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BRIEF ARTICLE

Efficacy of infliximab in acute severe ulcerative colitis: A single-centre experience

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Abstract

AIM: To suggest infliximab (IFX) is effective for acute severe ulcerative colitis, from real-life clinical practice.

METHODS: All patients receiving IFX for the treatment of acute severe ulcerative colitis in a single centre were included. Data were extracted from clinical records in order to assess response to IFX therapy. The primary endpoint was colectomy-free survival, and secondary outcomes included glucocorticosteroid-free remission and safety, which was evaluated by recording deaths and adverse events. Demographic and clinical characteristics of those who underwent colectomy and those who were colectomy-free, both at discharge from their index admission, and during follow-up after an initial response to IFX were compared.

RESULTS: Forty-four patients (16 females, mean age 36 years) received IFX between May 2006 and January 2012 for acute severe ulcerative colitis. The median duration of follow-up post-first infusion was 396 d (interquartile range = 173-828 d). There were 21 (47.7%) patients with < 1 year of follow-up, 10 (22.7%) with 1 years to 2 years of follow-up, and 13 (29.5%) with > 2 years of follow-up post-first infusion of IFX. Overall, 35 (79.5%) responded to IFX, avoiding colectomy during their index admission, 29 (65.9%) were colectomy-free at last point of follow-up (median follow-up 396 d), and 25 (56.8%) were in glucocorticosteroid-free remission at end of follow-up. There was one death from post-operative sepsis, 20 d after a single IFX infusion. Colectomy rates were generally lower among those "bridging" to thiopurine. Of 18 patients "bridged" to thiopurine therapy, 17 (94.4%) were colectomy-free, and 15 (83.3%) were in glucocorticosteroid-free remission at study end. No predictors of response were identified.

CONCLUSION: IFX is effective for acute severe ulcerative colitis in real-life clinical practice. Two-thirds of patients avoided colectomy, and more than 50% were in glucocorticosteroid-free remission.

Key words: Ulcerative colitis; Severe; Azathioprine; Infliximab; Remission

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disorder of the gastrointestinal tract of unknown etiology, with a prevalence of between 160 and 240 per 100 000 people

in Western populations[1-3]. The condition is thought to arise from dysregulation of both the innate and adaptive immune systems, leading to an abnormal inflammatory response to commensal bacteria in a genetically susceptible individual[4].

The clinical course of UC is characterized by periods of remission and relapse, with acute inflammatory exacerbations of disease activity which, when severe, are potentially life-threatening. The standard initial management of these inflammatory exacerbations includes high dose intravenous glucocorticosteroids in the first instance, but this strategy may be unsuccessful in up to 50% of patients[5-7]. Immunomodulating drugs such as azathioprine, whilst effective in maintaining remission[8], act too slowly to be of use in the acute setting. Following the publication of a randomized controlled trial (RCT) by Lichtiger *et al*[9] in 1994, ciclosporin has been used as medical rescue therapy in acute severe UC, in order to avoid colectomy in the short-term, and to act as a "bridge" to long-term thiopurine therapy[10]. Several case series have since been published[11-14], but despite response rates in the order of 50%-70%, many patients require colectomy in the longer term.

In recent years, biological therapies have emerged as a treatment option in inflammatory bowel disease (IBD). Infliximab (IFX) (Remicade®, Centocor Ortho Biotech Inc, PA, United States), a chimeric monoclonal antibody directed against human tumor necrosis factor-alpha was the first biological therapy to be approved for use in acute severe UC. The efficacy of IFX in UC has been investigated by a limited number of RCTs[15-18]. When data from all these trials were pooled in a recent meta-analysis the number needed to treat over placebo to achieve remission in one patient with moderately or severely active UC was only 4, suggesting this is a highly efficacious therapy[19].

However, only two of these trials studied the use of IFX in acute severe UC[15,18], one of which found no significant difference in response between IFX and placebo[18]. In addition, data from RCTs do not always translate into normal clinical practice. Data from small retrospective case series' suggest that as many as one-third of patients given IFX for acute severe UC still require colectomy during the acute admission[20-23], but larger datasets, with longer follow-up, may provide more accurate insight into the efficacy of IFX in this setting. We therefore report our 6-year experience of using IFX in acute severe UC.

