

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Cyclosporine Versus Infliximab for the Treatment of Severe Ulcerative Colitis

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G&H When do clinicians typically consider cyclosporine or infliximab as a treatment for severe ulcerative colitis?

AK Physicians often consider the use of infliximab (Remicade, Centocor) when a patient has severe ulcerative colitis (UC) and does not have the luxury of waiting for high-dose prednisone to start working. Other scenarios in which infliximab could be considered include when a patient has been on high doses (40–60 mg) of prednisone but has not improved after 7–10 days, when a patient is on a lower dose of prednisone (20 mg) but cannot be tapered further and has not improved with 6-mercaptopurine (6-MP) or azathioprine (or the patient cannot wait 3 months for 6-MP or azathioprine to start working), or when a patient has already had at least one course of prednisone during the prior 1–2 years and now needs a second course of the drug.

Cyclosporine is used by far fewer physicians; when cyclosporine is used, it is typically as rescue therapy for hospitalized patients who have not improved after 3–5 days of treatment with intravenous (IV) steroids.

G&H How frequently do clinicians resort to either cyclosporine or infliximab?

AK Looking at all practices, including population-based practices and community practices—not just tertiary care centers—I would estimate the incidence of infliximab use to be approximately 10–15%. Cyclosporine is rarely used outside of a few academic centers.

G&H What data are available regarding the efficacy of cyclosporine or infliximab for the treatment of patients with acute UC who have not responded to IV steroids?

AK In the short term, 80% of patients will be discharged from the hospital on oral cyclosporine and prednisone. While follow-up durations and colectomy-free survival rates vary among different studies, on average 40% of patients will have avoided colectomy at the 5-year follow-up.

There are less data on the use of infliximab in the setting of acute IV steroid failure because infliximab has been available for fewer years for severe UC, but the data on infliximab seem to be very similar to the data on cyclosporine: 70–80% of patients will improve in the short term, and approximately 40% of patients will have avoided colectomy after 2 years.

G&H A study that was presented by Laharie and colleagues at Digestive Disease Week 2011 directly compared cyclosporine and infliximab for the treatment of acute severe UC in patients who had failed IV steroid treatment. Can you comment on this study?

AK The study by Laharie and colleagues is very important, as it is the first head-to-head comparison of IV cyclosporine versus IV infliximab in UC patients who failed IV steroids. For reasons of logistic difficulty, this trial was an open-label study rather than a double-blind study, but it included a sizable number of patients. Overall, this study found that outcomes were almost identical in the cyclosporine and infliximab arms after 7 days of treatment.

G&H How does this finding impact clinical practice?

AK Most physicians have not been using IV cyclosporine for hospitalized, steroid-refractory UC patients, and I think this study will reassure them that use of infliximab is perfectly appropriate in this setting. I would be eager to see a post-hoc subanalysis of the Laharie data addressing the question of whether the sickest patients did as well with infliximab as with cyclosporine; I believe cyclosporine may work more quickly in this subset of patients, but we do not yet have any data to support or refute this hypothesis.

G&H What factors predict the efficacy of cyclosporine or infliximab in patients with severe UC?

AK Patients with severe hypoalbuminemia who have failed IV steroids almost always fare poorly. Patients who present with very deep colonic ulcerations or denudation of the mucosa are also far less likely to achieve remission, probably with either cyclosporine or infliximab. Patients who are superinfected with *Clostridium difficile* are also less likely to respond to either drug. However, I do not think we will find any specific factors that will differentiate a priori between patients who are more likely to respond to infliximab and patients who are more likely to respond to cyclosporine.

G&H Overall, what factors do you consider when choosing cyclosporine or infliximab for patients who have failed IV steroid therapy?

AK I am one of a few physicians who has long relied on cyclosporine to treat hospitalized patients who have failed IV steroid therapy. Lichtiger at Mount Sinai Hospital pioneered the use of cyclosporine in this setting, and I had the good fortune to train at Mount Sinai Hospital and to adopt many of his practices regarding the use of cyclosporine. I think cyclosporine may actually be the better drug for patients who have “hyperacute” severe UC, since therapeutic levels of cyclosporine can be achieved within 24 hours. On the other hand, infliximab showed a response as early as Day 3 in the Laharie study, and the response to infliximab at Day 7 was equivalent to the response seen with cyclosporine, but we do not know how quickly infliximab will show a benefit in a wider group of patients.

