Management of fulminant ulcerative colitis

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Surprisingly limited evidence is available to show that cyclosporin, the most commonly used agent in severe ulcerative colitis (UC), is more effective than standard treatment alone. Infliximab, a potent anti-inflammatory agent, might be of similar activity and is much easier to handle. Although data for this agent also are limited, it is expected that soon more information will be available, making this drug the treatment of choice in this population. The relatively quick response both to cyclosporin and infliximab make the short-term use attractive, but the long-term benefit especially for cyclosporin is unclear, and adverse events such as nephropathy may become a significant problem. Severe UC should be managed jointly by gastroenterologists with a colorectal surgeon. Patients should be kept informed of treatment and prognosis, including a 25%-30% chance of needing colectomy. [Indian J Gastroenterol 2006;25(Suppl 1): S37-S38]

There have been recent advances in the treatment of ulcerative colitis (UC), including the anti-tumor necrosis factor (TNF) agent infliximab, both in patients with severe acute and in those with chronic active disease. Successful therapy depends on the timely use of appropriate drugs in relation to severity and localization of disease, with aminosalicylates being the mainstay for mild-to-moderate disease. Corticosteroids are still the major therapy option for severe acute flares. Although the potent immunomodulators azathioprine and 6-mercaptopurine have gained increasing acceptance for steroid-dependent disease, concerns about toxicity have restricted the usefulness of high-dose cyclosporin for patients with severe active UC.

Background
UC is characterized by a life-long chronic course with remissions and exacerbations. Approximately 15% of patients have a severe attack requiring hospitalization at some time during their illness. These patients are usually treated with intravenous corticosteroids, showing a response rate of approximately 60%. Often such patients require surgical removal of the large bowel (proctocolectomy or colectomy with ileo-anal pouch). This may cure the patient from the devastating disease but is associated with complications such as pouchitis, further supporting the need for better medical treatment options.

Patients who do not respond to corticosteroid treatment usually receive treatment with IV cyclosporin. The use of infliximab in such patients has demonstrated impressive efficacy. Cyclosporin acts mainly by suppressing T-lymphocyte function, which is essential for propagation of inflammation. Usually azathioprine therapy is started in parallel as this medication has a slow onset of action and therefore is initially ineffective. Unlike other immunosuppressants, cyclosporin does not suppress the activity of other hematopoietic cells, does not cause bone marrow suppression, and has a rapid onset of action.

Cyclosporin in severe (fulminant) UC
Only two randomized controlled trials with overall less than 50 patients have been published so far. In the first trial, 11 patients received IV cyclosporin (4 mg/Kg). Of these, 3 patients (versus 4/9 on placebo) eventually underwent colectomy. In the second trial 15 patients each were treated with IV cyclosporin and IV methylprednisone. Five patients on cyclosporin failed to respond to therapy compared with 7/15 in the steroid group. The colectomy rate was similar in the two groups. The mean time to response in the cyclosporin group in the two trials was short (7 days vs 5.2 days).

These results should be interpreted with caution given the small numbers of patients evaluated. There was no evidence that cyclosporin was more effective than standard treatment for preventing colectomy but such an effect cannot be excluded. A later study from Leuven showed that cyclosporin in a dose of 2 mg/Kg showed similar activity compared to the 4 mg/Kg dose. It is surprising how little evidence satisfies the medical community and leads to a so-called “state-of-the-art” therapy using cyclosporin in this indication.

Infliximab in severe acute UC
This agent has become standard therapy in Crohn’s disease and recently also in the management of chronic active UC. It is a chimeric monoclonal antibody to human TNF that is constructed by linking the variable regions of mouse anti-TNF monoclonal anti-
body to human immunoglobulin G1 with light κ chains. TNF has been shown to play an important role in the inflammatory process in UC, especially in severe cases as it controls the dilatation of the colon.

In a recent randomized double-blind trial of infliximab or placebo in severe to moderately severe UC not responding to conventional corticosteroid treatment, patients received either infliximab (single infusion of 5 mg/Kg body weight) or placebo on day +4 after initiation of corticosteroid therapy. The primary endpoint was colectomy rate within 3 months. Secondary end-points were clinical and endoscopic remission in patients who did not undergo surgery. Forty-five patients were included (24 on infliximab, 21 placebo); no patient died. Seven patients on infliximab and 14 on placebo had colectomy, a difference that was significant. Three patients on placebo needed surgery for septic complications. The authors concluded that infliximab might reflect a safe and effective rescue therapy in patients with severe UC not responding to corticosteroid therapy. Even though this has only been so far a single clinical study, this treatment approach is very attractive as patients receive a single infusion with a biological agent, whereas the alternative treatment, namely, cyclosporin, is much more difficult to handle.

**Practical points**

Patients who have failed to respond to optimal oral treatment with a combination of mesalazine and corticosteroids with or without topical therapy, or those who present with severe disease should be admitted for intensive IV therapy. Monitoring of pulse rate, stool frequency, C-reactive protein (CRP), and plain abdominal radiograph help identify those who need colectomy. Acute-onset UC is sometimes difficult to distinguish from infective colitis, but treatment with corticosteroids should not be delayed until stool microbiology results are available.

The approach to treatment of severe UC involves:

- Physical examination daily to evaluate abdominal tenderness
- Recording of vital signs four times daily
- Stool chart to record number and character of bowel movements, including presence or absence of blood and liquid versus solid stool
- Measurement of CRP, serum electrolytes, serum albumin, and liver function tests every 1-2 days
- Daily abdominal radiography if colonic dilatation is detected at presentation. If not dilated, there should be a low threshold for further radiological assessment if there is clinical deterioration

- IV fluid and electrolyte replacement to correct and prevent dehydration or electrolyte imbalance, with blood transfusion to maintain hemoglobin >10 g/dL
- Subcutaneous heparin to reduce risk of thromboembolism
- Nutritional support, preferentially enteral, if patient is malnourished
- IV corticosteroids (hydrocortisone 400 mg/day or methylprednisolone 60 mg/day). Higher doses offer no greater benefit, but lower doses are less effective
- Withdrawal of anticholinergic, antiarrheal agents, NSAID and opioid drugs, which risk precipitating colonic dilatation
- IV antibiotics only if infection is considered, or immediately before surgery. Controlled trials of IV metronidazole and oral vancomycin in acute severe UC have shown no significant benefit
- Immediate surgical referral if there is evidence of toxic megacolon (diameter >5.5 cm, or cecum >9 cm). The urgency with which surgery is undertaken after recognition of colonic dilatation depends on the condition of the patient: the greater the dilatation and the degree of systemic toxicity, the sooner surgery should be undertaken, but signs may be masked by steroid therapy. Any clinical, laboratory or radiological deterioration mandates immediate colectomy
- Objective re-evaluation on the third day of intensive treatment. Stool frequency of >8/day or CRP >45 mg/L at 3 days appears to predict need for surgery in 85% of cases. There is no benefit from IV steroids beyond 7-10 days
- Consideration of colectomy, IV cyclosporin 2 mg/Kg/day or infliximab 5 mg/Kg if there is no improvement during the first 3 days. Following induction of remission, oral cyclosporin for 3-6 months is appropriate. In parallel, treatment with azathioprine should be started. IV cyclosporin alone may be as effective as methylprednisolone, but potential side effects mean that it is rarely an appropriate single first-line therapy

**References**


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