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<th>Journal:</th>
<th><em>Alimentary Pharmacology &amp; Therapeutics</em></th>
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<tr>
<td>Manuscript ID:</td>
<td>APT-0264-2010.R3</td>
</tr>
<tr>
<td>Wiley - Manuscript type:</td>
<td>Review Article</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>08-Jun-2010</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Hart, Ailsa; St Mark's Hospital, IBD Unit Ng, Siew; Institute of Digestive Diseases, Chinese University of Hong Kong</td>
</tr>
<tr>
<td>Keywords:</td>
<td>Ulcerative colitis &lt; Disease-based, Inflammation &lt; Topics, Inflammatory bowel disease &lt; Disease-based, Biologics (IBD) &lt; Topics</td>
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Review Article: Acute Severe Ulcerative Colitis, An Update on Optimal Medical Management

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Keywords: Acute severe ulcerative colitis, ciclosporin, infliximab, corticosteroids

Abbreviations: UC: ulcerative colitis; 6-MP: 6-mercaptopurine; CRP: C-reactive protein; CyA: ciclosporin; ESR: erythrocyte sedimentation ratio

Short running title: Medical management of acute ulcerative colitis
Conflict of interest: nil
SUMMARY

Background: Management of acute severe ulcerative colitis (UC) is a clinical challenge, with an associated mortality rate of approximately 2-3% reported early post-colectomy. Traditional management with intravenous corticosteroids has been modified by introduction of ciclosporin and more recently infliximab.

Aim: To provide a detailed and comprehensive review of the medical management of acute severe UC

Methods: PubMed and recent conference abstracts were searched for articles relating to treatment of acute severe UC.

Results: Two thirds of patients respond to intravenous steroids in the short term. In those who fail steroids, low-dose intravenous ciclosporin at 2mg/kg/day is effective. Approximately 75% and 50% of patients treated with ciclosporin avoid colectomy in the short and long term, respectively. Long term outcome of ciclosporin therapy is improved by introduction of azathioprine on discharge from hospital, together with oral ciclosporin as a bridging therapy. Controlled data show that infliximab is effective as rescue therapy for acute severe UC and the effect appears to be durable although longer term follow up data are needed.

Conclusions: Both ciclosporin and infliximab have demonstrated efficacy as rescue medical therapies in patients with acute severe UC, but surgery needs to be considered if there is failure to improve or clinical deterioration.
INTRODUCTION

Acute severe ulcerative colitis (UC) will affect 15% of UC patients at some point in their disease course (1). Twenty percent of first attacks of UC are “acute severe” in nature (1). Acute severe UC has been defined by the Truelove and Witt’s criteria: the patient passing more than six bloody stools per day plus one or more of the following: temperature >37.8°C; pulse greater than 90bpm; Hb <10.5g/dL or ESR >30mm/hr (2). In this review, we will focus on the management of patients classified as having acute severe UC by the Truelove and Witt’s criteria and who are hospitalised.

The goal of medical therapy is to avoid colectomy while preventing complications of disease, side effects of medications and mortality. Corticosteroids, ciclosporin and infliximab have been used in the setting of acute UC. In addition to these medical therapies, optimisation of the overall supportive care of patients with acute severe UC is essential. This includes intravenous fluid replacement with potassium supplementation, careful exclusion of enteric infection by stool cultures and Clostridium difficile toxin testing, and an unprepared flexible sigmoidoscopy (and biopsy) with minimal air insufflation in patients not responding or those slow to respond to medical therapy to assess mucosal severity of inflammation and to exclude cytomegalovirus infection. Patients presenting with acute UC with co-existing Clostridium difficile infection have an increased colectomy rate and worse long-term clinical outcome (3), and should be treated with metronidazole or vancomycin (4). The presence of cytomegalovirus inclusion bodies on
colonic biopsies should prompt treatment with ganciclovir, in particularly in patients slow to respond to conventional therapy. Malnourished patients should be considered for calorie supplementation and should be weighed and reviewed by a dietician. Additionally, prophylactic subcutaneous heparin to reduce the risk of thromboembolism, and blood transfusions to maintain the Hb >10g/dL are crucial (5;6). Any medications which may precipitate toxic dilatation in the colon including opioids, non-steroidal anti-inflammatory drugs and anti-cholinergics should be stopped. Topical therapy (mesalazine or corticosteroids) is effective if tolerated although there are no systematic studies in acute severe UC (7). Careful daily monitoring of the patient with clinical assessment (bowel frequency and presence of blood, abdominal pain, temperature, pulse, abdominal tenderness), biochemical assessment (blood count, inflammatory markers, biochemistry) and radiological monitoring (abdominal radiography with the frequency determined by the clinical status and response of the patient) with integration of input from the physician and surgeon is imperative for optimal outcome.