One contraindication to cyclosporine is that this drug should not be used in patients who are severely hypocholesterolemic (serum cholesterol <110 mg/dL) because of the increased risk of seizures in these patients. In my mind, the presence of hypocholesterolemia would clearly be an indication for infliximab rather than cyclosporine.

G&H Would you ever consider using both cyclosporine and infliximab, either concomitantly or sequentially?

AK Concomitant use of both drugs is severely contraindicated, given the very severe immunosuppression that would be expected to occur with combined cyclosporine and infliximab therapy. Sequential use of both drugs should be very cautiously considered because of its significant potential toxicity.

A study by Maser and colleagues assessed patients who were sequentially treated with both cyclosporine and infliximab within a 30-day period. This study found a significant risk of serious infections, including 1 fatal infection among a total of 19 patients studied; furthermore, the likelihood of steroid-free remission at 1 year was only 30–40%.

Another study, by Leblanc and coworkers, found similar colectomy-free survival rates at 1 year. This study also had 1 fatality in a group of 86 patients; this fatality was due to a fatal pulmonary embolism, not infection, but it can be argued that this patient would not have been subjected to the ongoing risk of pulmonary embolism had he not been given 2 treatments, which prolonged his time to surgery.

Overall, I think any clinician considering the sequential use of cyclosporine and infliximab needs to be very cognizant of the likelihood of significant toxicity.

G&H If cyclosporine or infliximab has been tried and it failed, would you then try the other drug as second-line medical therapy?

AK I would be very cautious in selecting which patients I would treat with the second drug. I would only consider second-line medical therapy for a patient who does not have any other significant comorbidities or signs of possible infection, and I would not consider this option for a patient who is very acutely ill.

G&H Are there other side effects or contraindications with cyclosporine or infliximab that have not already been mentioned?

AK Both cyclosporine and infliximab can cause infections, and occasionally these infections can be severe—on rare occasions, even fatal. The concomitant use of steroids significantly increases this risk of infection. With cyclosporine, there is also the risk of renal insufficiency and/or hypertension, although both of these problems can usually be managed without much difficulty. Finally, as I previously mentioned, cyclosporine treatment is associated with a risk of seizures in the setting of hypocholesterolemia.

With infliximab, side effects include infusion reactions, the risk of opportunistic infections and/or delayed hypersensitivity reactions, arthralgias, and lupus-like reactions. There is also a low but real risk of developing lymphoma—including a very rare condition called hepatosplenic T-cell lymphoma—when infliximab is used in conjunction with 6-MP or azathioprine; this rare malignancy has been reported almost exclusively in young males.

G&H What further research is needed regarding treatment options for severe UC?

AK Unfortunately, the Laharie study is not going to be replicated anytime soon because it is very hard to accumulate such a large number of patients. In fact, it took a number of years to complete enrollment for that study. Rather than trying to replicate these results, I hope patients from the Laharie study can be followed in the future to see whether long-term results are better with

cyclosporine or infliximab. Also, I hope that retrospective analyses of the Laharie study data can be performed to address the question of whether certain patients might respond better to one drug or the other.

Suggested Reading

Laharie D, Bourreille A, Branche J, et al. Cyclosporin versus infliximab in severe acute ulcerative colitis refractory to intravenous steroids: a randomized trial. Presented at Digestive Disease Week; May 7–10, 2011; Chicago, Illinois. Abstract 619.

Maser EA, Deconda D, Lichtiger S, Ullman T, Present DH, Kornbluth A. Cyclosporine and infliximab as rescue therapy for each other in patients with steroid-refractory ulcerative colitis. *Clin Gastroenterol Hepatol*. 2008;6:1112-1116.

Leblanc S, Allez M, Seksik P, et al; GETAID. Successive treatment with cyclosporine and infliximab in steroid-refractory ulcerative colitis. *Am J Gastroenterol*. 2011;106:771-777.

Swaminath A, Kornbluth A. Optimizing drug therapy in inflammatory bowel disease. *Curr Gastroenterol Rep*. 2007;9:513-520.

Huamán Ríos JW, Casellas Jordá F, Malagelada Benaprés JR. Predictive factors of poor response to intravenous cyclosporine in steroid-refractory ulcerative colitis. *Rev Esp Enferm Dig*. 2009;101:163-171.