Treatment of acute ulcerative colitis with infliximab, a retrospective study from three Danish hospitals

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Rescue therapy;
Steroid-refractory

Abstract

Background: In acute steroid-refractory ulcerative colitis, rescue therapy with infliximab has become a therapeutic option in patients facing colectomy. Data on efficacy and safety in this setting are sparse.

Methods: Patients with ulcerative colitis and acute and severe steroid-refractory disease, who were given infliximab as rescue therapy, were identified by a review of patients’ records and databases of infliximab-treated patients. Data on patient background, concomitant medication, endoscopic and laboratory results, clinical activity and adverse events were collected.

Results: Fifty-six patients, all admitted because of high disease activity of short duration, and failing high-dose glucocorticoid treatment, received infliximab treatment and were followed up for a median of 538 days (range 2–1769). Colectomy was avoided in 61% of cases. No fatalities were observed. Concomitant medication at the end of follow-up indicated a low number of relapses in patients without colectomies.

Conclusions: Our results show a lasting benefit of infliximab rescue therapy in 61% of patients with acute, steroid-refractory ulcerative colitis, a low incidence of late colectomies, and low frequency of steroid use in patients who avoided colectomy. High levels of C-reactive protein on admittance and at the first infliximab infusion were associated with colectomy. Our study adds to the growing experience of infliximab treatment of patients with acute, steroid-refractory ulcerative colitis.

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1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterised by periodic flare-ups of colonic mucosal inflammation. Medical treatment consists of 5-aminosalicylates, steroids, immunomodulators, and biological agents with the aims of preventing flare-ups, treating active inflammation, and preventing surgery.

In acute and severe disease, which does not respond adequately to corticosteroid treatment, colectomy has formerly been the sole therapeutic option. Data have shown that about 30% of patients admitted for acute and severe diseases will not respond to corticosteroids and will need urgent colectomy. This strategy, high-dose corticosteroids and subsequent colectomy in non-responders, has reduced the mortality rate from more than 30% to 1–2%. However, the consequences of colectomy, which include the risk of surgical complications, reduced fecundity, a poorer quality of life and increased psychosocial burden, make the prospect of colectomy unattractive to many patients.

Over the past two decades, additional medical treatment as an alternative to colectomy has emerged as an attractive strategy in patients with steroid-refractory disease. However, the potential benefits of rescue therapy, remission, and the avoidance or significant postponement of colectomy, may be accompanied by risks to patients, including life-threatening adverse events.

Several agents have been used as rescue therapy, including cyclosporine and infliximab.

Cyclosporine, although effective in acute, severe UC, has been associated with risk of severe adverse events, in some cases with a fatal result, and a disappointing outcome in the longterm, prompting clinicians to consider alternatives.

Infliximab is a biological agent with proven efficacy in the treatment of moderate to severe UC. Despite its widespread use as therapy in steroid-refractory acute colitis, data on the safety and efficacy in this setting are sparse. Few randomized trials have been conducted, most of them with a small number of patients. The largest trial, included 45 Scandinavian patients with steroid-refractory colitis, who were randomized to infliximab or placebo. All patients had severe or moderately severe colitis according to the Seo clinical activity index. A subgroup of 28 patients had fulminant colitis as defined by the fulminant colitis index. Although the study documented the efficacy of infliximab in steroid-refractory UC, there was no significant difference in the fulminant colitis subgroup. Few retrospective studies have since been published.

Sporadic data and follow-up time on outcomes in acute infliximab rescue therapy raise the question whether the current approach to treatment of UC in this setting is appropriate.

Accordingly, we reviewed retrospectively colectomy rates, safety, and possible predictors of colectomy in Danish patients treated with infliximab for an acute steroid-refractory flare-up.

