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Infliximab three-dose induction regimen in severe corticosteroid-refractory ulcerative colitis: Early and late outcome and predictors of colectomy

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KEYWORDS
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Abstract

Background: Infliximab is effective as rescue therapy in severe corticosteroid-refractory ulcerative colitis. The optimal dose regimen and the long term benefits are not well defined. The aim of the present study was to evaluate short- and long-term colectomy rate in a cohort of patients with severe corticosteroid-refractory ulcerative colitis who received a three-dose infliximab induction regimen.
Methods: One hundred and thirteen patients admitted to 11 Italian IBD referral centres and treated with infliximab according to an intention to treat three-dose regimen were included. The co-primary endpoints were 3- and 12-month colectomy rate. The secondary end-points were the overall colectomy-free survival and the identification of predictors of colectomy.
Results: The 3- and 12-month colectomy rates were 18.6% (95%CI 11.8%–26.9%) and 25.6% (95%CI 17.9%–34.7%) respectively. High CRP values and severe endoscopic lesions were associated with the risk of colectomy: Risk Ratio (RR) = 2.15 (95%CI 1.05–4.36), and RR = 5.13 (95%CI 1.55–16.96), respectively. In patients escaping early colectomy, the probability of a colectomy-free course at 12, 24, 36 and 60 months was 91%, 85%, 81% and 73%, respectively. Endoscopic severity was the only predictor of long term colectomy (RR = 7.0; 95%CI 1.09–44.7). Adverse events occurred in 16 patients (14%); there was one death (0.88%) due to pulmonary abscess.
Conclusions: Infliximab is an effective and safe rescue therapy for severe corticosteroid-refractory ulcerative colitis. A three-dose induction regimen seems to be the treatment of choice for preventing early colectomy. Severe endoscopic lesions appear to be predictor of short- and long-term colectomy.

1. Introduction

Approximately 15% of ulcerative colitis (UC) patients will experience a severe attack at some point in their disease course.[1] Severe UC is a potentially life-threatening condition although mortality has dropped dramatically over the past 30–40 years to less than 2%. Early recognition of prognostic factors, intensive medical therapy, and early surgery for non-responders have all contributed to improved outcome.[2] In spite of the use of intensive intravenous glucocorticoid treatment (IIVT), approximately 20–30% of patients fail to respond and will require surgery. The short term colectomy rate has remained stable during the last 30 years[3]; moreover, approximately one third of patients who escape early colectomy will require surgery in the long term, for a further severe attack or for frequent relapsing disease.[4]

Although surgery is considered to be curative for patients with UC, the quality of life after restorative proctocolectomy is generally poorer than in patients who respond to medical therapy and avoid surgical treatment.[5] Therefore, rescue attempts have been made to avoid surgery in patients with severe UC not responding to intravenous steroids, while maintaining mortality at a low rate.

Intravenous (i.v.) cyclosporine (CyA) has been proposed as rescue therapy for severe IIVT-refractory UC in the nineties.[6] In spite of high short term remission rate, approximately 50% of patients who initially respond will require colectomy in the long-term.[7] Moreover, CyA has a limited use because of the risk of major toxicity, including occasional fatalities. Infliximab (IFX), an anti-tumour necrosis factor α (TNFα) chimeric monoclonal antibody, has more recently been used as rescue therapy for severe IIVT-refractory UC. In a randomised placebo-controlled trial, a single 5 mg/kg infusion reduced colectomy rate within 3 months by 40% compared to placebo.[8] Although the benefits of rescue therapy with IFX seem to remain in the subsequent 3-year follow-up,[9] few data are available concerning the efficacy in the long-term. Open label series with different length follow-up and different IFX dose regimens report an overall colectomy rate ranging from 18% to 75%.[10–14]

In a previous study on IIVT-refractory severe UC patients who were treated with IFX as rescue therapy, we reported the results of an Italian open-label study with an overall colectomy rate of 29% after a median follow-up of 23 months.[15] Although in this study there was no predefined IFX infusion regimen and patients received different number of infusions at different time intervals according to clinical judgement, the short-term colectomy rate was significantly higher in patients receiving a single infusion when compared to patients who received two or more infusions.

The aim of the present multicentre study was, therefore, to evaluate the overall colectomy rate in a cohort of patients who received IFX as rescue therapy for severe IIVT-refractory UC, according to a predefined 3 dose standard induction regimen (5 mg/kg at 0, 2 and 6 weeks).