MATERIALS AND METHODS

Participants and setting

Patients have been treated with IFX for acute severe UC since 2006 in the Leeds Gastroenterology Institute, which operates across two large teaching hospitals serving a local population of approximately 800 000, as well as receiving tertiary referrals from the surrounding area. After their first IFX infusion of 5 mg/kg in hospital, patients attend for their second and third infusions on an outpatient basis at 2 wk and 6 wk. These are administered at a dedicated biological therapy clinic by specialist IBD nurses, who maintain a prospective database detailing demographics, response to therapy, number of infusions received, and any adverse events experienced.

All patients who received at least one dose of IFX for acute severe UC in Leeds between May 2006 and January 2012 were included. Patients were identified by cross referencing our IBD database with pharmacy records, which are accurate as all IFX infusions for in-patients are prepared in the pharmacy department. The use of IFX to treat an episode of acute severe UC was defined as need for the drug during an in-patient admission with an acute inflammatory exacerbation of disease activity. Patients receiving IFX for IBD-unclassified or pouchitis were excluded.

Data collection

Inpatient medical records, computerized outpatient clinic letters, histopathology, endoscopy, and blood results were reviewed by one investigator. Data were collected onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, United States) designed prospectively. These included demographic details, date of UC diagnosis, extent of disease according to the Montreal classification[24], drug therapy at time of admission, prior or current use of thiopurine or 5-aminosalicylate (5-ASA), physiological and biochemical parameters at day 0 and day 3 (mean number of stools per day, pulse, temperature, and C-reactive protein (CRP) level in mg/L), severity of UC on day 3 of their admission, according to the Travis criteria[25], and duration of admission (in days). Total number of infusions received, any adverse events experienced (including death), requirement for colectomy, and current drug therapies were collected at discharge from the index admission, as well as at last point of follow-up.

The primary outcome of interest was colectomy-free survival, and secondary outcomes included glucocorticosteroid-free remission and safety. Patients were judged to have had an initial response to therapy if they were discharged from their index admission colectomy-free. Recording of the patient's current drug therapy at last contact allowed assessment of the achievement of glucocorticosteroid-free remission. Safety data included deaths or adverse events during the study period that were potentially related to IFX.

Statistical analysis

The proportion of individuals who were colectomy-free at discharge from their index admission, and who were in colectomy- and glucocorticosteroid- free remission at the last point of follow-up was calculated. Demographic and clinical characteristics of those who underwent colectomy and those who were colectomy-free, both at discharge from their index admission, and during follow-up, after an initial response to IFX were compared using

Table 1 Baseline characteristics and demographics of 44 patients with acute severe ulcerative colitis receiving infliximab *n* (%)

Characteristic	All patients (*n* = 44)
Age at index admission[1]	35.7 ± 15.9
Female	16 (36.4)
Extent of disease (Montreal classification)	
E1 (limited to rectum)	2 (4.5)
E2 (distal to splenic flexure)	13 (29.5)
E3 (proximal to splenic flexure)	29 (65.9)
Current or previous smoker	18 (40.9)
Prescribed oral 5-ASA on admission	24 (54.5)
Prescribed thiopurine on admission	14 (31.8)
Median disease duration, in days, prior to first IFX infusion (IQR)	409 (16.25 to 1896.5)
First presentation of UC	12 (27.3)
Mean CRP (mg/L) on day of admission[1]	90.1 ± 81.9
CRP ≤ 5 on day of admission	6 (13.6)
Mean number of stools per day on admission[1]	12.1 ± 5.8

[1]Data are presented as mean ± SD. UC: Ulcerative colitis; IQR: Interquartile range; 5-ASA: 5-aminosalicylate; CRP: C-reactive protein; IFX: Infliximab.

an independent samples *t*-test for continuous variables, and Fisher's exact test for categorical variables. Multivariate logistic regression was performed in an attempt to identify independent risk factors for colectomy during the index admission, or during follow-up, controlling for all baseline demographic and clinical characteristics. All statistical analyses were performed using StatsDirect version 2.7.2 (StatsDirect Ltd, Sale, Cheshire, England), and SPSS for Windows version 19.0 (SPSS Inc, Chicago, IL, United States).

