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Steroid-Refractory Severe Ulcerative Colitis

What are the Available Treatment Options?

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Abstract

Approximately 15% of patients with ulcerative colitis will experience a severe episode requiring hospitalization. Although intravenous corticosteroids are the current first-line therapy for these patients, about 30% of patients do not respond to corticosteroids and require either an alternative anti-inflammatory agent or surgery. Ciclosporin has proven its efficacy in a number of controlled trials in this setting and is characterized by high early response rates. Patients who respond to ciclosporin and avoid colectomy are more likely to retain their colon if they bridge to immunomodulators in the medium term. Infliximab has also demonstrated efficacy in reducing early colectomy rates and longer term data are awaited. Other agents, such as tacrolimus and basiliximab, and leukocytapheresis, have been studied in small trials and may be alternative options. Key issues remain as to what should be first- and second-line therapies, when surgery should be undertaken, and the risk of switching between immunosuppressants in these critical patients.

Patients with ulcerative colitis typically experience a chronic course where periods of remission are interspersed with episodes of relapse. Severe relapses of ulcerative colitis are an infrequent but serious development for these patients. About 15% of patients with ulcerative colitis will develop an episode of severe ulcerative colitis requiring hospitalization, often early after the initial diagnosis.[1] Prior to the 1960s, mortality rates for these patients were as high as 25%, but the introduction of intravenous corticosteroids, modern intensive care unit care, earlier recognition of treatment failure and improvement in surgical techniques has dramatically lowered mortality to less than 1% in specialist centres.[2-4] Nonetheless, approximately 30% of patients with severe ulcerative colitis have no response to intravenous corticosteroids, a figure which has remained constant over the last 50 years.[5-7] For these patients, the only other treatment option for many years was colectomy and ileostomy, or ileal-pouch anal anastamosis (IPAA). Recent therapeutic trials have focused on this patient population in an attempt to provide 'colon-sparing' options. The re-

sults of clinical trials on this topic, and their controversies, are reviewed in this article.

1. Characteristics of Steroid-Refractory Ulcerative Colitis

Severe ulcerative colitis, defined according to the original criteria established by Truelove and Witts,[4] is characterized as follows: more than six stools with blood per day; temperature >37.8°C; pulse >90 beats/min; haemoglobin <10.5 g/dL; and erythrocyte sedimentation rate (ESR) >30 mm/hour.[4] These criteria were used to categorize patients with severe disease in the original clinical trial of corticosteroids and have stood the test of time. Six other clinical criteria, three combined clinical and endoscopic criteria, four evaluation scores and two quality of life (QOL) evaluations have since been published, which grade the severity of ulcerative colitis.[8] They have variously added other symptoms, sigmoidoscopic findings and overall well-being to the original criteria of Truelove and Witts.[4] Various supplementary markers, such as arterial blood pH and C-reactive protein (CRP) levels, have been added over the years to identify those patients with severe ulcerative colitis who are at high risk for colectomy.[9,10] Endoscopic scores of severity have defined severe ulcerative colitis similar to Baron's description of the presence of spontaneous bleeding and ulceration on sigmoidoscopy.[11]

Patients meeting these criteria have traditionally been treated with high-dose intravenous corticosteroids, in keeping with international guidelines.[12,13] In clinical trials, 50–70% of patients treated in this manner have obtained a response with an equivalent dose to 1 mg/kg/day of prednisolone, usually within 5–7 days.[4-7,10,14-18] In view of this, 'steroid-refractory' severe ulcerative colitis has been defined as failure to respond to an adequate daily dose of intravenous corticosteroids within 5,[19] 7[20] or 10 days[18] in clinical trials. As alternative agents for steroid-refractory disease have appeared, the time allowed before considering the corticosteroids to have 'failed' has obviously shortened.