2. Patients and methods

This study consisted of a "real life" observational cohort study of adult UC patients admitted to Italian IBD referral centres and treated with IFX according to an intention to treat three-dose induction regimen for acute severe IIVT-refractory UC. The diagnosis of UC was established according to standard criteria.[16] All patients had required hospitalization for an acute severe attack as defined by Truelove and Witts criteria[17] and modified by Chapman et al.[18]: six or more bloody stools per day with at least one of the remaining criteria: fever (mean evening >37.5 °C or >37.8 °C for 2 days out of four), tachycardia

(mean pulse rate >90 per minute), anaemia (decrease in haemoglobin levels greater than 75%), and erythrocyte sedimentation rate (ESR) > 30 mm/h. All patients were candidates for colectomy because of resistance to i.v. methylprednisolone 40–60 mg daily or equivalent, administered for at least 7 days.

A shared common database was used to collect demographic and clinical data. Data collected at baseline were: gender, age at the time of rescue therapy, disease duration, disease extension (left sided or extensive), smoking habits, and previous treatment. Clinical activity was measured by the Lichtiger Clinical Activity Score (CAI) for acute UC.[6] The CAI score takes into account symptoms (diarrhoea, nocturnal diarrhoea, visible blood in stools, faecal incontinence, abdominal pain, general well-being, abdominal tenderness, need for anti-diarrhoeal drugs) with a maximal score of 21 points. Severe clinical activity matches with a score ≥12 points. A score of <10 points, on two consecutive days, was considered as clinical response; clinical remission was defined by a CAI score of 4 points or less.[19]

Laboratory studies on admission included full blood count, serum electrolytes, renal and hepatic function tests, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). All patients were tested for enteric stool pathogens and *Clostridium difficile* toxin. Abdominal X-ray films were obtained to exclude impending megacolon, toxic megacolon or perforation, and to establish the approximate extent of colitis.[20] A flexible sigmoidoscopy was performed to assess endoscopic severity. Severe endoscopic activity was defined by the presence of deep colonic ulcerations[21] and/or spontaneous bleeding. Rectal biopsies to rule out cytomegalovirus (CMV) infection were performed. A standard chest radiograph was performed in all patients: an intradermal test with PPD or QuantiFERON TB-Gold test, together with an accurate personal history evaluation, was performed in all patients to rule out ongoing or past tuberculosis infection. Screening for hepatitis B virus was also performed.

IFX rescue therapy consisted of an induction regimen of three infusions 5 mg/kg of body weight at 0, 2 and 6 weeks. Aminosalycilates, thiopurines, or scheduled infliximab was used as maintenance treatment according to clinical judgement. Patients whose condition worsened or failed to respond to rescue therapy underwent colectomy. The decision to perform colectomy in the individual patient was made in conjunction with the surgeon. Patients who avoided colectomy were followed up for at least 1 year.

The co-primary endpoints were early colectomy rate and 1-year colectomy rate. Early colectomy was defined as surgery performed within 3 months from the first infusion of IFX. The secondary end-points were the overall colectomy free survival and the identification of possible predictive factors of colectomy.

3. Statistical analysis

The intention-to-treat (ITT) population included all patients who had received at least one infusion of IFX. The percentage of patients requiring colectomy within 3 and 12 months was calculated according to ITT analysis. Descriptive statistics was used to summarize the data; frequencies and median with inter-quartile ranges (IQR) for categorical and continuous variables were used, respectively, as appropriate.

The Kaplan–Meier survival method was used to estimate the cumulative probability of a course without colectomy after the rescue therapy with IFX. To look for predictive factors of colectomy, univariate analysis with log-rank test was used considering the following covariates: gender, age at the time of rescue therapy, smoking habits, disease duration, disease extension, baseline CAI, baseline haemoglobin (Hb) and CRP values, need of blood transfusions, severe endoscopic lesions, previous treatment with immunomodulators and maintenance treatment following the rescue therapy. Hazard ratio (HR) was given with 95% confidence intervals (95%CI). A p value less than 0.05 was considered statistically significant. All variables with a p value less than 0.05 at log-rank test were entered into a Cox proportional hazards survival regression model to identify independent predictors of colectomy. Two separate analyses have been performed with the aim to look for: 1) predictive factors of the overall risk of colectomy and 2) predictive factors of the risk of long-term colectomy in patients escaping early colectomy.