RESULTS

Between May 2006 and January 2012, 44 patients were treated with IFX for acute severe UC. The median duration of follow-up post-first infusion was 396 d [interquartile range (IQR) 173-828 d]. There were 21 (47.7%) patients with < 1 year of follow-up, 10 (22.7%) with 1-2 years of follow-up, and 13 (29.5%) with > 2 years of follow-up post-first infusion of IFX. The mean age at presentation with acute severe UC was 35.7 years (range: 18-78 years), and mean age at diagnosis was 32.4 years (range: 13-78 years). Of the 44 patients, 16 were female (36.4%). Baseline demographic data and disease characteristics of the included patients are detailed in Table 1. All patients had abdominal X-ray performed on admission to exclude toxic megacolon, and this was repeated at the discretion of the treating physician during intravenous glucocorticosteroids. Confirmation of mucosal disease activity was obtained by flexible sigmoidoscopy.

All 44 patients met the modified Truelove and Witt criteria[26] for acute severe UC on the day of admission. Mean CRP at time of admission was 90.1 mg/L, although this was less than 5 mg/L in 6 (13.6%) patients, and mean number of stools per day on admission was 12.1. All patients received intravenous glucocorticosteroids from the time of admission for a median of 7 d prior to IFX. There were 12 (27.3%) patients for whom the index episode of acute severe UC was their first presentation with the disease. Among the other 32 patients with an existing diagnosis of UC, 24 (75.0%) were currently receiving oral 5-ASA therapy, 14 (43.8%) were currently receiving thiopurine therapy, and a further six had previously received thiopurines but were either intolerant of them, or had experienced adverse events.

Need for colectomy during index admission

Nine patients (20.5%) underwent colectomy during their index admission, at a median of 5 d after their first IFX infusion (range: 2-18 d). The remaining 35 patients were discharged after their first IFX infusion colectomy-free. Baseline demographic data and disease characteristics of patients according to colectomy status at discharge from hospital following the index admission are reported in Table 2.

Patients who underwent colectomy during the index admission were generally older (mean age 45.6 years versus 33.2 years), and a higher proportion were admitted with a first presentation of UC (55.6%), compared with those who were discharged without colectomy (20.0%), but these differences were not statistically significant (P = 0.18, and P = 0.09 respectively). Extent of disease, according to the Montreal classification, was not associated with need for colectomy on index admission. In terms of medication use, fewer patients who underwent colectomy were receiving oral 5-ASAs or thiopurines on admission to hospital, but only the latter difference was statistically significant (P = 0.04). Those who underwent colectomy had significantly higher CRP values both on admission, and at day 3, than those who avoided colectomy (P = 0.002, and P = 0.04, respectively). All nine patients who required colectomy met the Travis criteria at day 3, compared with only 15 (42.9%) of those who did not undergo surgery at the index admission (P = 0.002). Among those who were colectomy-free at discharge 31.4% received IFX at day 5 or sooner, compared with only 11.1% of those who underwent colectomy (P = 0.41). No predictors of need for colectomy during the index admission were identified by multivariate logistic regression.

Colectomy-free survival at study end

Of the 35 patients who avoided colectomy during their index admission, 33 received standard three-dose induction with IFX. At the last point of follow-up, 29 (65.9%) of 44 patients remained colectomy-free. Thus, 82.9% (29/35) of those who responded to IFX on the index admission remained colectomy-free during follow-up. Among these 35 patients, 17 (48.6%) had < 1 year of follow-up, 8 (22.9%) had 1-2 years of follow-up, and 10 (28.6%) had > 2 years of follow-up post-first infusion of IFX. Two patients in each of these groups underwent colectomy during follow-up (χ^2 for trend, P = 0.69). The median time from first IFX infusion to colectomy for the six patients who had colectomy following an initial response to IFX therapy was 278 d (IQR 136.5-401.25 d).