1. Corticosteroids

The mainstay of therapy for acute severe UC is corticosteroids. In 1955 Truelove & Witt published a ‘final report on a therapeutic trial’ of cortisone in UC. 213 patients were randomised to receive cortisone 100mgs each day or placebo for six weeks. The cortisone-treated patients did better than the corresponding control patients with cortisone being particularly beneficial in those with a first attack of disease. Furthermore, in 120 patients who had a
sigmoidoscopic examination at the end of treatment in addition to pre-
treatment, normal or improved sigmoidoscopic appearances were more
frequent in the cortisone group than the control group (8). Subsequently, in
1974, Truelove & Jewell published the results of a trial using an intensive
intravenous regimen for severe attacks of UC. Forty-nine patients were
treated with intensive intravenous corticosteroids and 36 out of 49 (73%) were
in complete remission at day five (7). A recent systematic review of 32 trials
consisting of over 2,000 patients treated with steroids for acute severe UC
between 1974 and 2006 showed that the overall response rate to steroids
was 67%. Approximately one third of patients came to a colectomy in the
short term (9). The introduction of steroids to the management of acute
severe UC has dramatically reduced mortality figures from more than 50% to
1-2 % (8). Mortality from acute severe UC in the first year from a study in
Birmingham in 1933 and a study from Oxford in 1950 was 75% and 22%,
respectively. However, after the introduction of steroids in 1955, the mortality
rate from acute severe UC had fallen to 7%. The current overall mortality in
specialist centres is less than 1% (10).

Acute severe UC is associated with both early post-colectomy in-patient
mortality and long-term mortality post colectomy. The United Kingdom (UK)
Inflammatory bowel disease (IBD) audit of more than 6000 adult patients
admitted to UK hospitals between 2007 to 2008 with IBD (863 patients had
acute severe UC), and a national study from Canada reported early post
colectomy mortalities of 2.9 and 2.3% respectively (11;12). In the UK IBD
audit, the reported inpatient mortality of 1.2% was strongly associated with
increased age, male gender and the presence of clostridium difficile infection (13). Kaplan et al. showed that short term mortality after surgery for UC was higher in those who had emergency than those who underwent elective surgery (14). Both advanced age and low volume of surgery at a given centre contributed towards increased mortality (15;16).

In a record linkage study from England which included more than 20,000 patients admitted to hospital for more than three days for IBD, mortality rates for patients admitted with UC three years after elective colectomy (3.7%) appeared to be significantly lower than those who had an emergency colectomy (13.2%) or no colectomy (13.6%) (17). Mortality was highest in the first twelve months after admission. It was suggested that the threshold for elective colectomy for UC in England may be too high. Using a national record linkage database from 1998 to 2000, Nicholls et al. recently demonstrated that in patients with UC requiring hospital admission, the overall three year mortality rate is lowest in patients who had an elective colectomy (5.6%) and highest in those who did not have surgery (9.8%) (18). Age greater than 50 years old at admission, male gender, co-morbidity, hospital stay beyond two weeks, and prior hospital admission for IBD were independently associated with mortality (18).

The timing of surgery is critical and should not be delayed for more than five days if the patient is not responding to medical therapy. Kaplan et al. showed that in patients admitted urgently for a UC flare, those whose surgery is performed more than six days after admission had an odds ratio of in-hospital
mortality of two compared with those who had earlier surgery (14). A multidisciplinary approach involving the gastroenterologist, surgeon, dietician, stomatherapist to educate patients on the options of rescue therapy and surgery is of paramount importance.

**Predictors of response to steroids**

In clinical practice, clinical response is assessed by improvement in symptoms (reduced bowel frequency, reduced urgency, improved stool constituency, reduced abdominal pain, reduced rectal bleeding, improved general well being, increased energy, reduced lethargy) and improvement in blood test parameters (reduced C-reactive protein (CRP), erythrocyte sedimentation ratio (ESR) and platelet count, improved albumin and haemoglobin).

Clinical response to steroids can be assessed on day three. In a prospective study by Travis *et al.* on 51 episodes of severe UC, more than 8 stools per day or 3 to 8 stools per day plus a C-reactive protein (CRP) >45mgs/L predicted a colectomy rate of 85% (19). In 1998, Lindgren *et al.* performed a prospective study on 97 episodes of severe UC and devised the following mathematical model to predict colectomy; number of stools per day + 0.14 x CRP (mgs/L) ≥ 8 predicted a colectomy rate of 72% (20). In a retrospective study by Ho *et al.* in 2004 on 167 episodes of severe UC, the number of stools per day (score 1-4); hypoalbuminaemia <30g/L (score 1) and colonic dilatation >5.5cm (score 4) were useful in predicting a colectomy or the need
for second line intervention. Eight-five percent of patients with a score greater or equal to four required a colectomy or second line intervention (21).

These studies highlight the importance of a time-bound approach in the management of patients with acute severe UC. Indeed in a group of 80 patients undergoing emergency colectomy for severe UC treated between 1994 and 2000 in Oxford, patients who had a significantly longer duration of preoperative medical therapy were more likely to have major post-operative complications. If medical therapy was continued for 8 days or more, a higher complication rate was noted if surgery ensued (22).