2. Materials and methods

Our study population consisted of patients from three hospitals in Denmark with an approximate referral population of 1.4 million. Patients who were given infliximab during the period of January 1999 to November 2008, and who met the predefined inclusion criteria set out below:

- A diagnosis of UC, based on clinical, endoscopic and histological criteria.
- Acute flare-up with severe clinical activity and onset of symptoms within 4 weeks of hospitalisation.
- Persistent activity despite treatment with high doses of systemic steroids for between three and 15 continuous days leading to subsequent infliximab therapy.
- Left-sided or more extensive disease at endoscopy.
- Surgical intervention considered in the event of treatment failure.

Exclusion criteria were significant comorbidities, which might influence short-term survival.

We designed a chart specifying the data to be registered: patient history, medication, clinical disease activity, and laboratory results before and during infliximab-administration, and recorded severe adverse events, defined as events resulting in death, disability, re-admission or prolonged hospital stay in the chart.

We reviewed local databases and cost-related registration systems for infliximab, in order to identify potential candidates for entry into the study. We systematically scrutinised a total of 263 candidate patient records, and excluded 102 infliximab-treated patients with colonic IBD type unclassified or Crohn’s disease and 105 infliximab-treated patients with UC, who were excluded according to the previous criteria, the majority (82%) because of chronically active disease or steroid-dependency. This left a total of 56 patients to be (Hvidovre: n=22, Aarhus: n=22 and Herning: n=12) entered in this study. None of the patients were excluded because of significant co-morbidity.

Activity was assessed by a simple colitis activity index (SCCAI) and Mayo score. Indices of activity were applied differently in the three hospitals, and were extracted from patients’ files if recorded at the time of admission and infliximab-administration, or calculated retrospectively from the data, if available.

Death, colectomy and medication use at the end of follow-up were taken as end points.

2.1. Statistics

Statistical analyses were performed using SPPS 17.0 (SPSS INC., Chicago, Illinois).

Unpaired data were analyzed statistically by Student’s t-test or the Mann–Whitney test as appropriate. Paired data were analyzed by paired Student’s t-test or Wilcoxon’s test as appropriate. Proportions between groups were analyzed by chi-squared test. Colectomy-free survival was plotted by the Kaplan–Meier survival analysis. A p value below 0.05 was considered significant.

2.2. Ethical considerations

The study was approved by the Danish Data Protection Agency, j.nr. 2008-41-2854.
3. Results

The patients’ background data for patients are listed in Table 1.

Patients were admitted for a median of 7 (range 2–22) days before infliximab therapy. Twenty-three patients received 80 mg of intravenous methylprednisolone and 33 patients received 1 mg/kg of oral corticosteroid for a median of 8 (range 3–15) days before initiation of infliximab, according to local practice at the time of the study. High-dose corticosteroids were in some patients started before admission. All patients received high-dose corticoids continuously at least until the first infliximab infusion. Almost half of patients were on oral 5-aminosalicylate treatment at admission, and about one in four were on oral corticosteroids (see Table 2).

On admission, patients had high indices of clinical activity, as reflected by the SCCAI (median 10, interquartile range 9–12) and modified Mayo scores (median 8, interquartile range 8–9).

Over a median of 538 (range 2–1769) days of follow-up, each patient received 1–9 doses of infliximab 5 mg/kg.

Clinical and laboratory characteristics of patients are shown in Table 3.

Twenty-two patients (39%) underwent colectomies on a median of 17 (range 2–651) days after the first infliximab infusion.

The 14-day colectomy rate was 18% (10/56). On day 90, this had increased to 30% (17/56), as shown in Fig. 1.

There were no statistically significant differences between patients who underwent colectomy and those who did not with regard to creatinine, haemoglobin and albumin on admission and at the first infliximab infusion. Patients who underwent colectomy had significantly higher CRP on admission (p = 0.036) and at first infusion (p = 0.012), and a tendency towards lower albumin, as shown in Table 4.

The SCCAI and Mayo scores were similar in the two groups (Table 4).

