Therapeutic Options in Steroid-Refractory Acute Severe Ulcerative Colitis

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ABSTRACT

Objective: To review therapeutic options in patients with steroid-refractory severe ulcerative colitis (UC).

Methods: Review of the literature.

Results: UC is characterized by periods of active and inactive disease, a pattern observed in 80% to 90% of patients with this disease. About 15% to 25% of patients with UC will present with a severe attack at least once in their lifetime. Usual treatment for acute severe UC is intravenous corticosteroids, but about 30% to 40% of patients fail to respond to steroids. Patients presenting with severe corticosteroid-refractory disease can be treated medically with cyclosporine, infliximab, or tacrolimus or undergo emergent proctocolectomy.

Conclusion: Currently there is no ideal treatment of choice in patients with severe steroid-refractory UC. Further studies are needed to determine the best treatment for these patients.

Ulcerative colitis (UC) is a chronic inflammatory disease involving the colon characterized by periods of active and inactive disease in 80% to 90% of patients [1,2]. Its prevalence in the United States has been estimated at 205.8 cases per 100,000 persons [3,4], with an annual incidence rate of 12 cases per 100,000 [4]. It has been estimated that 500,000 people in the United States are affected by this disease [5]. In a large, population-based cohort study that evaluated patients over 2 decades, 9% of patients had severe, 71% had moderate, and 20% had mild disease activity of UC at the time of initial presentation [6]. A systematic review from the UK of 750 patients with UC with a median follow-up of 12.7 years found that 24.8% of patients were hospitalized at least once due to acute severe UC, and 12% underwent a colectomy [7]. The colectomy rate was 39.8% in patients admitted to the hospital at least once with acute severe UC versus 12.4% in all patients with UC (P < 0.001) [7].

Patients who were never admitted to the hospital due to acute severe UC had the lowest colectomy rate of 3.4% [7].

Acute severe colitis can be defined as the occurrence of at least 6 bloody stools per day with signs of systemic toxicity (ie, fever, tachycardia, hemoglobin < 10.5 g/dL, elevated erythrocyte sedimentation rate [ESR], C-reactive protein [CRP] > 30) [7]. Patients having an acute severe flare of UC require hospitalization and should be started on intravenous (IV) corticosteroids [5]. Landmark trials by Truelove in 1955 and 1974 established that IV corticosteroids for 5 days is the mainstay of initial therapy in the treatment of severe UC [8,9]. Steroid-refractory acute severe UC can be broadly defined as the lack of response to an equivalent dose of 1 mg/kg/day of prednisolone within 5 days [10], although the definition varies among studies.

A systematic review of 32 studies with a total of 1991 patients with severe UC treated with corticosteroids determined that 581 of them underwent colectomy (weighted mean, 27% [95% confidence interval [CI] 26%–28%]) and that colectomy rates were stable during the last 30 years despite the introduction of new therapeutic agents [11]. There were more than 20 variables identified in 19 studies that predicted failure of corticosteroids; the factors that were consistently reproducible were greater disease extent, increased stool frequency, increased body temperature and heart rate, increased CRF, hypoalbuminemia, and radiologic assessment [11]. In addition, the authors suggested that according to the meta-regression no correlation was found between doses of IV corticosteroids beyond 60 mg/day and colectomy rate (R² < 0.01, P = 0.98), indicating that doses higher than that were not associated with an improved outcome [11].
Patients who fail to respond to corticosteroids within 3 to 5 days should be monitored closely and a surgeon experienced in management of UC patients should be consulted [5]. Abdominal x-ray to assess for colon dilatation and stool studies to exclude infection with enteric pathogens, C. difficile, and parasites should be done [5]. Flexible sigmoidoscopy should be performed to assess the extent of the disease and biopsies obtained to exclude other causes of colitis like cytomegalovirus, ischemia, and drugs [5]. Patients refractory to treatment with corticosteroids may be treated medically (cyclosporine, infliximab [alone or in combination with azathioprine or 6-mercaptopurine], or tacrolimus) (Table) or undergo colectomy. This review discusses therapeutic options in patients presenting with severe UC refractory to corticosteroids.

MEDICAL TREATMENT OPTIONS

Cyclosporine A

Cyclosporine is an immunosuppressive agent with a rapid onset of action that was discovered by Borel in 1976 [12]. There has been 1 randomized placebo-controlled trial that evaluated the use of cyclosporine in treating severe corticosteroid-refractory UC [13]. In their landmark trial, Lichtiger et al randomly assigned 20 patients with severe active UC with no response to IV corticosteroid therapy after at least 7 days to receive continuous IC infusion with either cyclosporine A (4 mg/kg day, n = 11) or placebo (n = 9) for up to 14 days [13]. All patients received IV corticosteroids (300 mg hydrocortisone daily) [13]. The primary endpoint was clinical response, defined as a Lichtiger clinical activity score of less than 10 on a 21-point scale on 2 consecutive days [13]. The active drug was significantly superior to placebo in achieving the primary endpoint. Response rates, which were achieved within a mean time of 7 days, were 82% for cyclosporine A and 0% for placebo (P < 0.001) [13]. There was a significant (P < 0.001) 7-point decrease in mean Lichtiger clinical activity score in patients treated with cyclosporine A (13 points at week 0 vs. 6 points at the end of trial) compared with a 1-point decrease among placebo recipients (14 points at week 0 vs. 13 points at the end of trial) [13]. After trial conclusion, the 9 patients who received placebo either underwent colectomy (n = 4) or received IV cyclosporine (4 mg/kg daily, n = 5) for up to 14 days [13]. All 5 patients responded to open-label treatment with cyclosporine, with a decline in mean clinical activity score from 11 points to 7 points over an average of 7 days [13]. Adverse events observed among patients treated with cyclosporine were paresthesias (36%), arterial hypertension (36%), grand mal seizure (9%), and nausea and vomiting (9%) [12]. Among placebo recipients, hypertension (11%) and nausea and vomiting (11%) were observed [13].