Given the consequences of corticosteroid failure, a number of studies have tried to determine both clinical and molecular predictors of those patients who are likely to not respond to intravenous corticosteroids (table I). Travis et al.[10] reported that that a stool frequency of more than eight per day or a CRP level >45 mg/dL after 3 days of intravenous corticosteroids had a positive predictive value (PPV) of 85% for colectomy. Lindgren et al.[17] developed a regression formula based on CRP and stool frequency after 3 days of intravenous corticosteroid therapy that had a 72% PPV in predicting the likelihood of colectomy. The activity index of Seo et al.,[21] based on blood in stool, bowel movements, ESR, haemoglobin and albumin levels, had a PPV of 52% to predict colectomy after 1 week of intravenous corticosteroids. Turner et al.[7] reviewed all published clinical predictors of failure of medical therapy in severe ulcerative colitis and found that only disease extent, stool frequency, temperature, heart rate, CRP levels, albumin levels and radiological assessment were consistently reproduced. Levels of metallothionein IIa in blood and P-glycoprotein in rectal mucosa have also been reported as significantly different between corticosteroid responders and non-responders in small studies.[22,23] These markers have not been validated in large series. These studies can provide clinicians with a means to identify those patients who are likely to not respond to intravenous corticosteroids as early as day 3 of treatment, and allow consideration of an alternative agent.

2. Ciclosporin

Ciclosporin (cyclosporine) is a metabolite of a soil fungus, which was first identified as an immunosuppressant in 1971 and used to prevent organ transplant rejection.[26] In humans, it inactivates the nuclear factor of activated T cells, inhibits

Table I. Clinical and laboratory predictors of failure of corticosteroid therapy in patients with ulcerative colitis

Study (year)	Factors associated with colectomy	Factors associated with failure of intravenous corticosteroids
Benazzato et al.[14] (2004)	ESR >75 mm/hour or temperature >38°C on admission	Less than 40% reduction in bowel movements within 5 days
Bernal et al.[5] (2006)		Blood in stools on day 3, more than six stool per day on day 3
Carbonnel et al.[24] (2000)		Severe endoscopic findings (extensive deep ulceration; mucosal detachment on the edge of these ulcerations; well-like ulcerations; large mucosal abrasion) Attack lasting >6 weeks Severe Truelove and Witts[4] grade
Chakravarty[15] (1993)	Low albumin levels Severe diarrhoea	
Ho et al.[16] (2004)		Colonic dilatation >5.5 cm by day 3 Mean stool frequency Albumin levels <30 g/L on day 1
Lindgren et al.[17] (1998)	CRP ≥25 mg/L on day 3, more than four stools per day on day 3	
Meyers et al.[18] (1987)		Fulminant disease, extensive disease, prolonged attack, frequent stools, high ESR, low haemoglobin
Oshitani et al.[25] (1990)		Elevated CRP, low total protein/albumin/cholinesterase levels, extensive disease, polypoid mucosal tags
Travis et al.[10] (1996)	More than eight stool per day on day 3, CRP >45 mg/L on day 3	
Seo et al.[21] (2002)	Blood in stool, no. of bowel movements, high ESR, low haemoglobin, low albumin levels	

CRP = C-reactive protein; **ESR** = erythrocyte sedimentation rate.

the expression of CD40 ligand (CD40L) and prevents stimulation of dendritic cells by tumour necrosis factor (TNF)-α.[27] In ulcerative colitis, it has been demonstrated to suppress interleukin (IL)-2 and IL-3 production, inhibit chemotaxis of neutrophils and induce apoptosis in T cells.[27,28] Since many of these factors play a role in the pathogenesis of ulcerative colitis, use of ciclosporin in this condition makes therapeutic sense. A number of open-label controlled trials have examined its role in severe ulcerative colitis.