We suggest that at day 3, careful assessment is made of the response of the patient in terms of stool frequency, inflammatory markers and radiological assessment. In cases of clear non-response, the decision should be made to consider other medical or surgical options. If there is a degree of response in the parameters mentioned then a balanced judgement needs to be taken regarding continuing with current therapy for a further time-bound period. We suggest that if a patient’s clinical condition does not improve after 5–7 days of IV steroid treatment then consideration should be made for other medical options or surgery. Recently, Ananthakrishnan et al. showed that anaemia, the requirement for blood transfusion, malnutrition and total parenteral nutrition were independent predictors of colectomy and a simple risk score has been proposed to stratify the severity of UC hospitalizations which helped to predict colectomy (23). Preliminary data suggested that faecal calprotectin may be a potential non-invasive biomarker to predict response to
corticosteroids and colectomy. In 90 patients with acute severe UC treated with corticosteroids, faecal calprotectin was significantly higher in patients requiring colectomy with a trend toward significance when comparing corticosteroid responders and non-responders (24). In daily clinical practice, we propose using simple clinical and biochemical parameters including stool frequency, CRP, serum albumin levels and abdominal radiograph as predictive factors in assessing for response to medical therapy. The use of a simple index in clinical practice may help to quantify the risk of colectomy and aid decision making.

2. Ciclosporin

**Short term efficacy**

Approximately one third of patients with acute severe UC will fail to respond to corticosteroids. Several medical options exist for these patients. One option is ciclosporin, the fungal metabolite originally derived from a Norwegian soil sample. Two controlled trials have assessed the efficacy of ciclosporin in the setting of severe UC. In 1994, Lichtiger et al. performed a randomised placebo-controlled trial of intravenous ciclosporin at a dose of 4mg/kg per day administered over a mean of seven days. The study was stopped early for ethical reasons because of the marked favourable response to ciclosporin. Nine out of 11 and 0 out of 9 patients treated with ciclosporin and placebo, respectively, had a response. When five patients who had placebo were crossed over to ciclosporin, all five patients responded (25). A subsequent
European controlled trial compared intravenous ciclosporin (4mg/kg) with intravenous steroids. Nine of 14 (64%) ciclosporin-treated patients and eight of 15 (53%) corticosteroid-treated patients responded (22). Ciclosporin was used as monotherapy and not as an adjunct to corticosteroid therapy. This trial highlights the efficacy of ciclosporin monotherapy in severe attacks of UC and it can be considered as an option for patients who wish/need to avoid steroids or who have failed oral steroid therapy. The largest ciclosporin trial to date of 73 patients by Van Assche et al. in 2003 was a head to head comparison study of ciclosporin 4mg/kg versus 2mg/kg. Response rate at day eight was not different in the “high dose” group (84%) versus the “low dose” group (86%) (26). Several other uncontrolled trials have also assessed the initial response of UC to intravenous ciclosporin (27-33) and these are detailed in Table 1. Overall the short term response to ciclosporin is in the range 64-86%.

Side effect profile

One of the major issues pertaining to the use of ciclosporin relates to its side effect profile. As ciclosporin is generally used as a bridge to azathioprine in the setting of acute severe UC, the short term side effects represent the main issue and include hypertension, tremor, nausea/vomiting, renal insufficiency, headaches, anaphylaxis, infection, paraesthesia and seizures (34). There is a mortality rate associated with ciclosporin in IBD (approximately 1.8%) (34), although some centres have reported higher mortality rates of up to 3.5%. Side effects of ciclosporin can be limited in a number of ways. One such way
is by using a reduced dose. Actis et al. in 1993 treated eight patients with severe steroid resistant UC with 2mg/kg a day of intravenous ciclosporin. Seven patients responded, and two patients had reversible renal insufficiency (35). In a separate cohort of patients treated at St Mark’s Hospital, 31 patients with acute severe steroid resistant UC were given 2mg/kg a day of intravenous ciclosporin followed by the early introduction of azathioprine. 77% of patients responded and no deaths, major infective episodes or seizures were reported (28). In the trial by Van Assche et al. comparing 2mg/kg with 4 mg/kg ciclosporin, although no seizures, infections or deaths were reported, there was a trend towards increased hypertension in the 4mg/kg dose group.

The neurotoxicity and seizure risk associated with ciclosporin can be limited by monitoring and ensuring normal levels of magnesium and cholesterol or alternatively the use of oral ciclosporin. Data from the transplant literature has shown an increased seizure risk with low total cholesterol. In liver transplant patients treated with ciclosporin, toxicity occurred with a cholesterol concentration below 3.1 mm (36;37). It has been suggested that lower cholesterol levels increased ciclosporin bound to low-density lipoprotein particles and that this may result in increased delivery of ciclosporin to astrocytes, which have low-density lipoprotein receptors (38). Hypomagnesaemia increases the risk of seizures in patients treated with ciclosporin therefore correcting deficiencies can limit neurotoxicity. Oral ciclosporin is also effective in the treatment of acute severe colitis (33), and there is also some evidence that oral formulations of ciclosporin may limit
neurotoxicity (39). In a retrospective study of patients with severe UC, 54 patients were treated with intravenous ciclosporin and 22 patients with oral ciclosporin. Oral ciclosporin (used as rescue therapy) was superior to intravenous ciclosporin with regards to the time to first relapse and time to surgery at a median follow up of 2.9 years (range 0.2 to 7 years) (33). Once ciclosporin has been started, drug levels should be monitored on day two to three and dosage should be adjusted to the levels of 150 to 300 ng/mL (28;33). Random levels can be measured during intravenous infusion, and trough levels for oral formulations.