### Table 1 Background data.

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32 (16–78)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>31 / 25</td>
</tr>
<tr>
<td>Smoking (current/previous)</td>
<td>6%/37%</td>
</tr>
<tr>
<td>Duration of disease since diagnosis (days)</td>
<td>274 (94–9554)</td>
</tr>
<tr>
<td>No. of patients on high-dose corticosteroid treatment in the preceding 2 years of current attack</td>
<td>11/56 (19.6%)</td>
</tr>
<tr>
<td>Diagnosis of UC at current admission</td>
<td>21/56 (37.5%)</td>
</tr>
</tbody>
</table>

### Table 2 Patient medication at admission.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral 5-ASA</td>
<td>26/56 (48%)</td>
</tr>
<tr>
<td>Local 5-ASA</td>
<td>9/56 (35%)</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>13/56 (23%)</td>
</tr>
<tr>
<td>Local corticosteroids</td>
<td>7/56 (13%)</td>
</tr>
<tr>
<td>Azathioprine/6-monophosphates</td>
<td>1/56 (2%)</td>
</tr>
</tbody>
</table>

### Table 3 Clinical and laboratory characteristics on admission and at the first infliximab infusion.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>On admission</th>
<th>At first infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP mg/L [1–10]</td>
<td>42 (19–87)</td>
<td>29 (10–53)</td>
</tr>
<tr>
<td>Albumin, g/L [36–45]</td>
<td>38.0 (33–41)</td>
<td>34.1 (31.1–38.8)</td>
</tr>
<tr>
<td>Haemoglobin, mmol/L [8–10.3]</td>
<td>8.1 (7.4–8.9)</td>
<td>7.8 (7.2–8.4)</td>
</tr>
<tr>
<td>Creatinine, μmol/mL [70–110]</td>
<td>74 (66–83)</td>
<td>74 (62–84)</td>
</tr>
<tr>
<td>SCCAI score</td>
<td>10 (9–12)</td>
<td>9 (6–11)</td>
</tr>
<tr>
<td>No. of stools/24 h</td>
<td>10 (8–15)</td>
<td>8 (6–10)</td>
</tr>
<tr>
<td>Modified Mayo score</td>
<td>8 (7–8)</td>
<td>7 (6–8)</td>
</tr>
</tbody>
</table>

All numbers are medians; brackets indicate reference intervals, parentheses interquartile ranges.

3.1. Follow-up

Patients who avoided colectomy (n = 34) were followed for a median of 919 days (range 146–1769 days).

In the group of patients who did not undergo surgery, 16 patients were on maintenance treatment with 5-ASA, 22 with azathioprine or 6-mercaptopurine, and six patients were receiving local 5-ASA alone or in combination with oral treatment at follow-up.

Infliximab treatment regimens varied, according to clinicians’ assessment. In some instances, only one infusion was planned, in others a three-dose induction regimen of infusions on weeks 0, 2 and 6 was preferred.

Beyond the eighth week of the initial infusion, 16 patients had further infliximab infusions and five of these were colectomised.

In the 34 patients who avoided colectomy, seven patients had a subsequent flare-up, which was treated with high-dose corticosteroids. Two of these patients were tapering off corticosteroids at follow-up. One of the seven patients had two flare-ups.

Of the 24 patients, who had three or more infusions, six had colectomies after a median of 256 (range 54–651) days of...
follow-up. Twenty-six patients had only one infusion, and 50% of these patients underwent colectomy after a median of 7 days (range 2–61). All patients were accounted for at follow-up.

In patients who avoided colectomy, 18 patients had either steroid or further infliximab infusion beyond week 6. In the 11 patients who received further infliximab infusions, six patients had a total of four infusions, and five patients had between five and nine infusions. One patient was planned to have further infliximab infusions.

Twenty-one patients were diagnosed with ulcerative colitis at the admission leading to infliximab treatment. There were no statistically significant difference in the colectomy rate of patients suffering their first attack of ulcerative colitis (9/21) and patients with a previously established diagnosis of ulcerative colitis (13/35) (p = 0.78).

Patients with a CRP below the median of 29 mg/L at the first infusion had a significantly reduced risk of colectomy (log-rank test, p = 0.035) when compared to patients with CRP above 29 mg/L (see Fig. 2).