The evidence for the efficacy of intravenous ciclosporin in severe ulcerative colitis is limited, based on only three published randomized controlled trials (one that compared ciclosporin with placebo in patients with steroid-refractory disease,[20] one that compared ciclosporin with corticosteroids[29] and one that compared two doses of ciclosporin[30]). Lichtiger et al.[20] enrolled 20 patients with severe ulcerative colitis who had not responded to at least 7 days of intravenous corticosteroids, and gave them ciclosporin 4 mg/kg/day by continuous infusion or placebo. Patients whose clinical activity score fell below 10 (mean enrollment score 13) on 2 consecutive days were considered 'responders'; this occurred in 82% of the ciclosporin group and 0% of the placebo group. Colectomy was necessary because of clinical deterioration in 44% of the placebo arm and 18% of the ciclosporin arm. Paresthesias or hypertension occurred in 36% of the ciclosporin group, but there was no short-term nephrotoxicity. A similar study by D'Haens et al.[29] enrolled 30 patients with severe ulcerative colitis (mean activity score 13) and randomized them to intravenous ciclosporin 4 mg/kg/day or intravenous methylprednisolone 40 mg/day for 8 days. At day 8, 64% of the ciclosporin group and 53% of the corticosteroid group had responded (score <10), and 78% of the ciclosporin responders maintained their remission to 12 months. The colectomy rate at 1 year was 36% in

the ciclosporin group and 40% in the corticosteroid group. There was no nephrotoxicity reported in the ciclosporin arm. Finally, Van Assche et al.[30] compared intravenous ciclosporin 4 mg/kg/day with 2 mg/kg/day in patients with severe ulcerative colitis, 55% of whom had not responded to corticosteroids. Response rates (85%), time to response (4 days) and short-term colectomy rates (8% and 13%) were not significantly different between the two dosages. There were no significant differences in the rates of parasthesia (≈8%), hypertension (≈24%) or creatinine increase (≈18%) between the two dosages.

All other studies using ciclosporin in ulcerative colitis were either open-label, non-randomized or included patients with mild to moderate disease; these 30 studies have been reviewed in detail elsewhere.[31-34] The cumulative experience suggests that, in severe ulcerative colitis, short-term response rates of 70–80% can be expected with intravenous ciclosporin 4 mg/kg/day or 2 mg/kg/day.[30] Target whole blood ciclosporin concentrations during intravenous therapy in clinical studies have ranged from 60 to 600 ng/mL (as determined by radioimmunoassay with a monoclonal antibody). In the three randomized controlled trials, mean blood ciclosporin concentrations were in the 350–450 ng/mL range in patients receiving intravenous ciclosporin 4 mg/kg/day and 237 ng/mL in patients receiving intravenous ciclosporin 2 mg/kg/day, but no correlation between clinical response and levels was found.[20,29,30] In view of this, a target blood ciclosporin concentration of 150–250 ng/mL has been recommended in practice.[32] It is unknown whether a lower target would produce similar initial outcomes.

Oral ciclosporin at dosages of 5–8 mg/kg/day have also been examined in a number of non-randomized studies in steroid-refractory ulcerative colitis.[35-39] Early response rates of 70–90% and long-term colectomy-free rates of 47–74% were reported in these studies, which are similar to the results with intravenous ciclosporin. One retrospective study compared the results with oral and intravenous ciclosporin, and noted that 100% of oral- and 65% of intravenous-treated patients achieved a short-term response, but 17% of patients receiving intravenous ciclosporin developed major toxicity, including one death.[35] The target trough ciclosporin concentrations in these studies were 150–350 ng/mL.