D’Haens et al compared the effect of IV cyclosporine monotherapy (4 mg/kg daily) with IV corticosteroid monotherapy (40 mg/day of methylprednisolone) given for 8 days in 29 patients with severe UC (Lichtiger score ≥ 10 points) in a randomized double-blind trial [14]. Some of these patients were refractory to 14-day treatment with oral corticosteroids before enrollment, which was discontinued upon onset of the trial [14]. However, the exact number of steroid-refractory patients was not reported. The primary endpoint was an improvement in clinical response, defined as a Lichtiger score less than 10 points on days 7 and 8 with at least a 3-point drop in score from day 1 to day 8 [13]. There was no statistically significant difference in response rates between arms (cyclosporine A 64%, corticosteroids 53%, P = 0.4) [14]. It was thus suggested that cyclosporine A may present a viable alternative to corticosteroids in treating severe flare of UC. Responders to either IV regimen were subsequently switched to oral medications. Oral methylprednisolone (32 mg/day) was administered for 3 weeks with subsequent tapering by 4 mg per week until discontinuation, whereas oral cyclosporine A (8 mg/kg daily) was given for 3 months [14]. Of note, all responders to IV cyclosporine A and 3 responders to IV corticosteroids also received oral azathioprine (2 to 2.5 mg daily). Among 9 patients who responded to initial therapy with IV cyclosporine A, 8 (89%) and 7 (78%) maintained their response on single therapy with azathioprine at 6 and 12 months, respectively. On the other hand, among 8 responders to IV corticosteroids, only 4 (50%) and 3 (37%) maintained their response at 6 and 12 months, respectively [14].

Among those who did not respond to either IV treatment within the first 8 days, IV cyclosporine A was combined with IV methylprednisolone; improvement in clinical activity score was observed in 33.3% (1/3 patients) of those who did not initially respond to IV cyclosporine and in 42.9% (3/7 patients) of those who did not initially respond to IV corticosteroids [14]. Responders to combined IV treatment (n = 4) were subsequently switched to a combination of oral cyclosporine and methylprednisolone, and oral administration of azathioprine was initiated [14]. After 6 and 12 months, 3 of 4 patients (75%) maintained their remission on...
Overall, the colectomy rates at 12 months were 36% for cyclosporine arm and 40% for the corticosteroids arm. This trial also demonstrated that cyclosporine A may serve as a bridge therapy to azathioprine (delayed onset of action after 3 to 4 months) after achieving initial clinical response in patients with severe UC. During the first 8 days of treatment the following adverse events were observed in the cyclosporine

| Table. Randomized Controlled Trials Assessing the Efficacy of Various Medications Administered Intravenously in Treatment of Severe Steroid-Refractory Ulcerative Colitis |
|-----------------------------------------------|----------------|----------------|----------------|----------------|
| Study                                        | Treatment Arms | Response Rates, % | Remission Rates, % | Colectomy Rates, % | Comments |
| Lichtiger, 1994 [13]                        | Cyclosporine A 4 mg/kg | 82 @14 d | Not reported | 27 @14 d | Clinical response: Lichtiger clinical activity score < 10 on 2 consecutive days |
|                                              | Placebo       | 0 @14 d | Not reported | 44 @14 d | |
| D’Haens, 2001 [14]                          | Cyclosporine A 4 mg/kg | 64 @8 d | 78 @1 yr | 36 @1 yr | Clinical response: Lichtiger clinical activity score < 10 on days 7 and 8 with drop in the score from day 1 to day 8 of at least 3 points |
|                                              | Methylprednisolone 40 mg/day | 53 @8 d | 37 @1 yr | 40 @1 yr | |
| Van Assche, 2003 [15]                       | Cyclosporine A 4 mg/kg | 84.2 @8 d | Not reported | 13.1 @14 d | Clinical response: Lichtiger clinical score < 10 at day 8 with a drop of ≥ 3 points from baseline |
|                                              | Cyclosporine A 2 mg/kg | 85.7 @8 d | Not reported | 8.6 @14 d | |
| Sands, 2001 [59]                            | Single infusion infliximab (5 mg/kg, 10 mg/kg, 20 mg/kg) | 50 @2 wk | Not reported | 12.5 @2 wk | Treatment failure: (1) failure to achieve a clinical response, ie, Truelove and Witts score < 10 with 5-point reduction from baseline; (2) patient received > 60 mg/day steroids or treated with cyclosporine A or other immunomodulators because of no improvement or worsening clinical condition; (3) nonelective colectomy; (4) death due to UC; (5) elective colectomy |
|                                              | Placebo       | 0 @2 wk | Not reported | 100 @2 wk | |
| Probert, 2003 [60]                          | 2 infusions of infliximab 5 mg/kg | 13 @2 wk | 39 @6 wk | Not reported | Clinical remission: ulcerative colitis symptom score at week 6 ≤ 2 |
|                                              | Placebo       | 5 @2 wk | 30 @6 wk | Not reported | |
| Jarnerot, 2005 [61]                         | Single infusion infliximab 5 mg/kg | Not reported | Not reported | 29 @3 mo; 50 @3 yr | Primary endpoint was colectomy or death within 90 days after infusion |
|                                              | Placebo       | Not reported | Not reported | 67 @3 mo; 76 @3 yr | |
| Rutgeerts, 2005 [62]                        | Infliximab 5 mg/kg | 69 @8 wk | 52 @30 wk | Not reported | Clinical response: at least a 3-point and at least a 30% drop in the total Mayo score from baseline with concurrent rectal bleeding subscore of 0 or 1 point or decrease by at least 1 point |
| ACT 1                                        | Infliximab 10 mg/kg | 61 @8 wk | 51 @30 wk | Not reported | |
|                                              | Placebo       | 37 @8 wk | 30 @30 wk | Not reported | |
| Rutgeerts, 2005 [62]                        | Infliximab 5 mg/kg | 64 @8 wk | 47 @30 wk | Not reported | Same as ACT 1 |
| ACT 2                                        | Infliximab 10 mg/kg | 69 @8 wk | 60 @30 wk | Not reported | |
|                                              | Placebo       | 29 @8 wk | 32 @30 wk | Not reported | |

azathioprine alone. Overall, the colectomy rates at 12 months were 36% for cyclosporine arm and 40% for the corticosteroids arm. This trial also demonstrated that cyclosporine A may serve as a bridge therapy to azathioprine (delayed onset of action after 3 to 4 months) after achieving initial clinical response in patients with severe UC. During the first 8 days of treatment the following adverse events were observed in the cyclosporine
and corticosteroid arms: hypokalemia (28.6% vs 0%), hypomagnesemia (14.3% vs 0%), headache (14.3% vs 6.7%), myalgias (14.3% vs 6.7%), hypertension (7.1% vs 0%), superficial thrombophlebitis (7.1% vs 6.7%), vomiting (7.1% vs 0%), epigastric discomfort (0% vs 6.7%) and paresthesias (0% vs 6.7%) (P values not reported) [14]. Among patients who received cyclosporine beyond 8 days, the adverse events included gingival hyperplasia (n = 3), hypertension (n = 1), tremor (n = 1), hair loss (n = 1) and headache (n = 3), with complete resolution after cessation of medication [14]. Among patients who received cyclosporine beyond 8 days, the adverse events included gingival hyperplasia (n = 3), hypertension (n = 1), tremor (n = 1), hair loss (n = 1) and headache (n = 3), with complete resolution after cessation of medication [14].

