REVIEW

Managing acute severe ulcerative colitis in the hospitalised setting

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ABSTRACT

Ulcerative colitis affects approximately 146 000 people in the UK and is the most common form of inflammatory bowel disease. The majority of patients will have uncomplicated disease, but around 1 in 10 patients will develop acute severe colitis. Despite modern medical management, colectomy rates of 27% and mortality rates of 1% are still reported. Good supportive care and intravenous corticosteroids remain the mainstay of treatment, but up to one-third of patients will not respond. The Travis criteria allow early recognition of those patients failing to improve by day 3, allowing timely planning of medical rescue therapy or surgery. Rescue therapy with either infliximab or ciclosporin appears equally efficacious. Patients naive to thiopurines seem to have better colectomy-free survival rates following rescue therapy than those previously exposed. We review the published evidence behind the conventional management of acute severe ulcerative colitis.

INTRODUCTION

Ulcerative colitis (UC), which affects approximately 146 000 people in the UK, is the most common form of inflammatory bowel disease.¹ The majority of patients will have uncomplicated disease, but around 10% will develop acute severe colitis.²

The Truelove and Witts criteria were proposed in 1955 and define acute severe colitis as six or more bowel motions per day associated with one or more of the following: temperature $>37.8^{\circ}\text{C}$, heart rate >90 bpm, haemoglobin of <105 g/L or an erythrocyte sedimentation rate (ESR) >30 mm/h.³ This assessment tool allows simple and clear risk stratification of patients with UC and has been widely used over 50 years.

Standard care

Upon admission all patients with acute severe UC should have stool samples

analysed for common enteric pathogens and *Clostridium difficile* toxin. Observational studies have shown that *C. difficile* infection in patients with UC is associated with a fourfold to sixfold increase in mortality and a twofold increase in colectomy rates.^{4 5} Prevention of venous thromboembolism with low molecular weight heparin (LMWH) should be considered in every case and abdominal radiography performed to identify severe complications such as toxic megacolon. Intravenous fluids may be needed to treat dehydration. Corticosteroid use can cause hypokalaemia and hypomagnesaemia and prompt electrolyte correction can prevent ileus. The patient's nutritional status should be optimised early, bearing in mind that surgery may be required in the near future. Consideration should be given to performing a limited flexible sigmoidoscopy to confirm the disease severity and perform biopsies to exclude cytomegalovirus (CMV) infection. CMV infection is associated with reduced response rates to corticosteroids and higher colectomy rates.^{6 7} These measures should be considered to be 'standard', but the 2006 UK inflammatory bowel disease (IBD) audit highlighted that they can be easily overlooked.⁸

Steroids

Historical data from 1933 reported a mortality rate of 75% within 12 months after presentation with UC.⁹ This had reduced to 22% by 1950, probably due to improved supportive care, surgery and antibiotic use.¹⁰ In 1955, Truelove and Witts published the results of the first randomised controlled trial (RCT) using steroids to treat UC.³ In this trial, cortisone treatment reduced the mortality to 7% compared with 24% in those patients

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who received placebo. The largest meta-analysis of steroid use for UC included 32 studies and 1991 patients between 1974 and 2006, the mean mortality rates were reduced to 1% and colectomy rates to 27%.¹¹ A recent retrospective case review reported 3-year mortality rates of 5.7% following an admission to hospital with UC, although all deaths occurred in the elderly and only one case could be directly linked to UC.¹²

Steroids are usually given as intravenous hydrocortisone 100 mg four times per day or methylprednisolone 60 mg/24 h, which are equally effective. Lower doses are less effective but higher doses do not confer any advantage and may lead to more adverse events. Most patients will achieve complete or partial remission with corticosteroid treatment but approximately one-third will not respond.¹¹ The Travis criteria (stool frequency >8/day or C-reactive protein (CRP) >45 mg/L at day 3) allow early identification of patients with a high colectomy risk who are not responding to steroids, allowing timely planning of rescue medical therapy or colectomy.¹³

Rescue therapy: ciclosporin

Ciclosporin was confirmed as an effective treatment for severe UC refractory to steroids in 1994, when the first RCT was terminated early having demonstrated an 82% response rate to ciclosporin compared with 0% in those who received placebo ($p < 0.001$).¹⁴ Subsequent studies have consistently shown acute response rates of 60%–85%.^{15–17} Ciclosporin dosing at 2 mg/kg has been shown to reduce adverse events, yet remains as effective as doses of 4 mg/kg.¹⁵ Ciclosporin is administered as a continuous intravenous infusion for 5–7 days before converting to oral ciclosporin, which is continued for up to 3 months. After initial weight-based dosing, random ciclosporin levels are measured and the ciclosporin dose adjusted to maintain a therapeutic range. Recent trials have used doses of 2 mg/kg initially, aiming to maintain levels between 100 and 200 ng/mL¹⁸ or 150 and 250 ng/mL.¹⁹ Trough levels are used with oral dosing.