It is difficult to directly compare the uncontrolled ciclosporin studies because the definitions of what constitutes severe disease, steroid-refractory disease and response to therapy vary from study to study. A randomized controlled trial comparing intravenous ciclosporin 2 mg/kg/day, oral ciclosporin 5 mg/kg/day and placebo in steroid-refractory patients would be helpful to clarify the safest and most effective mode of administration of ciclosporin. The data on oral ciclosporin suggest equivalent efficacy to intravenous delivery, with less toxicity; however, this has not been tested in a controlled trial. A few studies have identified predictive factors of those most likely to respond to ciclosporin, including clinical, endoscopic and biochemical criteria.[40-42]

Apart from efficacy, safety remains a concern in patients receiving ciclosporin, given the risks of opportunistic infections, nephrotoxicity and neurotoxicity. Significant adverse effects occur in up to 20% of patients, and appear to be more prevalent in those receiving high-dose intravenous ciclosporin.[36,43-46] In one study of high-dose ciclosporin, safety in 86 patients was followed-up for up to 3 years, and showed a 3.5% mortality rate from opportunistic infections, notably pneumonia caused by *Pneumocystis jirovei* or *Aspergillus fumigatus*.[47] Viral, fungal and bacterial infections have been described in case reports in ciclosporin recipients, particularly those taking concomitant immunosuppressants; however, many other series in the literature have noted no opportunistic infections. Those patients receiving high-dose intravenous

ciclosporin alongside corticosteroids plus azathioprine or mercaptopurine (6MP) should probably receive *Pneumocystis* prophylaxis with co-trimoxazole while receiving both agents, although this is not based on evidence. Neurotoxicity from ciclosporin can manifest as parasthesia, tremor or seizures, and appears to be more prevalent in those with low cholesterol (<100 mg/dL) or low magnesium levels during intravenous therapy.[48,49] Less serious and reversible adverse effects include hirsutism, tremor, headache, gum hyperplasia and abnormal liver function tests.

Finally, in patients who respond to ciclosporin, and transition to oral ciclosporin plus azathioprine or 6MP, what are the long-term outcomes? Cohen et al.[43] reported that 72% of patients with severe steroid-refractory ulcerative colitis who initially responded to ciclosporin were able to avoid colectomy at 5.5 years. Importantly, the colectomy-free rates were higher in those who subsequently received azathioprine or 6MP (80%) than those who did not (55%), highlighting the importance of transitioning to azathioprine or 6MP. In a similar study from the UK in which all patients transitioned to oral ciclosporin plus azathioprine, 56% of patients had avoided a colectomy 3 years later.[50] A study by Campbell et al.,[51] that had up to 7 years follow-up, reported that 42% of patients had retained their colon at 7 years, although not all were also taking azathioprine or 6MP in addition to ciclosporin. Even in those patients with steroid-refractory disease who switch to azathioprine alone after intravenous ciclosporin, a retrospective study found that only 42% had required colectomy at 5 years.[52] In contrast to these studies, a recent Belgian article described a probability of colectomy of 88% by 7 years in patients who had responded to ciclosporin, and of whom 46% had started azathioprine or 6MP treatment after the ciclosporin therapy.[53] Patients who were already receiving azathioprine or 6MP prior to their severe flare in this cohort had almost double the colectomy rate (59% vs 31%) of those who started azathioprine or 6MP after ciclosporin, suggesting these patients will not respond to ciclosporin. However, of particular interest to patients is that those patients who were treated with ciclosporin and avoided colectomy had fewer intestinal symptoms and hospitalizations than those who had a colectomy after not responding to corticosteroids for severe disease in a separate study.[54]

In summary, ciclosporin is an effective agent for achieving a clinical response in patients with severe ulcerative colitis who have not responded to intravenous corticosteroids. Using oral or low-dose intravenous ciclosporin is probably as effective as higher intravenous doses, with less toxicity. Patients who respond to ciclosporin should be transitioned to azathioprine or 6MP for the medium to long term. These patients should meet a surgeon and discuss elective colectomy in view of the 50–80% chance that they will require a colectomy in the future.