Limiting infective complications associated with intravenous ciclosporin can be achieved by minimising concomitant immunosuppressant use and using prophylactic antibiotics. The risk of infection is greater with triple and double immunosuppressive therapy than with single therapy. In a case-control study the relative risk of opportunistic infections is highest in those who are on two or three immunosuppressive agents (Odds Ratio; OR 14.5) compared with those on any one of steroids, azathioprine or infliximab (OR 2.9) (40). In clinical practice, rapid weaning of steroids as appropriate is one means of limiting the risk of infections. Prophylaxis with Cotrimoxazole for patients on triple immunomodulators is advised. In patients on two immunomodulators, one of which is a calcineurin inhibitor or an anti-TNF agent, the European Crohn’s and Colitis Organisation (ECCO) consensus could not reach a verdict on the use of prophylactic Cotrimoxazole (41).

Long term efficacy
The long term benefit of ciclosporin is an important issue. In a cohort of 42 patients with severe UC treated with intravenous ciclosporin and followed up long term, the probability of avoiding colectomy was 67% within one year and 58% at 5.5 years. If only the patients who initially responded to ciclosporin were included in the analysis, the probability of avoiding colectomy was 80% at 1 year and 70% at 5.5 years (31). In a separate cohort of 31 patients with acute UC treated with intravenous ciclosporin, 45% of patients did not require a colectomy over a median of 17.5 months (28). In a retrospective long term follow up study from Oxford of 76 patients with acute UC treated with ciclosporin, 42% of patients had avoided colectomy after 7 years (33). A recent study from the same unit in Oxford showed that incomplete responders to ciclosporin within one week after admission with acute severe UC had a 50% chance of colectomy within a year and 70% within five years (42).

Investigators from Leuven showed that of all treated patients, 55% would avoid colectomy during a period of 3 years using prediction from life table analysis (43). When this cohort of patients was followed up long term, the probability of avoiding colectomy after successful intravenous ciclosporin therapy was 63% at one year, 41% at 4 years, 16% at 6 years and 12% at 7 years (44). Overall, there is a long term benefit in preventing colectomy when ciclosporin is used in a subgroup of patients. The likelihood of avoiding colectomy over 2 to 3 years is approximately 50%.

**Influence of immunomodulators on long term efficacy**
What is the influence of concurrent immunomodulator therapy on the long term outcome of patients with acute severe colitis treated with intravenous ciclosporin? Data from the trial by Cohen et al in 1999 showed that the probability of avoiding colectomy was 66% at long term follow up (5.5 years) in patients receiving ciclosporin and azathioprine/6-mercaptopurine (6-MP) compared with 40% in those who received ciclosporin alone, suggesting that azathioprine improves the long term efficacy of ciclosporin (31). In patients who had an initial response to ciclosporin, this rate increased to 71% in those who were treated with azathioprine/6MP, versus 55% in those who received ciclosporin alone. The timing of azathioprine/6MP in the ciclosporin responders was such that 28% had started azathioprine/6MP a mean of 15 months before starting ciclosporin; 32% started azathioprine/6MP “during” ciclosporin therapy; 8% started azathioprine/6MP simultaneously with stopping ciclosporin and the remaining started azathioprine/6MP a mean of 8 months after stopping ciclosporin.

Further studies have suggested that in patients who were already on immunomodulators at the time of admission with acute severe UC, the likelihood of needing a colectomy following treatment with ciclosporin is high. Moskowitz et al. showed that 77% of patients who were taking azathioprine at the time of admission with acute severe colitis required a colectomy compared with 35% of patients who were started on azathioprine during the same admission as their intravenous ciclosporin. 88% of patients already on
azathioprine and requiring colectomy underwent surgery within the first year of receiving ciclosporin (44).

Overall, it is beneficial in patients with acute severe UC naive to thiopurine to be started on thiopurine during the acute admission when treated with intravenous ciclosporin to optimise long term outcome and avoid colectomy. If a patient presenting with acute severe UC is already taking a thiopurine at the time of admission, the outcome with ciclosporin is less favourable and other medical options or early surgery need to be considered (45).

**Predictive factors of response to ciclosporin**

In addition to determining predictive factors for response or non-response to corticosteroids, several studies have assessed predictive factors for response to ciclosporin. In one study, two clinical parameters (body temperature >37.5 and pulse rate >90bpm) and one biochemical marker (CRP level >45) predicted colectomy. Rates of colectomy at 6 months were 0.22, 0.47, 0.55, and 0.90 when 0, 1, 2, and 3 of these factors were present, respectively (46). Cautious sigmoidoscopy within a few days of starting ciclosporin can be helpful. Severe endoscopic lesions (deep ulceration or large mucosal abrasion or weld-like ulceration or mucosal detachment) were independent predictors of colectomy. The rate of colectomy at 6 months in patients with severe endoscopic lesions was 73% versus 42% in patients without them. Colonoscopy was particularly helpful in patients with intermediate clinical and biological severity of their disease such that colonoscopy changed the
therapeutic decision in patients with one or two of the criteria mentioned above: 71% of the patients with severe endoscopic lesions had a colectomy versus 17% of the patients without severe endoscopic lesions (46). Rowe et al. showed that low serum albumin, tachycardia and neutrophils were predictors of poor response to ciclosporin (47). Taken together, the monitoring of ciclosporin using clinical, biological and endoscopic criteria is crucial to help to predict response to the drug. This is necessary to help a timely move to the next therapy and minimise procrastination.