Muskovitz *et al* treated 142 patients with acute severe UC using intravenous ciclosporin, followed by oral ciclosporin for 3 months, and demonstrated an initial response rate of 83%.¹⁷ If a patient was already taking azathioprine, the colectomy rate was 59% (with 88% of these requiring colectomy within the first 12 months), but if the patient was naive to azathioprine, and it was commenced alongside ciclosporin treatment, then the colectomy rate was reduced to 31% ($p = 0.05$).

It has been suggested that oral ciclosporin may be as effective as intravenous ciclosporin yet associated with fewer adverse events such as anaphylaxis and neurotoxicity. Weber *et al* treated 19 consecutive steroid-refractory UC patients with oral ciclosporin for 3 months (Neoral) and demonstrated a response

rate of 85% at 3.5 days and a remission rate of 75% at 13 days, with 74% of patients remaining colectomy free at 8 months.¹⁹ No randomised placebo-controlled or head-to-head trials with intravenous ciclosporin have been performed on hospitalised patients with acute severe UC and, as such, oral ciclosporin cannot be widely recommended.

Rescue therapy: infliximab

An early pilot study in 2001 demonstrated the potential of infliximab as a treatment for severe steroid refractory UC. Eight patients received a single dose of infliximab and three received placebo. Clinical improvement was demonstrated in 50% of the infliximab patients with corresponding improvements in ESR, CRP and interleukin-6 levels. The study was terminated early due to poor recruitment and therefore underpowered, but, suggested that infliximab was well tolerated and may provide some clinical benefit.²⁰ In 2003, Probert *et al* examined the use of infliximab given at 0 and 2 weeks in moderately severe steroid resistant. In total, 9 of 23 patients receiving infliximab and 6 of 20 patients receiving placebo achieved remission by week 6, although there were no significant differences in endoscopy scores, quality of life scores or CRP values.²¹ The biggest step forward came in 2005 when Järnerot *et al* published the results of a small RCT comparing single-dose infliximab (5 mg/kg) with placebo.²² Colectomy rates at 3 months were 29% in the infliximab group and 67% in the placebo group ($p = 0.017$). Although the evidence for infliximab treatment in acute severe UC was less comprehensive than that for ciclosporin, infliximab began to be more widely used for this indication, perhaps driven by safety concerns about ciclosporin and physician familiarity with infliximab from established use in Crohn's disease.

Choosing between infliximab and ciclosporin

Laharie *et al*²³ published the first head-to-head comparison between ciclosporin and infliximab, in a multicentre, open-label, RCT of 115 patients with severe UC refractory to intravenous steroids. The study design randomised patients to receive either intravenous ciclosporin for 7 days, followed by oral ciclosporin thereafter, or intravenous infliximab on day 0, 7 and 42. Azathioprine was started, or continued, in all patients with clinical response at day 7. Eighty-six per cent of patients in the ciclosporin group had a clinical response at day 7 compared with 84% of patients in the infliximab group ($p = 0.76$). Day 98 colectomy rates were 17% in the ciclosporin group and 21% in the infliximab group ($p = 0.60$). In total, 9 patients (16%) receiving ciclosporin and 14 (25%) receiving infliximab had severe adverse events. There were no significant differences in the composite treatment failure rates. Infliximab performed better than in previously reported trials; the authors conclude that this

may due to the coadministration of azathioprine. Further evidence is expected from the ongoing CONSTRUCT trial, which is designed to examine the clinical and cost-effectiveness of infliximab versus ciclosporin in acute severe UC.¹⁸ The UK IBD audit may provide a guide for real-world outcomes and reported response rates of 52.6% (2008) and 63.8% (2010) for ciclosporin compared with 80.4% (2008) and 85.5% (2010) for infliximab, when used for inpatients with steroid refractory UC.⁸

Present National Institute of Health and Care Excellence (NICE) guidance recommends ciclosporin as the second-line drug of choice with infliximab remaining an option for patients in whom ciclosporin is contraindicated or clinically inappropriate.¹ Revised NICE guidance on the use of infliximab, adalimumab and golimumab for the second-line treatment of moderately to severely active UC is currently in development and is due to be published in spring 2015.

Successive treatment with ciclosporin and infliximab

Is there any value to using a second rescue therapy if the first agent fails? The largest retrospective study included 86 patients, most of whom received ciclosporin followed by infliximab.²⁴ Remission rates of 30% were achieved with colectomy-free survival rates of 61.3% and 41.3% at 3 and 12 months, respectively. There were 20 adverse events in 19 patients including one death in the ciclosporin–infliximab group attributable to pulmonary embolism day 1 postcolectomy. Nine patients (10%) developed serious infections. The European Crohn's and Colitis Organisation²⁵ and the American College of Gastroenterologists²⁶ both recommend colectomy after failure of one rescue therapy with the caveat that a second rescue therapy could be considered in specialist centres.