3. Infliximab

Infliximab is a monoclonal antibody against serum and membrane-bound TNFα. As a ligand, TNFα promotes neutrophil transmigration, stimulation of T helper-1 (CD4+) T-cell responses and activation of matrix metalloproteinase within the inflamed mucosa.[55] TNFα can also inhibit apoptosis of lymphocytes by binding TNF-receptor 2 and activation of the nuclear factor-κβ pathway.[56,57] Such inhibition of apoptosis in effector T cells may prolong their survival and amplify chronic inflammation.[58] These functions play a key role in the pathogenesis of inflammatory bowel disease. In patients with ulcerative colitis, infliximab has been demonstrated to down-regulate TNFα in the colonic mucosa and this was associated with reduced histological inflammation.[59]

There have been four published randomized controlled trials of infliximab in patients with severe steroid-refractory ulcerative colitis. Sands et al.[19]

randomized 11 patients who had not responded to 5 days of intravenous corticosteroids for severe ulcerative colitis to a single infusion of infliximab or placebo. Clinical response was seen in 50% (four of eight) of the infliximab group and 0% (zero of three) of the placebo group by 2 weeks. This study was prematurely ended because of poor patient enrolment. A subsequent study by Probert et al.[60] randomized 43 similar patients to two infusions of infliximab or placebo, and assessed them 6 weeks later. There were no significant differences between treatments in terms of remission rates, endoscopy scores or QOL, although given the small numbers this study was probably under-powered to detect such differences. Järnerot et al.[61] specifically examined the utility of infliximab in 45 patients who were hospitalized for severe or fulminant colitis who did not respond to intravenous corticosteroids by day 4 (fulminant) or day 6–8 (severe). A total of 29% of patients receiving a single infusion of infliximab required colectomy by 3 months compared with 67% of patients receiving placebo ($p = 0.017$). The benefit was better defined for the severe group than the fulminant group. Finally, Rutgeerts et al.[62] published the results of two controlled trials (ACT [Active ulcerative Colitis Trial]-1, ACT-2) that contained over 700 patients with moderate to severe ulcerative colitis, 217 of whom were categorized as steroid-refractory (i.e. had not responded to either 7 days of intravenous corticosteroids or 14 days of oral prednisone 40 mg/day). In these trials, the early clinical response rates were 63–77% for the steroid-refractory patients. No separate data on their remission rates were published.

A meta-analysis of these studies concluded that the odds ratios of short- and long-term remission with infliximab 5 mg/kg versus placebo were 5.28 (95% CI 2.3, 12) and 2.61 (95% CI 1.69, 4), respectively, for moderate to severe ulcerative colitis.[63] There were 29 other uncontrolled studies examined in this systematic review and of 322 evaluable patients, 64% had severe disease and 52% were steroid-refractory. The mean short- and long-term remission rates were 40% and 39%, respectively, in patients who received infliximab in these studies. Many of these studies just administered a single infliximab infusion, whereas current practice is to administer at least three infusions at 0, 2 and 6 weeks, and continue maintenance infusions in responders. Based on the experience in Crohn's disease, this may prove to be a more efficacious strategy.

As noted in section 2, patients already receiving azathioprine or 6MP at the time of their severe flare did poorly when receiving ciclosporin in a long-term follow-up study.[53] Four uncontrolled studies in adults and children, in which almost all patients were receiving azathioprine or 6MP prior to starting infliximab for moderate to severe colitis, reported similar response rates (≈80%) to those reported in azathioprine or 6MP-naive patients in other studies.[64-67] These data suggest that infliximab may be the agent of choice in patients already receiving azathioprine plus 6MP who do not respond to corticosteroids for severe ulcerative colitis. However, overall, about 30–50% of patients treated with infliximab will have had a colectomy by 1–2 years follow-up,[68,69] and only 17% were in steroid-free remission at 1 year in one study.[68]