In summary, ciclosporin is effective in the treatment of acute severe UC in the short term. In the longer term ciclosporin can prevent colectomy in a subgroup of patients. Careful patient selection is critical to identify those most likely to benefit in the short and long term; patients who are naïve to thiopurines and those who show good early response with clinical, biological and endoscopic parameters are most likely to do well. The side effect profile of ciclosporin needs to be taken into consideration in each individual patient and its safety optimised by careful monitoring.

3. Infliximab

Infliximab is a chimeric monoclonal antibody to human tumour necrosis factor (TNF)-α which is known to play an important role in the inflammation process of UC. Increased levels of TNF-α have been found in faeces from patients with active UC (48).
In an open label study, six patients with severe steroid refractory UC were treated with a single infusion of Infliximab 5mg/kg. All patients experienced marked clinical improvement at the end of seven days and colonoscopy confirmed significant healing of endoscopic lesions. Four of the six patients experienced long term remission at median follow up of 5.5 months (49). Sands et al. reported the results of a placebo-controlled trial of Infliximab in patients with severe steroid refractory UC, which was terminated early due to slow enrolment. Of the patients treated with Infliximab four out of eight (50%) were treatment successes at 2 weeks compared with zero out of three patients treated with placebo (50). A further randomised controlled trial was performed in 13 hospitalised patients with acute UC randomised to three infusions of 5mg/kg of Infliximab or high dose corticosteroids. Five out of 6 patients on Infliximab and six out of seven patients on high dose corticosteroids were better (51).

The largest randomised placebo controlled trial to date of Infliximab in acute severe UC was reported in 2004 by Jarnerot et al. Forty-five patients with moderately severe UC were given a single infusion of 5mg/kg Infliximab four days after initiation of steroids. Significantly more patients who had placebo (67%) required surgery than those who had infliximab (29%) within 90 days of randomisation (52). The greatest benefit of infliximab was seen in patients who had severe or moderately severe but not fulminant UC. Lees et al. reported experience of 39 patients hospitalised for acute severe UC treated with Infliximab. They found that 66% responded and avoided colectomy during the acute admission (53) and higher early responses were reported by
Kohn et al. with 85% of hospitalised patients with acute severe UC avoiding colectomy initially (54). Table 2 summarised clinical studies of infliximab in acute UC.

**Influence of immunosuppression**

Does treatment with Azathioprine influence the outcome of patients with acute severe UC treated with Infliximab? Some studies suggest that whether the patient was on existing azathioprine or not at the time of admission with acute severe UC did not affect the outcome (52). If patients were on azathioprine at the initiation of infliximab, 80% avoided a colectomy at 90 days. This is in contrast with the data using ciclosporin where the chance of a colectomy in patients who were already on azathioprine and needed ciclosporin was high. However, other studies suggest that Infliximab is less efficacious as rescue therapy if patients are on immunosuppression at the time of admission. In a Scottish cohort of 39 patients with acute severe colitis treated with Infliximab, although previous treatment with azathioprine/6MP did not affect urgent colectomy rates, two additional colectomies were performed at longer follow up in patients who had had prior exposure to azathioprine (53).

**Screening for opportunistic infections**

A complete history of risk factors for infection and an immunisation history needs to be obtained prior to infliximab (and immunomodulators). Recommended screening tests include a full blood count, hepatitis B virus
serology, varizella zoster virus serology (in the absence of a history of chickenpox), HIV serology, a chest radiograph and tuberculin skin test or interferon γ release assay according to local or national practice guidelines (41;55;56).

**Side effect profile**

The periodic safety update report (2008) showed that the benefit risk profile of Infliximab is well defined and positive. There are over 15 years of clinical trial experience and over ten years of post marketing experience in which 1,700,682 infliximab-treated patients have been assessed. There are two registries in Crohn's Disease, The Crohn's Disease Therapy, Resource, Evaluation and Assessment Tool (TREAT) and European National Crohn's Observational Registry (ENCORE) with a total of approximately 10,000 patients monitored for five years. Although data in such registries may be incomplete and/or biased, they do serve to provide information on drug safety. Data from the US TREAT registry consists of more than more than 6000 patients treated with infliximab with a mean follow-up of 3.4 year has not shown a significant increase of malignancy, mortality, incidence of lymphoma in IBD patients treated with infliximab compared with other therapies (57). A recent meta-analysis assessing the safety of anti-TNF therapy showed that there was no increased risk of death, serious infection, or malignancy in overall, subgroup and sensitivity analyses (58). The TREAT registry and the
European ENCORE CD registry have identified steroid use as an independent risk factor for serious infections. In a recent longer term study of the TREAT registry with a follow-up of 4.8 years, infliximab-treated patients showed similar rates of mortality and malignancy (including lymphoma), but an increased risk of serious infections compared with non-infliximab treated patients (59). A very rare form of non Hodgkin’s lymphoma, hepatosplenic T cell lymphoma has been reported in patients with inflammatory bowel disease, predominantly Crohn’s disease, usually treated with combination anti-TNFalpha agents and azathioprine. This malignancy was first described in 1990 as distinct subtype of lymphoma. There are only about 150 cases documented in the literature. It predominantly affects paediatric and young adult patients (predominantly male) and tends to have a very aggressive disease course with a usually fatal outcome. This form of lymphoma has been described in 14 Crohn’s Disease patients, one patient with indeterminate colitis and one with UC (age 12-40 years) (60;61).