Screening for tuberculosis and latent tuberculosis

International guidelines recommend evaluation of patients for latent tuberculosis (TB) before commencing anti-tumour necrosis factor (TNF) treatment.²⁷ A careful history, examination and chest X-ray must always be undertaken and treatment started in those deemed to be at risk of latent TB.²⁸ Tuberculin skin testing (TST) can help to identify patients with latent TB but can be difficult to interpret in immunosuppressed patients within a largely BCG-vaccinated population. Interferon gamma release assays (IGRAs) are increasingly available and are often used in the elective setting prior to initiating anti-TNF therapy. Studies have shown improved diagnostic yield and cost-effectiveness compared with TST.^{29,30} IGRAs can take several days for laboratories to process. In the patient with acute severe UC, one should not delay or avoid rescue therapy while awaiting an IGRA result and it may be more appropriate to consider rescue therapy with ciclosporin or surgery.

Chemoprophylaxis of *Pneumocystis jiroveci*

A recent large retrospective cohort study matched 108 604 IBD patients with 434 416 controls in the USA. The crude incidence of *P. jiroveci* was 10.6/100 000 in the IBD cohort and 3.0/100 000 in the controls. Immunosuppressant therapy was the major risk factor and was implicated in 21 of the 38 (53%) cases of *P. jiroveci*, with corticosteroid monotherapy accounting for 11 (28.9%) of these.³¹

The benefits of *P. jiroveci* prophylaxis are well established in other immunocompromised groups such as those undergoing bone marrow transplantation, solid organ transplantation and HIV-infected patients with low CD4 counts. A large meta-analysis of 1245 immunocompromised non-HIV-infected patients demonstrated a 91% reduction in the occurrence of *P. jiroveci* with a number needed to treat of 15.³² Care must be taken when extrapolating these results to IBD patients as there are several important differences. CD4 counts are rarely affected, the level of immunosuppression is generally lower than for organ transplantation, and multiple immunosuppressant regimens are likely to be used for a relatively short time period. In one 7-year follow-up study of 86 patients treated with ciclosporin for up to 12 months, there was one case of *P. jiroveci* pneumonia that proved fatal.³³ In another 7-year follow-up study of 72 patients who received 3–6 months of ciclosporin coadministered with azathioprine and steroid therapy, there were no cases of *P. jiroveci*.³⁴ No chemoprophylaxis of *P. jiroveci* was used in either study. An ECCO consensus statement recommends chemoprophylaxis of *P. jiroveci* in patients receiving triple immunosuppression based on voting by an expert panel, no consensus could be agreed for lower doses of immunosuppression or corticosteroid monotherapy.²⁷

Heparin as a treatment for acute severe UC

In addition to its anticoagulant activity, heparin is known to have anti-inflammatory properties. In an early case series of steroid refractory patients treated with heparin, 12/16 achieved clinical remission at 4 weeks.³⁵ Further uncontrolled studies showed similarly positive results, but evidence from RCTs was less convincing. Panes *et al* examined the efficacy of continuous intravenous unfractionated heparin monotherapy in severe UC and found a response rate of zero compared with 69% for the group treated with corticosteroids.³⁶ Two further studies showed no benefit of subcutaneous LMWH compared with placebo in addition to conventional therapy.^{37,38} There is emerging evidence that LMWH administered via an extended colon-release tablet (CB-01-05 MMX) may be useful in mild to moderately active left-sided disease.³⁹ A total of 121 patients received CB-01-05 MMX or placebo in addition to stable doses of 5-ASA, there were improvements in clinical remission rates (83.3% vs 63.3%, $p=0.011$) and resolution of rectal bleeding

(75.4% vs 55.0%, $p=0.018$). These results may be due to the oral delivery system allowing larger dose of LMWH to be delivered directly to the colon without drug distribution to other systemic tissues. Although there does not seem to be any disease-modifying effect in acute severe UC, LMWH will remain an essential treatment because of the increased risk of venous thromboembolism.

Antibiotics in acute severe UC

Antibiotic treatments may be required to treat coexistent *C. difficile* infection or to manage postoperative complications. They do not have a place in the management of acute severe UC and several historical trials have reported no additive effect to conventional management.^{40 41 42}

CONCLUSIONS

With modern management, acute severe UC should have a mortality approaching zero. Patients identified as having acute severe colitis according to the Truelove and Witts criteria should be managed in hospital and receive intravenous corticosteroids alongside good supportive care. We can use the Travis criteria to identify those patients not responding to steroid treatment as early as day 3 and begin to consider rescue therapy or surgery. At present, there is no convincing evidence to suggest the superiority of either infliximab or ciclosporin as the rescue therapy of choice. Patients naive to thiopurines who receive rescue therapy seem to have better colectomy-free survival than those already exposed to thiopurines, and this should be taken into account when individualising a patient's treatment.

Correction notice Conclusion has been corrected since this article was published Online First.

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