Analyses were performed using StatsDirect statistical software (version 1.9.8, copyright © 1990–2001) and Epistat (copyright © Epistat Services, 1991).

4. Results

From March 2003 to October 2009, 113 patients (49 male and 64 female), with a median age of 37 years (IQR 14–76), were included in the study. Patients were treated in 11 Italian IBD referral centres. Thirty-seven patients (33%) were included also in the previous study.[15] Demographics and clinical characteristics of the study group are summarized in Table 1.

Table 1 Demographic and clinical characteristics of patients.

Gender	
Male, n (%)	49 (43)
Female, n (%)	64 (57)
Age at rescue therapy (years) median (IQR)	37 (14–76)
Disease extension	
Left sided, n (%)	33 (29)
Extensive, n (%)	80 (71)
Disease duration (months) median (IQR)	36 (0–323)
Smoking habits	
Not smoker/ex smoker, n (%)	105 (93)
Active smoker, n (%)	8 (7)
CAI at baseline median (IQR)	14 (9–19)
Hb at baseline (mg/dl) median (IQR)	11 (5.5–15)
CRP at baseline (mg/dl) median (IQR)	3 (0.1–21)
Severe endoscopic lesions (deep ulcers/spontaneous bleeding), n (%)	81 (72)
Need of blood transfusions, n (%)	30 (26.7)
Previous steroids, n (%)	74 (65.4)
Previous/concomitant immunomodulators, n (%)	39 (34.5)
Duration of IIVT (days) median (IQR)	10 (3–15)

IQR = interquartile range; CAI = Colitis Activity Index; Hb = haemoglobin; CRP = C-reactive protein; IIVT = intensive intravenous steroid treatment.

The vast majority of patients had extensive colitis (70.8%) and were not smokers or ex-smokers (93%). The median duration of disease was 36 months (IQR 0–223). Eighty-one out of 113 patients (72%) had severe endoscopic activity at baseline flexible sigmoidoscopy; 74 out of 113 (65.4%) received at least one steroid course in the past and 39 out of 113 (34.5%) were receiving immunosuppressant treatment at the time of hospital admission. No patient had received previous IFX therapy. IFX was started after a median of 10 days (IQR 3–15) of i.v. steroids and a 3 dose induction regimen (5 mg/kg at 0, 2 and 6 weeks) was intentionally planned for all patients.

Ninety-three out of 113 patients (82%) completed the three dose induction regimen, while 20 patients had to discontinue treatment after the first (n = 12) or the second infusion (n = 8). Fifteen out of 20 patients who could not complete the induction regimen underwent colectomy because of worsening and/or complications (one patient developed also a systemic CMV infection); 4 patients discontinued IFX because of early severe adverse events (1 patient died within 10 days after the first infusion because of pulmonary abscess, 1 patient developed pneumonia, 1 patient developed varicella and 1 patient developed pneumonia and acute CMV-related hepatitis); finally 1 patient discontinued IFX because of intolerance to prophylactic treatment with isoniazide prescribed because of latent tuberculosis. The median follow-up after the first IFX infusion was 18 months (IQR 0–102).

4.1. Early and 1-year colectomy rate

Thirty-seven out of 113 patients required colectomy during follow-up (overall colectomy rate 32.7%; 95%CI 24.2% to 42.2%). Of 37 colectomies, 21 (56%) were carried out within 3 months, 8 (22%) between 4 and 12 months and 8 (22%) were carried out after one year. The early colectomy rate was 18.6% (95%CI 11.8% to 26.9%). The vast majority of patients requiring early colectomy underwent surgery within 1 month after rescue therapy (16 out of 21, 76%). Twenty-nine out of 113 patients required colectomy within 12 months (1 year colectomy rate = 25.6%; 95%CI 17.9% to 34.7%) (Fig. 1). Among 81 patients with severe endoscopic lesions at baseline 27 (33.3%) underwent colectomy within 12 months as compared to 2 out of 32 patients (6.2%) without severe endoscopic lesions.