### 3.2. Adverse events

Two patients had severe infusion-related adverse events and were switched from infliximab to adalimumab. One patient developed severe respiratory insufficiency requiring mechanical ventilation treatment 2 days after the first infliximab infusion. The presumed infectious agent was never identified, and the patient recovered fully.

No patients died during follow-up.

### 4. Discussion

The aim of the present study was to investigate, whether or not treatment with infliximab is a relevant therapeutic alternative to surgery with respect to safety and outcome. We found, that despite selection of patients with the most severe activity of the disease with insufficient response to high-dose steroids, 61% of the patients avoided colectomy.

The majority of colectomies were done shortly after the first treatment with infliximab.

The 90-day colectomy rate was 31% (17/55), and thus lower than the 47% noted in the fulminant colitis subgroup of the Järnerot trial.8

*Table 4* Influence of biochemical and clinical findings at admission on outcome.

<table>
<thead>
<tr>
<th>Patients who did not undergo surgery</th>
<th>Patients who underwent surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP mg/L [1–10]</td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td>(10–77)</td>
</tr>
<tr>
<td>Albumin, g/L [36–45]</td>
<td>38.8</td>
</tr>
<tr>
<td></td>
<td>(32.8–41.9)</td>
</tr>
<tr>
<td>Haemoglobin, mmol/L [8–10.3]</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>(7.5–9.2)</td>
</tr>
<tr>
<td>Creatinine, μmol/mL [70–110]</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>(68–86)</td>
</tr>
<tr>
<td>SCCAI score</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>(8–11)</td>
</tr>
<tr>
<td>No. of stools/24 h</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>(8–15)</td>
</tr>
<tr>
<td>Mayo score</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>(7–8)</td>
</tr>
</tbody>
</table>

All numbers are medians; brackets indicate reference intervals, parentheses ranges.

<sup>a</sup> P = 0.036 versus CRP of patients who did not undergo colectomy.

We assessed relapse in patients who avoided colectomy by use of medication, finding administration of additional infliximab infusions outside 8 weeks of the initial infusions in 18 patients, but few cases of further steroid-courses. In our opinion, this indicates a low frequency of relapse in these patients.

In the present study, we found significantly lower CRP on admission and at the first infliximab infusion in patients avoiding colectomy.

In an Italian multicentre study by Kohn et al.,9 86 patients with acute colitis which did not respond to intravenous corticosteroid treatment, received infliximab and were followed up for a median of 18 months. Seventy percent

![Figure 2](https://academic.oup.com/ecco-jcc/article-abstract/5/1/28/367057/6776)
avoided colectomy and 58% were in remission at follow-up. The Kohn study demonstrated a trend towards lower serum CRP at the first infliximab infusion in patients who avoided colectomy. On days three and seven after infusion, the difference in CRP reached statistical significance, low CRP predicting avoidance of colectomy. These findings, in accordance with our work, add weight to the suggestion that CRP may be a predictive factor for outcome in rescue therapy.

In their study from Scotland, Lees et al. identified 39 patients with acute UC who were treated with infliximab. A total of 67% avoided colectomy at the initial admission, and were followed up for a median of 203 days, although patients lost to follow-up hamper long-term conclusions. In that study, low albumin was found to predict colectomy, a finding parallel to the low albumin of patients who underwent colectomy in our study, where the difference, however, did not reach statistical significance.

If prospectively validated, the benefit of a predictor would be considerable, since the postponement of unavoidable colectomy prolongs the suffering of the patient, is associated with the risk of severe adverse events and higher costs, and because an increase in the risk of postoperative complications in infliximab-treated patients cannot be ruled out.

Severe adverse events were seen in 5.3% of patients, necessitating withdrawal of the drug in all cases. The types of adverse reactions observed, namely infectious complications and infusion-related reactions are of a similar nature to those reported in other studies of infliximab-treated patients. Our frequency was somewhat lower, though not dissimilar to numbers reported in Kohn’s work, and the Jänerot trial of infliximab in ulcerative colitis, and the retrospective design may have caused underreporting of adverse events.