Table 2 Clinical characteristics and demographics of 44 patients with acute severe ulcerative colitis receiving infliximab, according to colectomy status after index admission and at last point of follow-up *n* (%)

	Colectomy status after index admission			Colectomy status at last point of follow-up		
	Colectomy during index admission (*n* = 9)	Discharged colectomy-free (*n* = 35)	*P* value[2]	Colectomy during index admission or follow-up (*n* = 15)	Colectomy-free survival (*n* = 29)	*P* value[2]
Age at index admission[1]	45.6 ± 24.7	33.2 ± 12.1	0.18	42.2 ± 21.4	32.4 ± 11.3	0.11
Male	7 (77.8)	21 (60.0)	0.45	10 (66.7)	18 (62.1)	1.0
First presentation of UC	5 (55.6)	7 (20.0)	0.09	6 (40.0)	6 (20.7)	0.28
Disease extent	E1: 0 (0)	E1: 2 (5.7)		E1: 2 (13.3)	E1: 0 (0)	
	E2: 3 (33.3)	E2: 10 (28.6)		E2: 3 (20.0)	E2: 10 (34.5)	
	E3: 6 (66.7)	E3: 23 (65.7)	0.75[3]	E3: 10 (66.7)	E3: 19 (65.5)	0.10[3]
Current or previous smoker	4 (44.4)	14 (40.0)	1.0	6 (40.0)	12 (41.4)	1.0
Prescribed oral 5-ASA on admission	3 (33.3)	21 (60.0)	0.26	8 (53.3)	16 (55.2)	1.0
Prescribed thiopurine on admission	0 (0)	14 (40.0)	0.04	3 (20.0)	11 (37.9)	0.31
CRP (mg/L): day 0[1]	163 ± 62.5	71 ± 76	0.002	111.0 ± 83.0	79.0 ± 80.6	0.23
CRP (mg/L): day[1]	96 ± 69	39 ± 41.5	0.04	65.3 ± 65.5	42.9 ± 44.3	0.25
Number of stools per day: day 0[1]	13.3 ± 5.6	11.7 ± 5.9	0.46	13.0 ± 5.7	11.6 ± 5.9	0.44
Number of stools per day: day 3[1]	8.7 ± 4.6	6.5 ± 3.3	0.21	7.7 ± 4.2	6.6 ± 3.3	0.39
Met Travis criteria at day 3	9 (100)	15 (42.9)	0.002	10 (66.7)	14 (48.3)	0.34
Received IFX on day 5 or sooner	1 (11.1)	11 (31.4)	0.41			

[1]Data are presented as mean ± SD; [2]Independent samples *t*-test for continuous data and Fisher's exact test for categorical data; [3]χ^2 for trend. UC: Ulcerative colitis; 5-ASA: 5-aminosalicylate; CRP: C-reactive protein; IFX: Infliximab.

Demographic data and clinical characteristics of those who were colectomy-free at study end and those requiring colectomy at any point during the study are reported in Table 2.

Those who were colectomy-free at end of follow-up were generally younger, more likely to have had an established diagnosis of UC prior to their index admission, more likely to be receiving thiopurines on admission, and had lower mean CRP levels at admission, and on day 3, but none of these differences were statistically significant. Again, no predictors of need for colectomy at any point during follow-up were identified by multivariate logistic regression.

There were 18 of the 35 patients who avoided colectomy during their index admission who received IFX as a "bridge" to commencement of thiopurine therapy during, or soon after, the index admission. Of these, 17 (94.4%) were colectomy-free at the end of follow-up, compared with 12 of the 17 (70.6%) who did not commence thiopurine therapy ($P = 0.09$).

Glucocorticosteroid-free remission at study end

Of the 29 individuals who were colectomy-free at the last point of follow-up, 25 (86.2%) were in glucocorticosteroid-free remission. Therefore of the original 44 patients, 56.8% were colectomy-free and in glucocorticosteroid-free remission at the end of follow-up. Of the four patients who were colectomy-free but not in glucocorticosteroid-free remission, two had experienced a relapse of disease activity at their most recent assessment, one was receiving long-term low-dose oral glucocorticosteroids for co-existent inflammatory arthritis but was in remission clinically, and the fourth patient was still tapering the dose of glucocorticosteroids following recent index admission. Of the 18 patients who were "bridged" to thiopurine therapy during, or soon after, the index admission 15 (83.3%) were in glucocorticosteroid-free remission at the end of follow-up.