Finally, Van Assche et al compared 2 doses of IV cyclosporine (4 mg/kg/day vs. 2 mg/kg/day) given for 8 days in a cohort of 73 patients with severe UC in a double-blind randomized fashion [15]. Some of the included patients were refractory to IV corticosteroids given at a stable dose for at least 5 days prior to enrollment, and in such case IV steroids were continued through day 8 of the trial [15]. Some patients were refractory to oral corticosteroids given for at least 14 days from inclusion, and in such case patients were switched to IV steroids on day 1 of the trial with subsequent switching to oral corticosteroids at day 8 [15]. However, the number of corticosteroid-refractory patients was not provided [15]. The primary endpoint was a clinical response at day 8, defined as Lichtiger clinical activity score of less than 10 points with at least a 3-point decrease from baseline; (2) no remission without CS on day 98 (defined as Mayo score ≤ 2 points without any subscore > 1 point); (3) relapse between day 7 and 98 (increase in Lichtiger score of at least 3 points leading to modification of treatment); (4) severe adverse event causing treatment interruption; (5) death [15].

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Response Rates, %</th>
<th>Remission Rates, %</th>
<th>Colectomy Rates, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laharie, 2011</td>
<td>Cyclosporine 2 mg/kg/day IV for 1 week then orally for 98 days</td>
<td>84 @ 1 wk</td>
<td>40 @ 98 d</td>
<td>18 @ 98 d</td>
<td>Treatment failure: (1) no clinical response at day 7 (defined as Lichtiger score &lt; 10 points with at least 3-point decrease from baseline); (2) no remission without CS on day 98 (defined as Mayo score ≤ 2 points without any subscore &gt; 1 point); (3) relapse between day 7 and 98 (increase in Lichtiger score of at least 3 points leading to modification of treatment); (4) severe adverse event causing treatment interruption; (5) death</td>
</tr>
<tr>
<td></td>
<td>Infliximab 5 mg/kg at weeks 0, 2, 6</td>
<td>86 @ 1 wk</td>
<td>46 @ 98 d</td>
<td>23 @ 98 d</td>
<td></td>
</tr>
<tr>
<td>Pancione, 2011</td>
<td>Azathioprine 2.5 mg/kg + placebo</td>
<td>50 @ 16 wk</td>
<td>24 @ 16 wk</td>
<td>Not reported</td>
<td>Primary endpoint was steroid-free remission at week 16 defined as Mayo score ≤ 2 points</td>
</tr>
<tr>
<td></td>
<td>Infliximab 5 mg/kg + placebo</td>
<td>69 @ 16 wk</td>
<td>22 @ 16 wk</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infliximab 5 mg/kg + azathioprine 2.5 mg/kg</td>
<td>77 @ 16 wk</td>
<td>40 @ 16 wk</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Ogata, 2012</td>
<td>Tacrolimus</td>
<td>50 @ 2 wk</td>
<td>9.4 @ 2 wk</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>13.3 @ 2 wk</td>
<td>0 @ 2 wk</td>
<td>Not reported</td>
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</tbody>
</table>
(79% vs 5.7%), fever (79% vs 2.9%) and diabetes mellitus (2.6% vs. 0%) [15].

Several open-label studies assessed the efficacy of cyclosporine A administered either IV or orally in patients with severe corticosteroid-refractory UC. A 2005 systematic review by Garcia-Lopez et al [16] of 18 uncontrolled studies [17–34] with IV cyclosporine A in patients with severe UC found an overall short-term (5 to 16 days) response rate of 71.4% (95% CI 0.67–0.75), with 351 of the 491 patients avoiding colectomy. Among 9 uncontrolled studies with oral cyclosporine [25,35–42], 67 of 94 patients responded (71.2%, 95% CI 0.61–0.79) within a mean time of 5.19 days [16]. Another systematic review of 22 open-label studies [20,21,23–32,34,38,43–50] by Durai and Hawthorne was published in 2005; general short-term and long-term (2 years) response rates of 70% to 80% and 40% to 50%, respectively, were seen in patients treated with cyclosporine for severe UC [51]. Based on available data, the authors proposed an algorithm of treating severe UC with cyclosporine in a hospital setting (Figure) [51]. It was suggested that cyclosporine should be considered in patients with severe UC failing 7 days' treatment with corticosteroids and in those with fulminant UC without response to corticosteroids within 3 days [51].

The largest open-label study evaluating the efficacy of cyclosporine A in patients with severe steroid-refractory UC was performed by Moskovitz et al [52], which was an extension of a prior study by Arts et al [45]. A retrospective analysis of 142 patients with severe UC refractory to 5 to 7 days of IV corticosteroids and who were treated with IV cyclosporine (4 mg/kg or 2 mg/kg daily) showed an 81% response rate during a mean treatment duration of 9.3 days [52]. All patients also received IV corticosteroids during treatment with IV cyclosporine A [52]. In addition, 74 patients initiated treatment with azathioprine/6-mercaptopurine (6-MP) whereas 44 patients were already receiving these medications at the time of onset of therapy with IV cyclosporine [52]. After achieving response (no definition provided), 118 patients were switched to oral cyclosporine (8 mg/kg/day with adjustment to blood levels between 150 and 250 ng/mL) for 3 months and to tapering dose of oral corticosteroids [52]. Among 118 patients treated with oral cyclosporine A, 35% required colectomy after a mean time of 542 days [52]. According to Kaplan-Meier analysis, the probability to avoid colectomy after efficacious therapy with cyclosporine decreased with time—63% at 1 year, 41% at 4 years, 16% at 6 years, and 12% at 7 years [52]. The use of azathioprine/6-MP influenced the colectomy rates. The rates of colectomy were significantly greater among patients who were already on these agents (azathioprine/6-MP) at the time of initiation of therapy with cyclosporine A when compared to those individuals who were newly starting these agents concurrently with cyclosporine A (59% vs. 81%, P < 0.05) [52].

Another retrospective study of 61 patients with severe steroid-refractory UC observed a 63% initial response rate (39/61 patients) with cyclosporine given either IV or orally [53]. The cohort that was later analyzed consisted of 34 patients receiving maintenance treatment with oral cyclosporine A for 3 to 6 months with or without azathioprine [53]. Overall 61% and 35% remained colectomy-free after 1 and 7 years, respectively [53]. When patients were stratified according to the use of azathioprine, respective 1-year and 7-year colectomy-free rates were 80% and 60% for those treated with this agent and 47% and 15% for those not treated with azathioprine (P < 0.091 at 7 years, azathioprine vs. no azathioprine) [53].