The cumulative probability of a colectomy-free course within 5 years from rescue therapy is shown in Fig. 2. The probability of a course without colectomy was 73.9%, 69.2% and 66.1% at 12, 24 and 36 months, respectively. At 5 years the cumulative probability of colectomy was approximately 40%. At univariate analysis, a high CRP value (≥3 mg/dl) and the presence of severe endoscopic lesions during the acute attack were significantly associated with a higher probability of colectomy during follow-up (log rank test p = 0.0017 and p = 0.0026 respectively) (Fig. 3). No statistical significant differences were observed with regard to other considered clinical variables. In the multivariate model, both a high CRP value and the presence of severe endoscopic lesions were independently associated with the risk of colectomy: Risk Ratio (RR) = 2.15 (95%CI 1.05 to 4.36), *p = 0.003* and RR = 5.13 (95%CI 1.55 to 16.96), *p = 0.007*, respectively.

4.2. Long-term colectomy rate in patients escaping early colectomy

Ninety-one out of 113 patients avoided colectomy within 3 months. Of these, 13 received mesalazine as maintenance treatment (the majority of them were intolerant to thiopurines), 32 received immunosuppressant azathioprine or mercaptopurine, and 46 received scheduled IFX maintenance with or without thiopurines (n = 39 and n = 7, respectively), with a median number of infusion of 11 (IQR 2–24). Maintenance therapy was not randomised and aminosalycilates, thiopurines, or scheduled infliximab was used according to clinical judgement. During a median follow-up of 26 months (IQR 2–102) 16 patients required colectomy. The cumulative probability of a colectomy-free course at 12, 24, 36 and 60 months was 91%, 85%, 81% and 73%, respectively. At univariate analysis, severe endoscopic lesions at baseline were associated to a higher risk of colectomy (HR = 8.54; 95%CI 3.08 to 23.67; p = 0.01); conversely, maintenance treatment with scheduled IFX and/or immunosuppressant reduced the risk of colectomy (HR = 0.26; 95%CI 0.09 to 0.85; p = 0.02). In Cox

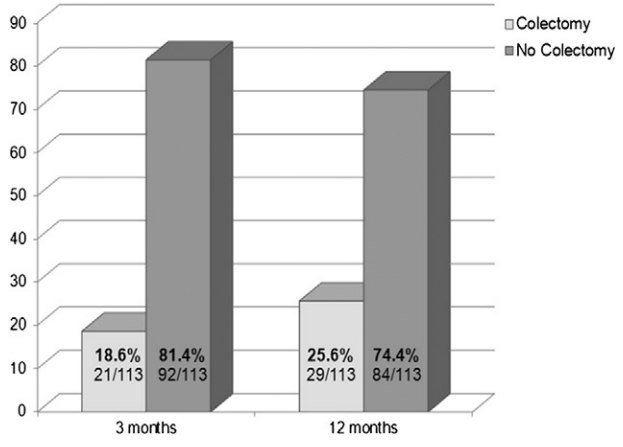

Figure 1 Colectomy rates within 3 and 12 months in the whole cohort (n = 113).

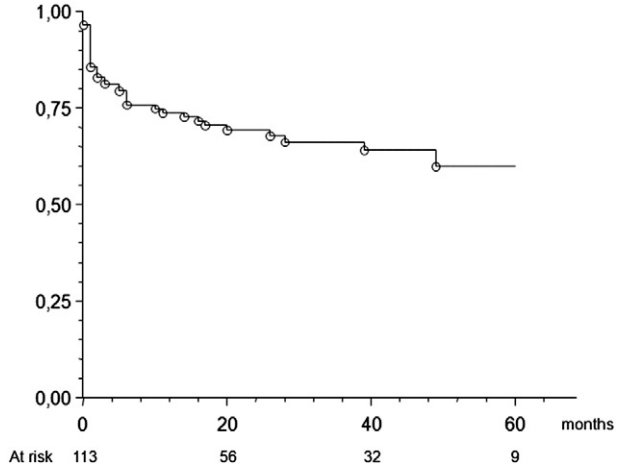

Figure 2 Kaplan–Meier plot showing colectomy free survival after rescue therapy with infliximab.

