Infliximab in inflammatory bowel disease: clinical outcome in a population based cohort from Stockholm County

T Ljung, P Karlén, D Schmidt, P M Hellström, A Lapidus, I Janczewska, U Sjöqvist, R Löfberg

**Background:** Several placebo controlled studies have demonstrated the efficacy of infliximab in inflammatory bowel disease (IBD) but the potential toxicity of this new biological compound has been less studied.

**Aim:** To assess the use of infliximab in IBD in a population based cohort, with special emphasis on the occurrence of severe adverse events and mortality.

**Patients:** All patients with IBD treated with infliximab between 1999 and 2001 in Stockholm County were evaluated.

**Methods:** Prospective registration of clinical data was carried out. Retrospective analyses were made of possible adverse events occurring in relation to infliximab treatment. Adverse events requiring pharmacological treatment or hospitalisation were defined as severe. Clinical response was assessed as remission, response, or failure.

**Results:** A cohort comprising 217 patients was assembled: 191 patients had Crohn’s disease (CD), and infliximab was used off label for ulcerative colitis (UC) in 22 patients. Four patients were treated for indeterminate colitis (IC). Mean age was 37.6 (0.9) years (range 8–79). The mean number of infliximab infusions was 2.6 (0.1) (range 1–11). Forty two severe adverse events were registered in 41 patients (CD, n = 35). Eleven of the severe adverse events occurred postoperatively (CD, n = 6). Three patients with CD developed lymphoma (of which two were fatal), opportunistic infections occurred in two patients (one with UC, fatal), and two patients with severe attacks of IBD died due to sepsis (one with CD, one postoperatively with UC). One additional patient with UC died from pulmonary embolism after colectomy. Mean age in the group with fatal outcome was 62.7 years (range 25–79). The overall response rate was 75% and did not differ between the patient groups.

**Conclusions:** Infliximab was efficacious as an anti-inflammatory treatment when assessed in a population based cohort of patients with IBD. However, there appear to be a significant risk of deleterious and fatal adverse events, particularly in elderly patients with severe attacks of IBD. Off label use of infliximab in UC and IC should be avoided until efficacy is proven in randomised controlled trials. The underlying risk of developing malignancies among patients with severe or chronically active CD in need of infliximab treatment is not known but the finding of a 1.5% annual incidence of lymphoma emphasises the need for vigilant surveillance with respect to this malignant complication.

**Abbreviations:** TNF-α, tumour necrosis factor alpha; CD, Crohn’s disease; UC, ulcerative colitis; IBD, inflammatory bowel disease; IC, indeterminate colitis; GCS, glucocorticosteroids; 6-MP, 6-mercaptopurine; 5-ASA, 5-aminosalicylic acid
azathioprine or 6-mercaptopurine (6-MP) does not seem to confer an increased risk of malignancy.16 17

The main aim of the present study was to evaluate the outcome of infliximab treatment for IBD conditions in a population based setting in Stockholm County, Sweden. Special emphasis was directed towards treatment of patients with severely active IBD and towards the outcome of major surgery in those patients where infliximab treatment failed. In addition, postoperative complications were monitored. The overall incidence of severe adverse events and mortality were also assessed.

Simple analysis of efficacy was carried out in order to compare the results in the study cohort with those obtained in previous clinical trials.

MATERIALS AND METHODS

Study population and design

To accurately assess the efficacy of infliximab and adverse events in clinical use, we evaluated all patients with IBD, including CD, ulcerative colitis (UC), and indeterminate colitis (IC) patients, treated with infliximab in Stockholm County between January 1999 and April 2001.

Eleven medical centres contributed to the study, including two academic paediatric gastroenterology units, accounting for all centres providing infliximab treatment for IBD in this area with a registered total population of 1 831 046 inhabitants (as of 31 December 2001). From the launch of infliximab in Sweden, consecutive patients with IBD in Stockholm County were prospectively included into the study database at the time of their first infusion. The following data were recorded: age, sex, diagnosis and anatomical distribution of IBD, concomitant medical treatment, indication for infliximab, number of infusions, clinical response, severe adverse events, surgical intervention, as well as 30 day postoperative outcome.