A recent retrospective study by Cheifetz et al attempted to determine factors associated with colectomy in patients with severe UC that were treated with IV cyclosporine A followed by oral cyclosporine A in responders to an IV regimen [54]. Among 71 patients treated with IV cyclosporine A, 85% responded while 15% underwent colectomy within 4 weeks [54]. Cumulative colectomy rates were 39% at 1 year, 42% at 2 years, and 46% at 5 years [54]. Initiation of 6-MP after onset of treatment with oral cyclosporine was the only factor associated with decreased risk of colectomy during follow-up (OR 0.01, 95% CI 0.001–0.09) [53].

A recent retrospective report from the UK observed 84% colectomy-free rates after a median follow-up of 3.8 years in the cohort of 25 patients with severe corticosteroid-refractory UC who responded to initial treatment with oral or IV cyclosporine A, with 85% placed on thiopurine therapy after hospital discharge [55].

The factors predictive of failure of cyclosporine therapy have been published in few studies [20,56,57]. Cacheux et al described 3 predictive criteria for colectomy in patients treated with cyclosporine: body temperature > 37.5°C (adjusted HR 1.94, 95% CI 1.51–2.49), heart rate > 90 bpm (HR 1.86, 95% CI 1.45–2.38), and CRP > 45 mg/L (HR 1.7, 95% CI 1.34–2.16) [56]. In addition, they also suggested that presence of severe endoscopic lesions on colonoscopy was an independent predictor of colectomy.
Ulcerative Colitis

Figure. Algorithm for using cyclosporin in severe colitis in hospital. Reprinted with permission from reference 51.
to place patients on Pneumocystis prophylaxis while on most common pathogens [45]. Therefore, it is advisable www.jcomjournal.com ment of UC. It is indicated for reducing signs and symp- antibody, has been approved by the FDA for the treat -bacterium, assay for variable region (VH) of monoclonal Infliximab, a monoclonal anti-tumor necrosis factor-α function monitoring. toxicity with frequent blood cyclosporine levels and renal be monitored closely for opportunistic infections and for initation of therapy with cyclosporine. Patients should compared with those who are already on them prior to initiation of therapy with cyclosporine. Patients should be monitored closely for opportunistic infections and for toxicity with frequent blood cyclosporine levels and renal function monitoring.

Infliximab

Infliximab, a monoclonal anti-tumor necrosis factor-α antibody, has been approved by the FDA for the treatment of UC. It is indicated for reducing signs and symp- toms and inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroids use in adult patients with moderate to severe active UC not adequately responding to conventional therapy [58].

There have been 5 randomized double-blind placebo-controlled trials that evaluated the efficacy of infliximab in patients with moderate to severe active UC [59–62]. The first trial by Sands et al consisted of 11 patients with severe steroid-refractory UC of at least 2 weeks’ duration that did not respond to treatment with corticosteroids for at least 7 days [59]. Patients were randomly assigned to receive a single IV infusion of infliximab (5, 10 or 20 mg/kg) or placebo [59]. After 2-week follow-up, response to treatment was observed in 50% vs. 0% of patients treated with active drug vs. placebo (P value not reported) [59]. On the other hand, Probert et al did not observe any benefit of 2 IV infusions of infliximab (5 mg/kg) over placebo given 2 weeks apart in treating 43 patients with moderately severe steroid-resistant UC [60]. Clinical and endoscopic remission was assessed using Ulcerative Colitis Symptom Score (≥ 2 points) and Baron score (0 points), respectively [60]. There was no statistically significant difference between infliximab and placebo in inducing endoscopic remission at week 2 (13% vs. 5%, P = 0.74) and week 6 (26% vs. 30%, P = 0.96) or in inducing clinical remission assessed at week 6 (39% vs. 30%, P = 0.76) [60].

A Scandinavian trial enrolled 45 patients with acute severe or moderately severe UC not responding to high doses of IV corticosteroids on day 3 (fulminant UC) or on days 5 to 7 (severe or moderately severe UC) who were randomly assigned to receive single infusion of either infliximab or placebo and were followed for 3 months [61]. The primary endpoint was colectomy or death [61]. Infliximab had statistically significant greater efficacy than placebo, with respective 3-month colectomy rates of 29% and 67% (P = 0.017) [61]. Patients who did not undergo colectomy within the first 3 months were further assessed after 3 years [63]. Combined data from 3-month and 3-year follow-up clinical evaluations showed that colectomy rates were significantly greater in patients who received placebo than in those treated with infliximab (76% vs. 50%, P = 0.012), suggesting that the benefit of rescue therapy with infliximab remained after 3 years [63]. It was also shown that mucosal healing at 3 months influenced later risk of colectomy, with 0% of pa-
[63]. However, some patients received additional infusions of infliximab or underwent leucytapheresis after completing the 3-month clinical trial [68].

Finally, Rutgeerts et al performed the largest 2 trials evaluating infliximab in 728 patients with moderate to severe UC (Active Ulcerative Colitis Trials [ACT] 1 and 2) [62]. There were 217 (29.8%) patients with steroid-refractory UC, which was defined as no improvement in UC symptoms after at least 2 weeks oral or at least 1 week IV treatment with an equivalent of at least 40 mg of prednisone daily [62]. Study medications were given at week 0, 2, and 6 and then every 8 weeks until week 46 in ACT 1 and week 22 in ACT 2 [62]. Published data on steroid-refractory patients from ACT 1 and ACT 2 include only clinical response rates at week 8 [62]. Clinical response was defined as at least a 3-point and at least a 30% drop in the total Mayo Score from baseline with a concurrent rectal bleeding subscore of 0 or 1 point or a decrease by at least 1 point [62]. In steroid-refractory UC patients participating in ACT 1, infliximab given either at a 5 mg/kg (77.4% vs. 35.3%, $P < 0.001$) or 10 mg/kg (67.7% vs. 35.3%, $P = 0.010$) dose was significantly more efficacious than placebo in achieving clinical response [62]. Similar results were obtained in the ACT 2 trial. In this trial, 63% of recipients of the lower dose ($P = 0.055$ vs. placebo) and 65.5% recipients of the higher dose ($P = 0.011$ vs. placebo) of infliximab achieved clinical response at week 8 compared with only 37.5% of placebo recipients [62].