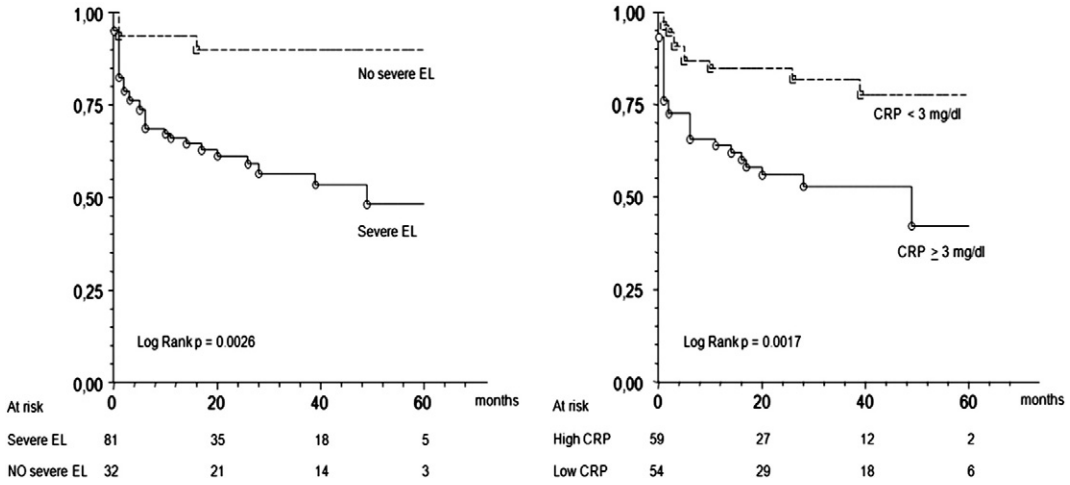

Figure 3 Kaplan–Meier plot showing long term colectomy free survival according to CRP value and endoscopic severity at baseline. EL = endoscopic lesions; CRP = C-reactive protein.

proportional hazard regression, only baseline severe endoscopic activity was independently associated with the long-term risk of colectomy in patients escaping early colectomy (RR =7.0; 95%CI 1.09 to 44.7; $p = 0.03$).

As far as corticosteroid use in the long term is concerned, of 84 patients who escaped colectomy within one year 73 (87%) were in steroid-free maintenance treatment.

4.3. Mortality and adverse events

Sixteen patients (14%) experienced at least one adverse event (Table 2). There was one death due to pulmonary abscess 11 days after the first IFX infusion. This case was already included and discussed in the previous study.[15] Four patients experienced early serious adverse events and discontinued IFX before completing the induction regimen: one patient developed pneumonia 2 months after the second infusion, 1 patient developed systemic cytomegalovirus (CMV) infection, 1 patient developed varicella infection and one patient developed CMV-related hepatitis and pneumonia. One patient had a *Candida albicans* sepsis that occurred 3 months after the last infusion, and probably it was not related to IFX. Herpes zooster occurred in 2 patients, systemic Herpes Simplex Virus (HSV) infection in one patient and pneumonia in one patient. Mild infusion reactions occurred in 6 patients. No newly diagnosed malignancies occurred. No surgery-related mortality occurred.

Table 2 Numbers of adverse events observed. One patient had more than 1 adverse event (CMV-related hepatits and pneumonia).

Adverse event	Number of patients
Pulmonary abscess (*Legionella pneumophila*)	1
Pneumonia	3
Systemic CMV infection	1
Varicella	1
CMV related hepatitis	1
Herpes zoster infection	2
Candida albicans sepsis	1
Systemic HSV infection	1
Infusion reactions	6

CMV = cytomegalovirus; HSV = Herpes Simplex Virus.

5. Discussion

This multicenter observational study is, to our knowledge, the largest series of severe IIVT-refractory UC patients in which a pre-defined three dose induction IFX regimen has been evaluated as rescue therapy. The results of our study confirm that IFX 5 mg/kg at 0, 2 and 6 weeks is effective to reduce the risk of colectomy in the short and long-term. The colectomy rates at 3 and 12 months were 18.6% and 25.6%, respectively. In patients escaping early colectomy, the cumulative probability of a course without colectomy was 73% after 5 years. These results are clinically relevant considering that all patients in our study were potential candidates for urgent colectomy, because of resistance to IIVT.

Prior to the immunosuppressive treatment era, higher colectomy rates after IIVT for UC have been reported both in the short and in the long-term (46% and 52%, respectively), with a 10-year colectomy rate, after the acute attack, as high as 64%.[4] Preliminary open label series of severe corticosteroid-refractory UC treated with IFX report a wide range of colectomy rate, starting from 18% up to 75%.[10–14] However, comparison with these studies is flawed by the small number of patients, different inclusion criteria and definitions of steroid failure, variable duration of follow-up and different rescue treatment schedules.