Infliximab (Remicade; Centocor, Malvern, Pennsylvania, USA) was administered at a dose of 5 mg/kg body weight as a two hour intravenous infusion. The total number of infusions given to each patient was dependent on the indication.

Patients received infliximab during their hospital stay in cases of severely active IBD or as outpatients if activity was moderate. All patients were monitored for adverse advents during and at least one hour after infusion. Clinical response and late adverse events were evaluated at the follow up clinical visit. To assess the clinical response, a simple three step category scale according to Cohen and colleagues18 was used: for patients with luminal disease, failure implied no change or worsening of symptoms; response implied improvement or tapering of glucocorticosteroids (GCS) without worsening; and remission implied absence or near absence of all clinical symptoms without an increase in GCS dose. For patients with fistulising disease, failure implied no change or worsening of symptoms, response implied improvement of at least one fistula, and remission implied closing of all fistulas.

Clinical outcome was assessed one month after the first infliximab infusion in cases of luminal disease, and one month after the third infliximab infusion in cases of fistulising disease.

A severe adverse event was defined as clinical symptoms that required active pharmacological treatment and/or hospitalisation, and thus did not include minor and more common infusion reactions such as pruritus, rash, headache, “flu”-like symptoms, or chest-pain, if those conditions did not require medication or observation.

The incidence of lymphoma and malignancy was compared with the overall incidence of malignancy in the Stockholm County background population 1999–2001, based on data from the National Cancer registry which records all cancers in Sweden.

The protocol was approved by the regional ethics committee at the Karolinska Institute in Stockholm.

Statistical methods

Quantitative variables are described as mean (SEM). Groups were compared using the Kruskal-Wallis test followed by Dunn’s post test. A p value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study population

A total of 217 patients (105 women and 112 men; mean age 37.6 (0.9) years (range 8–77)) received a mean of 2.6 (0.1) infliximab infusions (range 1–11)). The majority of patients had CD (n = 191), 22 had UC, and the remaining four had IC.

Among patients with CD, involvement was limited to the small bowel in 13 (7%), it was ileocolonic in 67 (35%), and colorectal in the remaining 111 (58%) patients. In CD patients, the indication for infliximab infusion was active luminal disease in 148 (77%) cases and perianal fistulas in 43 (23%). In nine patients with UC, the reason for infliximab infusion was longstanding GCS refractory left sided disease, and in the remaining UC patients the indication was acute GCS refractory extensive colitis (n = 12) or active inflammation in the remaining rectum after ileorectal anastomosis (n = 1). Four patients had longstanding GCS dependent IC.

A total of 111 (51%) were receiving concomitant therapy with azathioprine or 6-MP, 117 (54%) had GCS treatment, and 54 patients (25%) were receiving both azathioprine/6-MP and GCS treatment. Eighty patients (37%) were on long term 5-aminosalicylic acid treatment. Forty three patients (20%) received therapy with oral metronidazole.

Severe adverse events and mortality

In 41 patients, a total number of 42 severe adverse events were observed (table 1) during the study period. Eleven of those events were related to surgery.

Six fatal adverse reactions were encountered (table 2). Death was caused by lymphoma in two cases (both with CD),

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**Table 1** Severe adverse events

<table>
<thead>
<tr>
<th>Severe adverse event</th>
<th>No</th>
<th>Fatal</th>
<th>CD:UC</th>
<th>Specific comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>3</td>
<td>2</td>
<td>3:0</td>
<td>One NK cell lymphoma and two B cell lymphomas</td>
</tr>
<tr>
<td>Infection</td>
<td>11</td>
<td>2</td>
<td>7:4</td>
<td></td>
</tr>
<tr>
<td>Postoperative infection</td>
<td>7</td>
<td>1</td>
<td>4:1</td>
<td></td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>5</td>
<td>1</td>
<td>4:1</td>
<td></td>
</tr>
<tr>
<td>Delayed hypersensitivity reaction</td>
<td>5</td>
<td>0</td>
<td>5:0</td>
<td></td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>3</td>
<td>0</td>
<td>3:0</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>3</td>
<td>0</td>
<td>3:0</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** CD, Crohn’s disease; UC, ulcerative colitis; NK, natural killer.
three patients (one with CD, two with UC) died from infectious complications (of which one occurred postoperatively), and pulmonary embolism led to death in one patient with UC following colectomy. Mean age was 62.7 years (range 25–70).