A meta-analysis of data from the aforementioned 5 clinical trials showed that when compared with placebo, infliximab at a dose of 5 mg/kg was associated with more than a threefold greater short-term response rate (OR 3.64, 95% CI 2.59–5.11), a fivefold greater short-term remission rate (OR 5.28, 95% CI 2.3–12.1), nearly a threefold greater long-term response rate (OR 2.92, 95% CI 2.05–4.16) and more than a twofold greater long-term remission rate (OR 2.61, 95% CI 1.69–4.03) [64]. Likewise, infliximab at a dose of 10 mg/kg was associated with more than a threefold greater short-term response (OR 3.61, 95% CI 2.54–5.15) and remission rate (OR 3.59, 95% CI 2.52–5.81) and nearly a fourfold greater long-term response (OR 3.9, 95% CI 1.7–8.93) and a threefold greater long-term remission rate (OR 3.22, 95% CI 2.13–4.87) when compared with placebo [64]. It should be noted, however, that this meta-analysis did not separate steroid-refractory patients from steroid-nonrefractory patients participating in ACT 1 and ACT 2 [64].

In addition, Gisbert et al performed a systematic review of the literature as of January 2006 that included the 5 aforementioned trials and 29 other uncontrolled studies of infliximab in UC [64]. The 34 studies included 896 patients with UC, but disease severity was assessed in only 322 patients (64.2% with severe UC) [64]. Among 877 patients with established steroid resistance status, 52% were steroid-refractory [64]. Short-term response rates were similar in steroid-refractory (70%, 95% CI 66–75%) and steroid-nonrefractory patients (68%, 95% CI 63–72%) [64]. On the other hand, long-term response was 56% (95% CI 50–63%) in steroid-refractory patients and 84% (95% CI 65–94%) in steroid-dependent patients [64]. The pooled odds ratio for adverse events for infliximab was 1.52 (95% CI 1.03–2.24) with a number needed to harm of 14 [64]. It should be noted that analyzed studies included pediatric patients and many of them were administered only a single dose of infliximab [64].

During 2011 Digestive Disease Week, Pancione et al presented the results of their randomized double-blind controlled trial in patients with moderate to severe UC who failed steroid therapy and either were naive to azathioprine or discontinued azathioprine at least 3 months prior to trial onset [65]. The final cohort included 231 patients who were randomized to receive azathioprine (2.5 mg/kg) and placebo (arm 1), infliximab (5 mg/kg) and placebo (arm 2), or infliximab (5 mg/kg) and azathioprine (2.5 mg/kg) (arm 3) [65]. Those in arm 1 who did not respond (reduction in Mayo score < 1 point) at week 8 were permitted to be treated with infliximab 5 mg/kg at week 8, 10, and 14 [65]. The primary endpoint was steroid-free remission at week 16, defined as total Mayo score ≤ 2 points [65]. Combination therapy with infliximab and azathioprine resulted in achieving significantly ($P < 0.05$) greater steroid-free remission rates at week 16 (40%) when compared with monotherapy with azathioprine (24%) or infliximab (22%) [65].

The predictive factors of failure of infliximab therapy have been analyzed in patients with moderate to severe UC in a few controlled and retrospective studies. It should be noted that not all patients included in these studies had acute severe UC. In their randomized placebo-controlled study, Jarnerot et al found that infliximab did not significantly reduce colectomy rates in patients with high fulminant colitis index at admission compared with placebo [61]. Sandborn et al analyzed the data from ACT 1 and ACT 2 trials and found that patients with high baseline CRP (> 20 mg/L), concomitant steroid
use, baseline Mayo score 10 points, and duration of UC less than 3 years had higher colectomy rates [73]. A large single-center retrospective study by Jurgens et al showed that high colitis activity index (CAI) before initiation of infliximab, ANCA seronegativity, and IL23R genotype were predictive of early response to infliximab in UC patients [74]. In a recent study by Seow et al, patients treated with infliximab who had detectable trough serum infliximab had higher clinical remission rates and lower colectomy risk than those with undetectable trough serum infliximab. This was independent of antibody status of the patients [75].

Summary
In summary, infliximab is an effective treatment option in patients with acute severe steroid-refractory UC. Infliximab seems to be more beneficial in patients with less severe disease [76], but results of the Laharie study [68] show that both cyclosporine A and infliximab are equally efficacious. Also, addition of azathioprine to infliximab appears to increase the clinical response rates as suggested by the SUCCESS trial [65].

Cyclosporine A versus Infliximab
Two recently published retrospective studies from New Zealand and Europe (Scandinavia and Austria) compared the efficacy of infliximab and cyclosporine A in treatment of steroid-refractory moderate to severe UC [66,67]. Dean et al reviewed the records of 38 patients with severe UC refractory to IV hydrocortisone of whom 19 were treated with infliximab 5 mg/kg (37% received multiple infusions) and 19 were treated with IV cyclosporine (2 mg/kg/day) [66]. The colectomy rates at 3 months were significantly greater among patients treated with cyclosporine A (63% vs. 21%, P = 0.0094) [66]. At 12 months, there was a trend towards statistical significance for difference in colectomy rates (68% vs. 37%, P = 0.06) [66]. In the Cox regression model, treatment with cyclosporine A compared with infliximab was associated with nearly a threefold increased risk of colectomy (HR 2.7, 95% CI 1.07–6.84) [66]. On the other hand, the European study observed significantly greater colectomy-free rates at 15 days (95% vs. 73%, P = 0.005), 3 months (93% vs. 67%, P = 0.002), and 12 months (77% vs. 57%, P = 0.034) after rescue therapy with IV cyclosporine A compared with a single infusion of infliximab in a cohort of 92 patients with moderate to severe UC [67]. According to the Cox regression model, treatment with infliximab was associated with a significantly increased risk of colectomy at 3 months (HR 11.2, 95% CI 2.4–53.1) and 12 months (HR 3.0, 95% CI 1.1–8.2) when compared with cyclosporine A treatment [67]. The contradictory results in the 2 studies [66,67] might be explained by the retrospective design and low number of patients.

During 2011 Digestive Disease Week, Laharie et al presented their results of a multicenter randomized controlled trial comparing the efficacy of cyclosporine A to infliximab in patients with acute steroid-refractory UC [68]. The final cohort comprised of 111 patients who failed at least 5 days of treatment with IV methylprednisolone at a daily dose of at least 0.8 mg/kg (failure = Lichtiger disease activity score > 10 points) [68]. Patients were randomly assigned to therapy with either cyclosporine A (2 mg/kg/day, n = 55) for 1 week followed by switch to oral formulation for 98 days, or 3 infusions of infliximab (5 mg/kg, n = 56) administered at week 0, 2, and 6 [68]. The primary endpoint was treatment failure, which was defined as absence of clinical response at day 7 or absence of remission at day 98 or relapse between day 7 and day 98 or severe adverse event necessitating discontinuation of treatment or colectomy or death [68]. There were similar rates of treatment failure in the cyclosporine A and infliximab groups (60% vs. 54%, P = 0.49) [68]. There were 10 severe adverse events reported in 9 patients receiving cyclosporine A and 16 events in patients receiving infliximab, but no fatalities were observed in either group [68]. More prospective randomized trials on large numbers of patients are needed to compare the efficacy of infliximab versus cyclosporine in treatment of severe steroid-refractory UC.