The optimal induction dose of IFX is currently not well defined. In our previous report, including 83 patients with severe IIVT-refractory UC, the early colectomy rate (defined as surgery performed within 2 months) was higher in patients receiving one IFX infusion compared with those receiving two or more infusions (35% vs 5.3%, respectively), suggesting that

two or three infusions work better than one single infusion.[15] In the randomised controlled trial by Jarnerot et al.,[8] the early colectomy rate after one single IFX infusion was 29%. Similar percentages have been reported in two recently published large observational retrospective studies from Denmark and Sweden,[22,23] in which a flexible IFX induction regimen was used (approximately 50% of patients in both studies received a single IFX infusion). Conversely, our early colectomy rate of 19% is very close to the 21% reported by Laharie et al. in the ciclosporin versus infliximab open-label randomised controlled trial, in which a standard 3 dose IFX induction regimen was used.[24] Even though these comparisons do not provide strong evidence, we can speculate that a standard 3 dose IFX induction regimen may reduce early colectomy rate by approximately 10% compared to a single IFX infusion.

As far as the long term colectomy rate is concerned, the vast majority of patients escaping early colectomy were maintained with immunomodulators or scheduled IFX with or without immunomodulators (86%) and only a minority of patients received mesalazine as maintenance treatment. This figure is very similar to that reported by Sjöberg et al.[23] in which 79% of patients escaping early colectomy received thiopurines and/or scheduled IFX as maintenance treatment. Since maintenance therapy was not randomised, no conclusions can be made from these data and the best maintenance treatment after successful rescue therapy with IFX needs further evaluation.

As far as predictors of colectomy are concerned, a high CRP value and the presence of severe endoscopic lesions at baseline were independently associated with the cumulative risk of colectomy within 5 years of follow-up. In the subgroup of patients escaping early colectomy, the severity of endoscopic lesions at baseline was confirmed as the only independent predictor of long-term colectomy. The possibility of identifying at an early stage patients who will fail intensive treatment and will need colectomy is one of the most relevant clinical dilemmas in managing patients with acute severe colitis.[25] In a previous systematic review and meta-regression, more than 20 predictors of medical therapy failure were identified, even though only a few variables were consistently reproduced: disease extent, bowel movements, fever, heart rate, CRP, albumin, and radiologic assessment.[3] Most of these studies, however, focused on corticosteroid failure, and few data are available concerning predictors of response or failure to IFX rescue therapy.

CRP is a useful, objective marker of predictive value for corticosteroid failure, both in adult and paediatric patients with acute severe UC.[26,27] Conversely, in studies with IFX as rescue therapy, CRP is related to the risk of colectomy in some studies,[22,28] but not in others.[23]

The severity of endoscopic lesions, particularly the presence of deep or large ulcers, has been associated with the risk colectomy in several studies.[21,29–31] However, in the only randomised, placebo-controlled study by Jarnerot et al.[8] the severity of endoscopic lesions predicted response to neither IFX, nor colectomy. In our study, the presence of severe endoscopic lesions, defined as the presence of deep ulcerations and/or spontaneous bleeding, was independently associated with the overall risk of colectomy and with the risk of long-term colectomy in patients escaping early colectomy. This finding suggests that the colonic structural damage may be the major determinant for the need of colectomy both in the short- and in the long-term although it is possible that patients with severe endoscopic lesions were more likely to undergo colectomy because clinicians were convinced of their prognostic importance.

Safety issues of rescue therapy with IFX remain an important issue. In our study, the proportion of patients with adverse events (14%) is similar to that reported in the ACT 1 and ACT 2 studies.[32] The case of fatal *Legionella pneumophila* infection, possibly related to infliximab, is of major concern but our mortality (0.88%) is lower than that reported in other series.[13,23] Safety issues of rescue therapy in patients with acute severe UC should be counterbalanced with the surgery-related risks in the urgent or emergent setting. Recent population-based nationwide studies of mortality after colectomy for UC performed in United Kingdom, USA and Denmark, report a 30-day mortality after urgent colectomy of approximately 5%.[33–35] Preventing urgent colectomy may, therefore, impact mortality.

In conclusion, our data confirm that IFX is an effective and safe rescue therapy for acute severe corticosteroid-refractory UC. A standard three-dose induction regimen seems to be the treatment of choice for preventing early colectomy. The presence of severe endoscopic lesions at baseline appears to be predictor of short- and long-term colectomy. The long-term maintenance strategy to be preferred should be addressed in future studies.

Disclosure statement

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