Safety and tolerability of IFX

During the study period one patient died from severe sepsis in the post-operative period, 2 d post-colectomy, and 20 d after a single IFX infusion. A total of eight other patients experienced adverse events with IFX. Five of these were minor, including skin rash in two patients, flushing in one patient, elevated transaminases in one patient, and pruritus in the fifth. All of these resolved without the need for discontinuation of IFX. In the other three patients the adverse events were intolerable and led to discontinuation of the drug. These included infusion reactions in two patients, and a delayed hypersensitivity reaction in the third. Of the three patients who discontinued IFX, one underwent colectomy and ileal pouch formation 15 mo after the initial IFX infusion, one was receiving low-dose glucocorticosteroids (2.5 mg prednisolone daily) in combination with methotrexate for co-existent inflammatory arthritis, and was in clinical remission as detailed above, whilst the third was colectomy-free and in glucocorticosteroid- free remission on azathioprine at the last point of follow-up.

DISCUSSION

This study has demonstrated that IFX is an effective rescue therapy in acute severe UC. After failure of intravenous glucocorticosteroids to control the acute severe episode, 80% of patients receiving IFX avoided the need for colectomy during the index admission. Those who met the Travis criteria on day 3 and those who were not receiving thiopurine therapy on admission were more

likely to require colectomy on their index admission. Among those who responded to IFX during their index admission, 83% remained colectomy-free and, in those who were colectomy-free, glucocorticosteroid-free remission was achieved in 86%, after a median follow-up period of 396 d. Of the total cohort of patients, 57% were colectomy-free and in glucocorticosteroid-free remission at the end of follow-up. The efficacy of IFX as a "bridge" to commencing thiopurine therapy is reinforced by the finding that over 90% of those patients "bridged" to thiopurine therapy avoided subsequent colectomy. Serious adverse events, resulting in the discontinuation of IFX were rare. However, there was one post-operative death as a result of severe sepsis.

Strengths of the study include the use of our biologics database which is maintained prospectively, allowing the inclusion of data from every patient who received IFX for acute severe UC in a large tertiary referral centre. The relatively long duration of follow-up among included individuals provides valuable, real-life data on outcomes among patients with acute severe UC receiving IFX. There are some limitations of the study. We relied on data extracted from medical records and computerized outpatient clinic letters, which may not always be accurate. We did not measure improvement of disease activity using validated indices, but instead used the dichotomous outcome measures of need for colectomy and glucocorticosteroid-free remission. As the patients included in this study are from a tertiary referral centre, the data may not be generalizable to patients in other hospitals. However, the spectrum of disease is likely to be more severe in a population such as this, which may have led to an underestimate of the efficacy of IFX in this setting. Finally, although this is one of the largest retrospective single centre experiences of the use of IFX in acute severe UC reported, the absolute number of patients involved remains small, meaning that we were unable to identify any patient demographics or clinical characteristics that were independently associated with a response to IFX therapy or avoidance of colectomy during follow-up.

The results of this study are comparable with those found in an RCT conducted in Scandinavia by Järnerot *et al*[15], in which 71% of those treated with IFX for moderately severe or severe UC avoided colectomy over 90 d. Previous retrospective studies have demonstrated similar efficacy, with between 66% and 84% of other cohorts from the United Kingdom, Denmark and Canada avoiding colectomy during their index admission[20-23]. Retrospective studies comparing IFX with ciclosporin from New Zealand and Italy found that around 80% of patients treated with IFX avoided colectomy at 3 mo, compared with 37% and 72% respectively for ciclosporin[27,28]. Recent data from the United Kingdom national IBD audit suggest that, among those who failed first line treatment with intravenous glucocorticosteroids, response rates to IFX were generally higher than those with ciclosporin[29]. One multi-centre European RCT comparing IFX to ciclosporin head-to-head in this setting has been published recently[30], and another United Kingdom-based trial is ongoing[31]. The European trial recruited 115 patients with acute severe UC. There was no significant difference detected in rates of response to therapy at 7 d, failure of therapy after 98 d, or colectomy rates, leading the authors to conclude that the two treatments were equivalent, and that the choice of which of these therapies to use should be guided by physician and centre experience[30].