The strengths of the present study include the size and relatively long follow-up of patients; the limitations to this study include the retrospective nature of the study, and varying times of follow-up.

At the time of the study period, no guidelines on selection of treatment strategy with respect to single infusion or induction treatment followed by on demand or maintenance treatment of infliximab were available in Denmark. Accordingly, local or individual preferences guided the treatment strategy. Accordingly, local or individual preferences guided the treatment strategy. The present study cannot therefore provide any clue as to whether maintenance treatment or treatment on demand with infliximab should be preferred as follow-up to rescue therapy.

Although all patients were given high-dose corticosteroid treatment with clinically inadequate response, the selection of the maintenance therapy up to this flare-up may have influenced outcomes, and due to the retrospective design we cannot entirely rule out the possibility, that some patients might have avoided the flare-up and eventual infliximab treatment had the maintenance treatment strategy been different. A high proportion of patients was diagnosed with ulcerative colitis during admission and had never been previously treated with aminosalicylates or immunomodulators. Although newly diagnosed patients and patients with previously established disease did not differ significantly with regard to colectomy rates, the high proportion of treatment-naïve patients may have affected outcomes.

Infliximab is in Denmark only administered at public hospital centres, and the use of a unique personal identification number makes it possible to track patients with great confidence. We are therefore convinced that all patients with acute UC treated at the three hospitals were identified and included. The central hospital organisation for treatment of refractory IBD in Denmark makes it unlikely that patients could have died or been operated on without being registered in this study.

This study adds to the growing body of evidence of infliximab-use in acute, steroid-refractory UC, and, despite the occurrence of severe adverse events, we observed a considerable surgery-free follow-up time, with a low number of renewed infliximab infusions and steroid use. In our opinion, this indicates a low occurrence of relapse.

Whether the reason for this is the rather high number of patients treated with immunomodulators, or a change in the natural course of the disease after infliximab, or simply reflects that the natural course after a severe attack in many patients is followed by a much more benign course than previously expected, should be investigated in future studies.

The present and previously published retrospective studies indicate a favourable outcome in a high proportion of infliximab-treated patients with severe steroid-refractory disease. In cyclosporine rescue therapy however, even longer observation periods have been published, and although some authors find outcomes disappointing with regard to estimated avoidance of surgery in the long term (12% at 7 years by life-table analysis), others have found a considerable long-term avoidance of surgery 44% after a median follow-up of 5 years.

A randomised trial comparing infliximab and cyclosporine with a long-term follow-up would be informative, although similar colectomy rates of the two drugs in previously published studies suggest that a large number of patients would be needed to demonstrate superiority of one drug over another with regard to surgical outcome.

Other questions for future studies include whether long-term infliximab maintenance treatment as immunotherapy, or in combination with immunomodulators, or induction therapy with infliximab followed by immunomodulators should be preferred.

In conclusion: Treatment with infliximab in patients with a severe attack of UC is relatively safe and prevents colectomy in about 60% of patients after a median follow-up of 538 days.

Disclosures

Dr Mortensen has received an unrestricted grant from Schering-Plough, who marketed infliximab in Denmark during the study period. Dr Bendtsen and Dr Christensen are members of an advisory board for Schering-Plough.

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FB conceived the study. FB, LC and CM designed the study protocol. CM, SC, NT, LS, NC, and LC collected data. CM, SC,
and FB drafted the manuscript and coordinated data collection. All authors read and approved of the manuscript.

Christian Mortensen has received an unrestricted research grant from Schering-Plough, the company, who during the study period marketed infliximab in Denmark.

Dr. Bendtsen and Dr. Christensen are members of an advisory board for Schering-Plough. Schering-Plough had no influence on the study design, data collection, analysis or interpretation of data, writing of the manuscript, or the decision to submit the manuscript for publication.

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