high number. However, considering that all of the patients studied had failed intravenous steroids, which heretofore had meant that they would undergo colectomy, a colonic retention rate of 40% seems much more impressive.

## Suggested Reading

Kornbluth A, Present DH, Lichtiger S, Hanauer S. Cyclosporin for severe ulcerative colitis: a user's guide. *Am J Gastroenterol.* 1997;92:1424-1428.

Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med.* 1994;330:1841-1845.

Jarnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology.* 2005;128:1805-11.

Probert CS, Hearing SD, Schreiber S, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut.* 2003;52:998-1002.

Moskovitz DN, Van Assche G, Maenhout B, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastroenterol Hepatol.* 2006;4:760-765.