**Long term efficacy**

As with ciclosporin, it is important to determine the duration of response with Infliximab. There have been data up to one year in 110 patients with severe steroid refractory UC from ten Italian centres treated with Infliximab 5mg/kg at 0, 2 and 6 weeks and subsequently maintained on Infliximab, azathioprine or both. The colectomy rate at one year was 24.5% (61). These data are consistent with a separate study of 20 patients hospitalised for acute severe UC demonstrating that colectomy was prevented in 75% of patients one year
following initiation of infliximab (62). Additionally data up to three years from a Swedish/Danish trial showed a 50% colectomy rate in Infliximab-treated patients compared with a 76% colectomy rate in placebo-treated patients. However in this study the use of subsequent immunomodulators in the two groups were not equal, and this may influence the long term outcome (63;64).

Several other uncontrolled studies have also examined the long term effects of infliximab treatment for acute severe UC. A study from Edinburgh reported that approximately two thirds of patients treated with infliximab avoided colectomy during the acute admission and when patients were followed up to a median of 203 days there were 2 additional colectomies (53). A study from Oxford showed that about half of their patients with refractory UC treated with infliximab came to a colectomy at a median of 140 days after the first infusion (65). In a large Italian study of 83 patients with severe steroid-refractory UC treated with infliximab, 15% of patients underwent colectomy within two months, and more than 50% of the patients avoided colectomy up to a median of 23 months. Two or more infliximab infusions appeared to be more effective than a single infusion in the short term (54).

Overall infliximab is effective in preventing colectomy in acute severe UC in the short term and the response may be durable. A recent systematic review of 34 studies including 896 patients with moderate to severe UC showed that infliximab was more effective than placebo for inpatients and outpatients with severe UC. 40 percent of patients were in remission at approximately nine months follow-up (66).
Predictors of Response to Infliximab

Investigators from Leuven identified predictors of early clinical response to infliximab in their first 100 patients with severe UC treated with infliximab. The majority of patients received a single dose 5mg/kg infliximab whereas one third of patients received a three-dose infliximab induction at week 0, 2 and 6. More than half of the patients were on concomitant immunomodulators. Younger patients and those without a pANCA+/ASCA-ve serotype tended to have an early clinical response (67).

Independent predictors of failure to infliximab as rescue therapy for severe intravenous steroid-refractory UC have been assessed in another retrospective study and these factors include a disease duration of ≤ three years, bowel frequency of greater than six times per day on admission and prior hospitalisation in the past three months for UC (68).

Lees et al. showed that serum albumin at admission and day 3 of intravenous steroids predicted response to infliximab. A serum albumin of <34g/L at day 3 showed a sensitivity of 57% and specificity of 90% for colectomy (53).

4. Infliximab versus ciclosporin

No head to head trials comparing ciclosporin and infliximab in acute severe UC have been published but controlled trials comparing these two drugs for this indication are in progress. In a retrospective study presented in abstract form of an Austrian cohort of UC patients treated with ciclosporin (n=49) and a Swedish cohort of UC patients treated with infliximab (n=46), a lower
colectomy rate was observed at three and 12 months after rescue therapy with ciclosporin (12%, 33%) than with a single infusion of infliximab 5mg/kg (33%, 45%) in patients presenting with acute severe steroid-refractory UC. Both groups received subsequent maintenance therapy with azathioprine. However severity and extent of disease were not comparable in the two cohorts (69). In a separate Italian study of severe steroid-resistant UC, 19 infliximab-treated patients were compared with a historical cohort of ciclosporin-treated patients (33 patients). Rehospitalisation rates in the two groups up to 20 months were similar (70). Both ciclosporin and infliximab are effective in the treatment of acute severe UC and the therapeutic decision should be individualised. In patients naïve to thiopurine therapy presenting with their first episode of acute severe UC, intravenous ciclosporin followed by the introduction of azathioprine while still in hospital after having demonstrated a response, together with three months of bridging oral ciclosporin, is an effective strategy. In these patients, ciclosporin is being used as a bridge to azathioprine which is used as a maintenance therapy. In contrast, in patients who have been maintained on optimal dose azathioprine and present with a severe episode of UC, ciclosporin and probably infliximab are less likely to be successful (44) and there is the issue of what further maintenance therapy can be used. In this setting, the use of infliximab can be considered as this can be used as a maintenance therapy. However consideration for early surgery may be more appropriate.