On the basis of the available evidence, our practice is to first use ciclosporin in patients with severe ulcerative colitis in whom intravenous corticosteroids have failed. If further long-term follow-up data demonstrate better colectomy-free remission rates with infliximab than those observed with ciclosporin, this may change. The exception to this is those who have a contraindication to ciclosporin or those who are already receiving azathioprine or 6MP.[53] As a head-to-head comparison of infliximab and ciclosporin is unlikely to take place in the foreseeable future, local experience will probably dictate practice in this environment. An important

decision of switching to either ciclosporin or infliximab should be made by day 3 of treatment with intravenous corticosteroids, because, in our experience, prolonging unsuccessful therapy in these patients increases their risk of complications. In patients hospitalized with severe ulcerative colitis, we do not recommend progressing to infliximab if both corticosteroids and ciclosporin have failed, or to ciclosporin if both corticosteroids and infliximab have failed. The risk of serious adverse events from such an immunological 'triple hit' have been reported to be 15–80% in small case series.[70,71]

4. Alternative and Novel Medical Therapies

A number of other novel and established immunosuppressants have been used in the treatment of severe steroid-refractory ulcerative colitis in pilot studies or uncontrolled trials. Basiliximab is a monoclonal antibody that blocks the signalling of the IL-2 cytokine and inhibits T-cell proliferation. In an uncontrolled study, ten patients with moderate to severe disease were given a single infusion of basiliximab; three of the ten had severe disease refractory to intravenous corticosteroids.[72] Although 90% (nine of ten) were in clinical remission at 8 weeks, most of these (eight of nine) relapsed in a median of 9 weeks, and ended up receiving corticosteroids and azathioprine. A follow-up study in seven patients with severe steroid-refractory ulcerative colitis, reported that at 8 weeks three of seven patients were in remission, but by 24 weeks four of seven had required a colectomy.[73] Visilizumab blocks T-cell proliferation and has been studied in 32 patients with severe steroid-refractory ulcerative colitis in an open-label manner.[74] By day 30, 40% of patients had obtained both clinical and endoscopic remission, and 45% of patients avoided colectomy in the following year. Phase III studies have been discontinued by the developing company in this patient population, apparently as a result of insufficient efficacy and an inferior safety profile.

Other treatments that have been reported to have benefits in patients with moderate or steroid-refractory disease include pulse cyclophosphamide, selective leukocyte adsorption apheresis, antibodies to the $\alpha 4\beta 7$ integrin, tacrolimus, thalidomide, natural interferon-β and phosphatidylcholine.[75-81] None of these therapies has become standard practice outside of clinical trials.

5. Colectomy

The indications for surgical treatment of ulcerative colitis include perforation, severe haemorrhage, dysplasia or cancer, and disease that is refractory to the medical therapies described in this review. In the past, the standard surgery for ulcerative colitis was total proctocolectomy and Brooke (end) ileostomy. In the last 2 decades, major surgical advances have been made in IPAA. Surgical expertise and postoperative care has significantly improved over the last 50 years and the early complication rate is now less than 10%. The technical aspects and early complications have been reviewed elsewhere.[82] IPAA is the procedure of choice for most patients because it maintains the normal flow of faeces and does not leave them with an end ileostomy. Most studies of QOL report improvement in indices after surgery for ulcerative colitis.[83] In addition, removal of the colon minimises the future risk of the development of cancer, for which all of these patients are at higher risk.

However, for patients who undergo an IPAA, long-term functional results will not resemble their function prior to developing severe ulcerative colitis, and this is important to convey when patients are considering their options. Cohen et al.[54] reported that patients who responded to ciclosporin rather than a colectomy for severe ulcerative colitis had a better ability to sleep, better stool consistency, less abdominal or rectal pain, and fewer trips to the toilet

than surgical patients. Mean daytime stool frequency in patients who underwent IPAA at the Mayo Clinic was 5.7 at 1 year and 6.4 at 20 years.[84] On long-term follow-up, 11% of this cohort had daytime faecal incontinence and 21% had nocturnal incontinence. It is unclear whether IPAA function and sphincter strength deteriorates further with age or as a result of occult obstetric injuries in these patients. Overall, there is approximately a 10% long-term failure rate requiring end ileostomy.[85]