In the trial reported by Järnerot *et al*[15], IFX appeared to have a more marked effect in those with less severe disease activity. Our finding that surrogate measures of severity, including a higher CRP level on day 0 and day 3, and meeting the Travis criteria at day 3, were associated with higher colectomy rates during the index admission are consistent with this. In addition, over 30% of patients who avoided colectomy during their index admission received their first IFX infusion at day 5 or sooner, compared with only 11% of those who required colectomy. Although this result did not reach statistical significance it is noteworthy, and suggests that there may be a potential benefit associated with earlier use of IFX, before the acute episode has reached its full intensity. However, these results are not supported by the findings of a multi-centre Scottish study, in which colectomy rates were higher among those treated on day 5 or sooner, compared with those treated on or after day 6[20].

All patients in our study who underwent colectomy during the index admission were thiopurine-naïve. This is in contrast to both the Scandinavian and Scottish studies, in which thiopurine use prior to admission did not appear to affect need for colectomy[15,20], although the numbers of patients receiving thiopurines at the time of admission in both these studies were smaller. Those who were "bridged" to thiopurine therapy in our study, following an initial response to IFX, appeared less likely to require colectomy during subsequent follow-up, although a large French multicentre case series of IFX in UC, which included patients with both acute severe and chronic relapsing disease, found that immunomodulator use was not predictive of the need for IFX optimization, IFX failure, or colectomy[32]. However, the role of thiopurines and IFX in this setting is still evolving, with preliminary results from the UC SUCCESS trial showing superiority of combination IFX and azathioprine therapy over either therapy alone in the setting of moderate to severe UC[33].

In conclusion, this study provides further evidence for the efficacy and safety of IFX as rescue therapy in acute severe UC, in one of the largest cohorts of patients with a longer duration of follow-up than previously available from other retrospective, real-life data. Overall, 66% of patients were colectomy-free at study end, and 57% had also achieved glucocorticosteroid free-remission. Although serious adverse events were rare, the mortality rate of 2% is a reminder for clinicians of the profound effects of biological therapy on the im-

mune system, in a group of patients who are already seriously ill. The results of this study suggest that the use of IFX as a "bridge" to thiopurine therapy in patients with acute severe UC is highly effective, but even among patients who are already receiving, or are intolerant of, thiopurines the use of three-dose induction therapy with IFX may avoid the need for colectomy in a significant number.

COMMENTS

Background

Ulcerative colitis (UC) is a chronic inflammatory condition affecting the lower gastrointestinal tract. Acute exacerbations of inflammation are managed using intravenous glucocorticosteroids initially, but if these fail biological therapies can be used in an attempt to control inflammation and avoid the need for surgery. Infliximab (IFX) is a monoclonal antibody directed against tumour necrosis factor alpha.

Research frontiers

Whilst randomised controlled trials have established the efficacy of IFX in UC, there have been only two placebo controlled trials specifically in the context of acute severe UC. Since results from clinical trials are not always replicated under normal clinical conditions and over longer durations of follow-up, results from real-life experience are essential to provide further insight into the efficacy of IFX in this setting.

Innovations and breakthroughs

This single-centre review shows that, over longer follow-up periods and in real-life clinical settings, similar outcomes can be obtained to those in the original clinical trials, with two-thirds of patients avoiding the need for surgery. It also sheds light on the role of azathioprine alongside IFX therapy.

Applications

This study will inform clinicians and patients of the likely outcomes if IFX is used as rescue therapy in acute severe UC, unresponsive to steroid treatment.

Terminology

The use of IFX to treat an episode of acute severe UC was defined as need for the drug during an in-patient admission with an acute inflammatory exacerbation of disease activity.

Peer review

This is a well-done paper dealing with IFX rescue treatment of patients with UC. The authors are completely right that observations from real life situations are of much higher importance than those obtained from an artificial setting of a randomized controlled trial.

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