Several retrospective studies assessed the efficacy of infliximab and cyclosporine as second-line salvage therapy in patients with steroid-refractory UC who failed first-line therapy with either cyclosporine A or infliximab. Maser et al analyzed the data of 10 patients who received a median of 2 infusions of infliximab (range 1–9) after failing initial therapy with cyclosporine A (median duration 1.6 months, range 0.5–9.8 months) and 9 patients who received cyclosporine A for a median duration of 2 months (range 0.3–37.5 months) after failing initial therapy with a median of 2 infusions of infliximab (range 1–3) [69]. The colectomy rate among patients receiving infliximab salvage therapy was 40% with median time to colectomy of 2 months (range 0.9–5.2 months); among those treated with cyclosporine A salvage therapy, the rate was 44% with median time to colectomy of 3.8
months (range 0.1–11.6 months) [69]. Among patients who responded to infliximab salvage therapy and cyclosporine salvage therapy, the median duration of remission was 13.6 months (range 4.4–17 months) and 21 months (range 5–41.5 months), respectively [69]. However, 16% of patients experienced serious adverse events including 1 death, suggesting that second-line salvage therapy may not be beneficial to patients [69].

A multicenter retrospective study from Spain assessed data from 16 patients with steroid-refractory UC who failed treatment on cyclosporine [70]. The colectomy rate was 37.5% and occurred after a median 3 infusions of infliximab within a median time of 47 days from the first infliximab infusion (range 7–248 days) [70]. Adverse events were observed in 19% of patients but no fatalities were observed [70]. A multicenter retrospective study from France evaluated the largest cohort of 86 patients with 65 patients receiving infliximab salvage treatment after cyclosporine failure and 21 patients receiving cyclosporine salvage treatment after failing infliximab [71]. The overall colectomy rate was 57% during a median 22.6 months of follow-up, with a 54% rate (35/65) among patients receiving second-line salvage infliximab treatment and a 67% rate among (14/21) those treated with cyclosporine A as second-line treatment (P values not reported) [71]. The probabilities of colectomy-free survival were 59.9% (infliximab salvage) and 66.3% (cyclosporine salvage) at 3 months and 55.1% (infliximab salvage) and 44.6% (cyclosporine salvage) at 6 months [71]. Adverse events were observed in 22% of patients including 1 fatality [71].

The most recent retrospective study from 17 Spanish referral centers assessed data from 47 patients who were treated with infliximab after failing cyclosporine and observed a 30% colectomy rate within a median time of 8 weeks (range 1–162 weeks) with 57% of colectomies occurring within 12 weeks of the first infusion of infliximab [72]. The reported cumulative incidence of colectomy was 27% at 12 weeks, 29% at 1 year and 2 years and 35% at 3 years of follow-up [72]. Adverse events were described in 23% of patients including 1 death [68]. Of note, in the 3 studies discussed above there was a total of 3 fatalities, each occurring in patients treated with infliximab as salvage therapy [69,71,72]. In view of serious adverse events in patients treated with successive therapy of cyclosporine and infliximab, it cannot be recommended as a treatment option in patients with acute severe colitis.

**Tacrolimus**

Tacrolimus, a macrolide immunosuppressant produced by bacteria *Streptomyces tsukubaensis*, was assessed in a double-blind, placebo-controlled trial of 62 patients with moderate to severe steroid-refractory UC (failure to respond to 30–40 mg of prednisolone over 1–2 weeks) [77]. Patients were given orally either tacrolimus (1–2.5 mg twice daily) or placebo for 2 weeks [77]. The primary endpoint was clinical response, defined as decrease in disease activity index by at least 4 points and improvement in stool frequency, rectal bleeding, endoscopic image of mucosa, and physician’s assessment [77]. Tacrolimus was found to be significantly superior to placebo in achieving clinical response, with respective response rates of 50% and 13.3% (P = 0.003) [70]. In addition, mucosal healing rates were significantly greater in the tacrolimus arm (43.8% vs. 13.3%, P = 0.012) [77]. Adverse events occurred with the same frequency in both groups (81.3% vs. 70%, P = 0.379) [77].

Several open-label studies assessed the effect of tacrolimus on steroid-refractory UC. Fellermann et al assessed 38 patients with steroid-refractory colitis (33 patients with UC and 5 patients with indeterminate colitis), of whom 18 were given continuous infusion of tacrolimus (0.01–0.02 mg/kg/day) for 14 days with subsequent switching to oral formulation (0.1–0.2 mg/kg/day) while 20 received oral formulation of tacrolimus from the beginning for a mean duration of 7.6 months [78]. The overall colectomy rate was 34% and the mean follow-up was 16.2 months [78]. Among 24 patients with at least 2 years of follow-up, the colectomy rate was 50% [78]. An Austrian group analyzed the effect of oral tacrolimus (0.15 mg/kg/day) in 9 patients with active, moderate to severe steroid-refractory UC [79]. All patients responded to treatment with tacrolimus within 1 to 2 weeks and upon response, azathioprine was added to the treatment regimen [79]. The colectomy-free rate was 67% after mean follow-up of 21 months [79]. Baumgart et al performed an observational retrospective review of medical records of 53 IBD patients including 40 patients with severe corticosteroid-refractory or corticosteroid-dependent UC who were treated with oral tacrolimus for a mean time of 25 months (0.1 mg/kg/day) [80]. The colectomy rate was 22.5% between 1.6 and 41.3 months after initiation of treatment [80]. The estimated cumulative colectomy-free survival was 56.5% at 43.8 months and the mean colectomy-free survival time was 104.8 months [80].
Two recent studies showed that in patients with steroid-refractory UC who failed treatment with tacrolimus, therapy with infliximab might be considered [81,82]. In a retrospective case series of 12 patients with both steroid- and tacrolimus-refractory UC who received infliximab infusions, 50% achieved clinical remission within 30 days and 58.3% were colectomy-free at 41.4 months [81]. On the other hand, a prospective study of 24 UC patients without response to corticosteroids and tacrolimus who were treated with multiple infusions of infliximab observed that 25% of them achieved remission, 17% initially responded but later underwent colectomy, and 58% failed to respond [82]. The overall colectomy rate was 42% [82]. Tacrolimus seems to be an efficacious alternative to cyclosporine in treating steroid-refractory severe UC; however, the data are limited and further prospective randomized controlled trials are needed to assess its efficacy and safety in this patient population.