5. Switching between ciclosporin and infliximab
Some patients with acute severe UC will fail ciclosporin or infliximab. There have been reports of switching from ciclosporin to infliximab and vice versa. However, the strategy of switching between ciclosporin and infliximab or vice versa has significant risks which are outlined below and needs to be considered very carefully weighing up the risks and benefits of surgery with the risks and benefits of continuing medical therapy. We would not advocate switching as a “standard” treatment strategy. It is theoretically safer to use infliximab after ciclosporin than to use these drugs in the reverse order in view of the shorter half life of ciclosporin. In a Spanish study, 16 patients with acute UC were treated with infliximab after failing ciclosporin, 37.5% of patients required a colectomy at a median follow-up of 195 days from the first infliximab infusion (71). In a study from Mount Sinai, 19 patients with fulminant UC failed to respond to either ciclosporin or infliximab and crossed over to the other medication. Ten patients received infliximab after failing ciclosporin and 9 patients received ciclosporin after failing infliximab. Four (40%) and three (33%) patients in the infliximab- and ciclosporin salvage group achieved remission, respectively. Remission lasted a mean of 10.4 months and 28.5 months, respectively. One patient treated with infliximab salvage died from sepsis. Two patients who had Ciclosporin salvage developed herpetic oesophagitis and pancreatitis (72). In the largest study to date by the GETAID group of 86 patients, 65 patients had ciclosporin first followed by infliximab after a median time of two days after ciclosporin withdrawal, and 21 patients had infliximab first followed by ciclosporin after a median of 17 days since last infliximab infusion. Corticosteroids or immunosuppressants were continued in
about three quarter of patients. Thirty-three patients had a colectomy within three months. About one third of patients had adverse effects consisting mostly of infections. One patient died after surgery from pulmonary embolism (73).

6. Drug-related mortality

A single centre study from Leuven showed that ciclosporin was associated with deaths (3.5%) from opportunistic infections (2 aspergillus and 1 pneumocystis carinii) in 3 out of 86 patients with UC (40). Other trials have reported a mortality rate associated with ciclosporin in IBD of approximately 1.8% (34). The Scottish study showed that the major complication and mortality rate was 5.2% and 2.6% respectively in patients with acute UC treated with infliximab. An older man died from pseudomonas pneumonia following successful response to infliximab for severe UC, and a young patient had severe fungaemia post-colectomy after failing infliximab (53). Switching between infliximab and ciclosporin is associated with serious adverse effects and death as discussed above, and is not recommended as “standard” approach (72,73). Infliximab and ciclosporin appear to be efficacious as rescue therapy for patients with acute severe UC, but serious adverse events do occur. A risk/benefit analysis of medical therapy needs to be compared with “curative” surgery which carries a mortality of about 2-3% in the early post-operative period. Both short term and long-term post colectomy mortality is substantially reduced when an elective, and not an emergency colectomy is performed.
7. Other Experimental Therapies

There are no published studies reporting the efficacy of the humanised anti-TNF agent, adalimumab, in the setting of acute severe UC defined by the Truelove and Witt’s criteria, although two small studies have investigated the use of Adalimumab in patients with moderately severe UC who had failed infliximab (74;75). A recent larger study of 186 patients assessing the use of Adalimumab in moderately to severely active UC showed disappointing results at eight weeks with 19.2% of patients in the adalimumab group (160mg/80mg) in clinical remission compared with 9.2% in the placebo group (76). Other agents such as tacrolimus and leukocytapheresis have been studied and recently biological agents such as basiliximab and visiluzumab have been assessed. Intravenous and oral tacrolimus showed results similar to ciclosporin (77). A dose-ranging study of Visiluzimab, an anti-CD3 monoclonal antibody, in acute severe UC based on the Modified Truelove and Witt’s score, showed a 30-day remission and response rate of 30 and 60%, respectively (78).

8. Surgery

Surgery may be unavoidable in some patients with acute severe UC, therefore optimal management requires close collaboration between the gastroenterologist and the surgeon and the surgeon and stoma nurse should be involved early in the management. Indications for surgery include toxic megacolon, perforation, severe haemorrhage, or clinical deterioration during
medical therapy. Delayed surgery for patients who do not respond to medical therapy is associated with an increased risk of postoperative complications. In a group of 80 patients undergoing emergency colectomy for severe UC treated between 1994 and 2000 in Oxford, patients who had a significantly longer duration of preoperative medical therapy were more likely to have major post-operative complications. If medical therapy was continued for 8 days or more, a higher complication rate was noted if surgery ensued (22). This emphasises the importance of having a time-bound approach with both medical and surgical teams monitoring patients closely and making the decision to operate at the appropriate time. It has to be a part of the medical management plan to optimise the condition of the patient for potential surgery with regards to maximising nutrition and tapering steroids where possible.

Ferrante et al compared post-operative infectious complications between patients who had infliximab 3 months prior to surgery and those who did not. Corticosteroids and a restorative proctocolectomy without defunctioning ileostomy, but not infliximab, were associated with an increased risk of short-term postoperative infectious complications in UC (79). However a recent meta-analysis showed that pre-operative infliximab use increased the risk of total short-term post-operative complications (OR 1.8) which included wound infection, sepsis and abscess (80).

The recommended operation in the acute setting is total colectomy and ileostomy, with the rectum left in situ. Reconstructive surgery is best performed approximately six months after primary surgery (81). Although ileal
pouch anal anastomosis offers the prospect of a life without a permanent stoma, surgery does not always restore all aspects of quality of life to normal and a substantial number of patients still have problems with leakage, urgency, nocturnal soiling, sexual dysfunction, and pouchitis, and some patients may require conversion to a permanent ileostomy after ileal J-pouch-anal anastomosis failure (82).