The most frequent late complication is pouchitis, which occurs at least once in up to 50% of patients, with up to 15% developing chronic pouchitis.[86] Cuffitis and irritable pouch syndrome are also seen. Fistulae or abscesses can develop, and are seen more frequently in those patients who are ultimately found to have Crohn's disease. However, even in patients with ulcerative colitis, abscesses can be seen in 16% and fistulae in 14%.[84]

Sexual dysfunction is also seen in a significant percentage of patients. Dyspareunia has been reported in 7–26% of patients and impotence in 1.5%. Particularly concerning is the decrease in fertility, which probably results from surgical manipulation in the pelvis, and adhesions forming around the fallopian tubes and ovaries. Compared with medical therapy, proctocolectomy and IPAA approximately triples the risk of infertility for women with ulcerative colitis (response rate 3.17; 95% CI 2.41, 4.18). The meta-analysis of Waljee and colleagues[87] demonstrated that, compared with medical therapy, proctocolectomy and IPAA increases the average infertility rate from 14.6% to 48%. It is not clear whether the proctocolectomy or the pouch, is the risk factor for infertility, as patients after proctocolectomy and ileostomy also have lower fertility rates.[88]

In summary, colectomy is an option, sometimes the only option, for patients with severe steroid-refractory ulcerative colitis. Its short-term outcomes are satisfactory, given the physiological state of many patients with severe ulcerative colitis. Although proctocolectomy and ileostomy can be considered curative, it is important that colectomy with IPAA is not presented necessarily as a 'cure' because there is a significant incidence of functional complications in the long-term in those who proceed to IPAA.

6. Conclusions

Severe steroid-refractory disease is an uncommon but serious development for patients with ulcerative colitis. The most important factor in their management is close liaison between the patient, physician and surgeon so that key decisions may be made early in the course of hospitalization and adjusted as the clinical course proceeds. With the advent of rescue therapies, such as ciclosporin and infliximab, for these patients, it is likely that many patients in the future will only require colectomy after having therapy with at least two potent immunosuppressants fail. There does not appear to

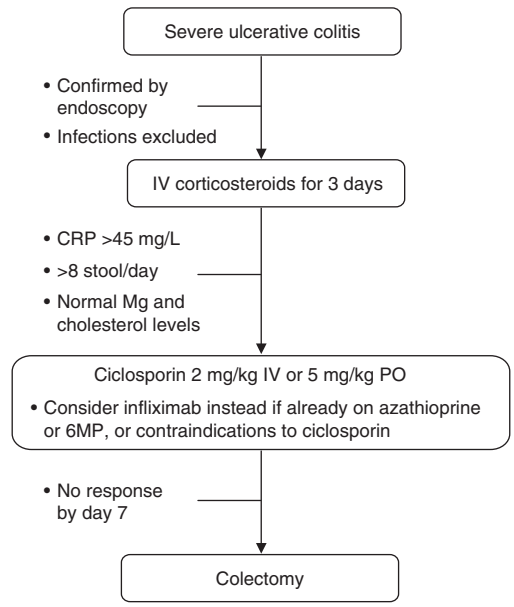

Fig. 1. Recommended treatment of severe ulceratice colitis. **6MP** = mercaptopurine; **CRP** = C-reactive protein; **IV** = intravenous; **PO** = oral.

be a higher rate of postoperative complications in those who have received either infliximab or ciclosporin with corticosteroids prior to surgery based on available data.[70,89] However, administering infliximab after ciclosporin and corticosteroids was associated with an 80% complication rate in one study.[70]

Currently, we recommend initial therapy with low-dose intravenous or oral ciclosporin if the patient is not responding to intravenous corticosteroids by day 3 (figure 1). Responders should transition to oral ciclosporin for no more than 3 months, while also initiating concomitant azathioprine or 6MP. Infliximab may be the agent of choice in patients who already are receiving azathioprine or 6MP or who have a contraindication to ciclosporin. If neither of these agents has provided a clinical improvement by day 7, then a colectomy should be considered.

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