**Experimental Drugs**

**Basiliximab**

Two pilot open-label trials assessed the efficacy of basiliximab, a monoclonal antibody that binds to the CD25 receptor of cytokine IL-2 and thus inhibits proliferation of T cells [83,84]. The authors hypothesized that blockade of CD25 receptor would improve sensitivity to corticosteroids, as IL-2 cytokine has been known to antagonize the action of corticosteroids [83,84]. In the first trial, 10 patients with moderate (n = 7) to severe (n = 3) steroid-refractory UC received a single IV infusion of basiliximab (40 mg) and concurrent steroid treatment and were followed for 24 weeks [83]. The primary outcome, complete clinical remission at 8 weeks, was observed in 90% of patients, however 8 of 9 patients who achieved remission experienced relapse of the disease within a median of 9 weeks, and the remission was later reinstated with corticosteroids and azathioprine [83]. The same group performed another open-label trial in which 20 patients with steroid-refractory moderate (n = 13) to severe (n = 7) UC were administered a single IV infusion of basiliximab (40 mg) and concurrent corticosteroid treatment with 24-week follow-up [84]. A complete clinical remission was observed in 42.8% (3/7 patients) of patients with severe disease at week 8 and 24, but the remaining 4 of 7 patients (57.2%) underwent colectomy within the first 2 weeks [84].

During 2009 Digestive Disease Week, Sands et al presented data from a randomized double-blind placebo-controlled trial that assessed the efficacy of basiliximab with concomitant corticosteroids in treatment of moderate to severe steroid-refractory UC (despite oral prednisone 40 to 50 mg/d prior to study entry) [85]. The trial included 149 patients who were assigned to receive 3 single doses each 2 weeks apart of either basiliximab (40 mg or 20 mg) or placebo [85]. There was no significant difference in rates of clinical remission (Mayo score ≤ 2 and no subscore > 1) at week 8 between basiliximab 40 mg and placebo (30% vs. 28%, P = 0.82) or between basiliximab 20 mg and placebo (27% vs. 28%, P = 0.94) [85]. Therefore, it has been suggested that basiliximab is not effective in treating patients with steroid-refractory UC [85].

**Visilizumab**

Two open-label and 1 placebo-controlled trial assessed the efficacy of visilizumab, a humanized monoclonal antibody that blocks human CD3 expressed on T cells in the treatment of severe steroid-refractory UC [86–88]. Plevy et al analyzed the effect of IV visilizumab (10 or 15 µg/kg) administered on 2 consecutive days to 32 patients [86]. After 30 days, clinical response was noted in 84% of patients, clinical remission in 41% and endoscopic remission in 44% [86]. The colectomy-free rate was 78%, and among those who underwent colectomy the median time to surgery was 160 days [86]. There were 22 patients evaluable for duration of response at 1 year and 45% of them did not require either medical salvage therapy or colectomy [86]. The second open-label trial determined that the optimal clinical dose of IV visilizumab was 5 µg/kg given for 2 days [87]. Among 33 patients who were treated in stage II with this dose, 55% achieved clinical response at 30 days [87]. The subsequent multicenter randomized placebo-controlled trial of visilizumab comprised 127 patients with severe active steroid-refractory UC who were treated with IV visilizumab 5 µg/kg given for 2 days and were followed for 90 days [88]. There was no statistically significant difference in response rates at day 45 between visilizumab and placebo (55% vs. 47%, P = 0.475) [88]. Likewise, no difference was observed in remission rates between visilizumab and placebo (8% vs. 9%, P = 0.704) [88]. The 18% colectomy rate in visilizumab patients was not statistically significantly different than the 9% colectomy rate in placebo patients (P = 0.130) [88]. Patients treated with visilizumab experienced cardiac disorders (12% vs. 5%, P = 0.3357) and vascular disorders (23% vs. 5%, P = 0.0107) more frequently than placebo-treated...
patients [88]. Seventy percent of patients treated with visilizumab experienced signs and symptoms of cytokine release syndrome [88]. This trial was discontinued prematurely by the data safety monitoring board due to lack of efficacy and safety of visilizumab upon enrollment of 127 of the planned 150 patients [88]. In the light of the findings, visilizumab cannot be recommended as a treatment option in severe steroid-refractory UC.

**Vedolizumab**

Vedolizumab (MLN02, MLN002) is a gut selective biologic that binds and inhibits α4β7 integrin found on select leukocytes [89]. A randomized placebo-controlled multicenter trial published by Feagan et al found that vedolizumab was more effective than placebo for induction of clinical and endoscopic remission in patients with active UC [90]. A total of 181 patients were randomized to receive vedolizumab (either 0.5 or 2 mg/kg) or placebo on day 1 and day 29. Clinical remission rates at 6 weeks were 33%, 32%, and 14% in the groups receiving 0.5 mg/kg of vedolizumab, 2 mg/kg of vedolizumab, and placebo, respectively (P = 0.03) [90]. However, in this study, an earlier version of vedolizumab derived from NS0 mouse myeloma cell line was used. A significant proportion of patients (44%) developed clinically relevant human anti-human antibodies (HAHA) titers, reducing the efficacy [90]. The manufacturer developed a new formulation of vedolizumab using a substance produced from the Chinese hamster ovary (CHO) [89]. Perik et al conducted a randomized controlled phase 2 dose-ranging trial using the new formulation in 46 patients with active colitis [89]. Patients were randomized to vedolizumab (2, 6, or 10 mg/kg) or placebo on days 1, 15, 29, and 85. Partial Mayo Scores (PMS) and fecal calprotectin levels were used to assess efficacy. The percentage of responders in the combined vedolizumab cohort between days 29 to 253 were consistently 50% compared with 22% to 33% in the placebo group. In a subgroup of patients (n = 23) with more active disease (PMS score 4–7), the response rates ranged between 68% and 89% in the vedolizumab group (n = 19) versus 25% to 50% in the placebo group (n = 4) between days 29 and 253. All 3 doses were well tolerated with no serious or opportunistic infections reported, including no cases of PML [89]. Currently, a phase 3 study (GEMINI 1) evaluating the efficacy of vedolizumab in patients with moderate to severe UC is ongoing [91].

**Interferon-b-1A**

Data from an open-label trial of 46 patients with severe steroid-refractory UC showed that 86% and 89% of patients treated with a greater (1.0 MIU) and lower (0.5 MIU) dose of interferon-b-1a achieved remission [92]. Patients receiving a greater dose of interferon had significantly lower frequency of relapses during maintenance treatment than those treated with lower dose (4% vs. 31%, P ≤ 0.05) [92]. However, a randomized placebo-controlled trial of 91 patients with steroid-refractory UC did not find interferon superior over placebo in inducing response after 8 weeks of treatment, with respective rates of 56%, 36%, and 34% for 3 MIU interferon, 1 MIU interferon, and placebo (P value not significant) [92]. Treatment with interferon cannot be recommended for treatment of severe steroid-refractory UC due to lack of sufficient published data showing its efficacy.