9. Conclusions

Approximately 15% of patients with UC will have a severe acute attack that requires admission to hospital. Standard intensive treatment with intravenous steroids is still the first line approach. Patients who do not respond within three days to first line medical therapy should be considered for second line rescue medical therapy or surgery. This decision should take into account the patient’s previous immunosuppressant history, age, and co-morbidity. Delaying surgery, especially in older patients, those who had prior IBD admissions and prolonged hospital stays, carries risk and is associated with increased mortality up to three years. Surgeons and stoma nurses should be involved early in the management of patients with acute severe UC. A time-limited approach with assessment of predictors of response to therapies and close collaboration between physicians and surgeons are needed to ensure optimised management of patients with acute severe UC.

As we gain more information regarding the genetics of inflammatory bowel disease there may well be genotypic predictors of disease course, likelihood
of colectomy and response to drugs, including but not limited to infliximab and ciclosporin, for the treatment of acute severe UC (83). Ultimately, additional data are required to better define the efficacy and safety of current treatment in the short and long term, and the optimal timing of colectomy if unavoidable, in an individual patient.

Figure 1: Proposed algorithm for the treatment of patients with acute severe UC

Acute Severe Ulcerative Colitis
(Defined by Truelove and Witts criteria)

IV Steroids
(IV Hydrocortisone 100mg qds or IV Methyprednisolone 40mg od)
Assess at Day 3

No response
Surgery

IV infliximab
5mg/kg (week 0,2,6)
Assess after 1st dose

Response
Consider Infliximab
8 weekly

No response
Surgery

Partial response
Continue steroids
Reassess day 5-7

IV Cyclosporine
2mg/kg
Assess at Day 5

Response
Oral cyclosporine for 3 months
(Start azathioprine 2mg/kg before discharge)

No response: defined as >8 stools daily or 3-8 stools with a CRP>45mg/L
Table 1: Ciclosporin in Acute Severe UC

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Dose (mg)</th>
<th>Short term response</th>
<th>Long term colectomy free-remission</th>
<th>Follow-up (years)</th>
<th>Trial type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichtiger et al. 1994 (22)</td>
<td>20</td>
<td>4</td>
<td>82%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>D’Haens et al. 2001 (78)</td>
<td>20</td>
<td>4</td>
<td>64%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Van Assche et al. 2006. (23)</td>
<td>73</td>
<td>2 vs. 4</td>
<td>82% vs 83%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Moskovitz et al. 2006 (41)</td>
<td>142</td>
<td>2 or 4</td>
<td>83%</td>
<td>-</td>
<td>12% 48% 63%</td>
</tr>
<tr>
<td>Holme et al. 2009</td>
<td>18</td>
<td>5</td>
<td>83%</td>
<td>-</td>
<td>56%</td>
</tr>
<tr>
<td>Campbell et al. 2005 (30)</td>
<td>76</td>
<td>4</td>
<td>74%</td>
<td>-</td>
<td>42%</td>
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<tr>
<td>Message et al. 2005 (29)</td>
<td>26</td>
<td>3.7</td>
<td>77%</td>
<td>-</td>
<td>52%</td>
</tr>
<tr>
<td>Arts et al. 2004 (40)</td>
<td>86</td>
<td>2 or 4</td>
<td>84%</td>
<td>-</td>
<td>55%</td>
</tr>
<tr>
<td>Rayner et al. 2003 (25)</td>
<td>31</td>
<td>2</td>
<td>77%</td>
<td>-</td>
<td>45%</td>
</tr>
<tr>
<td>Cohen et al. 1999 (28)</td>
<td>42</td>
<td>4</td>
<td>86%</td>
<td>-</td>
<td>62%</td>
</tr>
</tbody>
</table>

U = uncontrolled
Table 2: Infliximab in Acute Severe UC

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Infliximab</th>
<th>Placebo</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sands et al. 2001 (50)</td>
<td>11</td>
<td>50%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Ochsenkuhn et al. 2004 (51)</td>
<td>13</td>
<td>83%</td>
<td>-</td>
<td>3.5</td>
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<tr>
<td>Jarnerot et al. 2005 (52)</td>
<td>45</td>
<td>71%</td>
<td>33%</td>
<td>&gt;6</td>
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<tr>
<td>Lees et al. 2007 (53)</td>
<td>39</td>
<td>66%</td>
<td>-</td>
<td>6.7</td>
</tr>
<tr>
<td>Kohn et al. 2007 (54)</td>
<td>83</td>
<td>85%</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>Bressler et al. 2008 (84)</td>
<td>21</td>
<td>76%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Reference List


77. Baumgart DC, Wiedenmann B, Dignass AU. Rescue therapy with tacrolimus is effective in patients with severe and refractory
78. Targan SR, Salzberg BA, Mayer L. A phase I-II study: multiple dose levels of visilizumab are well tolerated and produce rapid and sustained improvement in ulcerative colitis patients refractory to treatment with intravenous steroids. Gastroenterology 2005;128:A75.