**COLECTOMY**

It has been estimated that approximately 30% to 40% of patients with UC will undergo surgery during the course of their disease [93,94]. Proctocolectomy with a Brooke ileostomy was the standard surgical procedure in patients with UC, but in the 1980s another procedure, termed restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA), was introduced, and it was associated with significantly improved performance in daily activities and quality of life [95]. According to current guidelines, the absolute indications for surgery are exsanguinating bleeding, perforation, and documented or strongly suspected carcinoma [5]. Patients with severe steroid-refractory UC not responding to 5 to 7 days of treatment with IV cyclosporine A or infliximab should also undergo colectomy [5]. Delayed surgery for acute severe UC has been shown to be associated with increased postoperative complications [96]. In a study of 80 patients who underwent urgent colectomy between 1994 and 2000, those who had a major complication at any time during follow-up had significantly longer duration of medical therapy before colectomy than patients with no major complications (median 8 versus 5 days; P = 0.036) [96]. Therefore, it is important not to delay surgery in patients not responding to maximal medical therapy. Treating patients with either cyclosporine or infliximab preoperatively has not been shown to increase postoperative complications in patients undergoing colectomy [97–99].

Cohen et al [100] compared quality of life in patients with severe steroid-refractory UC treated with IV cyclosporine A versus colectomy and observed that 18 pa-
Patients treated medically had better stool consistency, less abdominal or rectal pain, fewer daytime and nighttime bowel movements, and less disturbed ability to sleep than the 46 who underwent colectomy [100]. An analysis of 1885 patients who underwent colectomy with IPAA at the Mayo Clinic highlighted an overall high success rate of pouch surgery that was sustained throughout 20 years of follow-up (96.3% at 5 years, 93.3% at 10 years, 92.4% at 15 years, and 92.1% at 20 years) [101]. There was a statistically significant increase in mean daytime (5.7 vs. 6.4, P < 0.001) and nighttime (1.5 vs. 2.0, P < 0.001) stool frequency, daytime (5% vs. 11%, P < 0.001) and nighttime fecal incontinence (12% vs. 21%, P < 0.001) between 1 year and 20 years after the procedure [101]. It was demonstrated that the surgical approach eliminates the disease, protects patients from future colorectal cancer (though not completely given there still remains several centimeters of rectal mucosa), and preserves control of stool function and quality of life [101].

Despite its excellent results, colectomy with IPAA is associated with several potential complications. A meta-analysis of 43 observational studies comprising 9317 patients (87.5% with UC) who underwent colectomy with IPAA follow for a median of 3 years observed that pouch failure occurred in 6.8% of patients, with an increase to 8.5% when follow-up was longer than 5 years, pelvic sepsis occurred in 9.5% of patients, sexual dysfunction in 3.6% of patients, and severe, mild, and urge fecal incontinence occurred in 3.7%, 17%, and 7.3% of patients, respectively [102]. The chronic inflammation of the pouch reported in the literature ranges from 9% to 20% of patients [103,104]. A meta-analysis of 8 studies observed a threefold increased risk of infertility in women after IPAA in UC (RR 3.17, 95% CI 2.41–4.18), with infertility rate increasing from 15% before to 48% after surgery [105].

Certainly, total proctocolectomy with IPAA is the procedure of choice in patients with severe UC without other therapeutic options [106]. It should be noted, however, that quality of life and bowel function after surgery cannot be considered normal, since a substantial number of patients experience fecal urgency, leakage, nocturnal soiling, sexual dysfunction, and pouchitis, and even conversion to a permanent ileostomy in case of pouch failure [106].

**CONCLUSION**

Patients presenting with acute severe UC should be hospitalized and promptly started on IV corticosteroids and supportive care. Patients not responding to 3 to 5 days of corticosteroid therapy should be considered steroid-refractory. Currently, the options in patients presenting with severe steroid-refractory UC include medical therapy with IV cyclosporine or infliximab for 5 to 7 days or proctocolectomy with IPAA.

It is important to involve patients in decision-making and to assess their preferences. In a study by Arsenneau et al, patient preferences had a clear impact on optimal treatment for steroid-refractory UC [107]. Medical treatments were found to be superior to surgery (cyclosporine = 0.26 quality-adjusted life years gained versus surgery; infliximab followed by cyclosporine in treatment failures = 0.25 quality-adjusted life years gained vs. surgery) [107]. In addition, physician preferences and practice patterns may influence treatment. Spiegel et al surveyed community gastroenterologists and UC experts, using clinical vignettes to measure decision making in areas of treatment controversy. Although both groups favored infliximab (62%) over cyclosporine (6%), UC experts had a lower threshold to call for surgery consultation [108].

The practice of treating patients failing treatment with cyclosporine with infliximab and those failing infliximab with cyclosporine cannot be recommended at this time. The major concern in such an approach is patient safety, with adverse events occurring in 16% to 22% of patients [69,71]. In addition, no controlled trials have been done to assess the efficacy of such management.

We recommend treating steroid-refractory UC patients with infliximab, especially those who were exposed to thiopurines in the past. Previously it has been suggested that infliximab is less effective in patients with more severe acute colitis, but the results of the study by Laharie et al [68] show that both infliximab and cyclosporine are equally effective in achieving clinical response at day 7 and have equal colectomy rates at day 98 in patients with acute severe colitis. Other advantages of infliximab include lack of need to monitor blood drug levels, familiarity with use of infliximab among physicians, and lack of need to monitor for nephrotoxicity and seizures. We also recommend starting patients on azathioprine or 6-MP, since patients receiving both infliximab and azathioprine had higher response rates than infliximab alone in one of the most recent studies [65]. The centers with experience in using cyclosporine can use it, especially for patients who are thiopurine-naive. Patients responding to IV cyclosporine should be transitioned to oral cyclosporine. This will help to create a bridge to therapy with azathioprine or 6-MP. Patients not responding to medi-
eca trial. It is important to recognize patients who fail medical therapy and consult a surgeon experienced in managing UC early for colectomy. Delays in colectomy are associated with more postoperative complications.

The Table presents data from randomized controlled trials that assessed various therapeutic agents in treating patients with steroid-refractory UC. Currently there is no ideal treatment of choice in patients with severe steroid-refractory UC, and further studies are needed to determine the best treatment for these patients.

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