One further case of lymphoma developed in a patient with CD, a 24 year old woman with colonic CD in whom the indication for infliximab therapy was steroid refractory luminal disease in combination with a history of azathioprine intolerance. No other patient developed malignancy. The overall annual incidence of lymphoma was 1.5% in this cohort compared with an overall population based value of 0.015% in the background Swedish population.

Two patients experienced severe opportunistic infections. One patient with UC had a fatal infection with *Pneumocystis carinii*, and one patient with CD was infected with *Listeria meningitis* but recovered. No cases of tuberculosis occurred in this cohort.

### Surgical intervention and 30 day postoperative outcome

Forty one patients (mean age 39.5 (1.96) years (range 20–77)) required major surgical treatment due to an unsatisfactory response to medical treatment. Thirty three of the operated patients had CD and eight had UC.

In 26 patients, colectomy was performed. Four had small bowel resections and in two patients the remaining rectum was removed post-colectomy. In one case a loop ileostomy was performed. One patient had a parastomal abscess that was drained. In the remaining seven patients surgical interventions were directed towards perianal fistulas.

Eleven cases (six CD and five UC) with severe complications were seen within the first 30 day postoperative period. Two of those complications were fatal, and both occurred in elderly men given infliximab off label for UC (one case of sepsis in a 67 year old man and one case of pulmonary embolism in a 73 year old man). Two further thromboembolic complications were seen following colectomy in patients with UC. Two cases of impaired wound healing were seen after proctectomy in patients with CD and in two cases colectomy was complicated by the development of pelvic abscesses (one CD and one UC) (table 3).

### Efficacy data

The overall response rate in all forms of IBD was 75% (n = 163). In 48% (n = 104) remission was achieved and in 25% infliximab failed to show any response (n = 54). No significant difference in response rates was seen between the different diagnostic groups.

### DISCUSSION

The present study reports for the first time on the experience of infliximab in the clinical setting of IBD in a strictly population based cohort. The study comprised all IBD patients treated in Stockholm County between 1999 and 2001. This enabled us to assess infliximab therapy in an epidemiological context with regard to severe adverse events, including postoperative complications, serious infections, malignancies, and deaths. In our clinical experience with infliximab in an unselected IBD population, we encountered more severe adverse events than expected from earlier reports. A total of six deaths were seen; all of those


table 2

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age</th>
<th>Sex</th>
<th>Concomitant medication</th>
<th>No of infusions</th>
<th>Time between first infusion and adverse event</th>
<th>Cause of Death</th>
<th>Specific comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>25 M</td>
<td></td>
<td>Azathioprine+GCS</td>
<td>1</td>
<td>1 y</td>
<td>NK cell lymphoma</td>
<td>Tissue staining positive for TNF-α</td>
</tr>
<tr>
<td>CD</td>
<td>79 M</td>
<td></td>
<td>GCS</td>
<td>1</td>
<td>1 y</td>
<td>B cell lymphoma</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>57 M</td>
<td></td>
<td>GCS</td>
<td>1</td>
<td>6 weeks</td>
<td>Pneumocystis carinii, Progressive pulmonary fibrosis and respiratory failure</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>73 M</td>
<td></td>
<td>GCS</td>
<td>1</td>
<td>2 weeks</td>
<td>Post-op pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>67 M</td>
<td></td>
<td>GCS</td>
<td>1</td>
<td>2 weeks</td>
<td>Postop septicemia and respiratory failure</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>75 M</td>
<td></td>
<td>Rectal GCS</td>
<td>3 (0, 2, 6 weeks)</td>
<td>6 weeks</td>
<td>Purulent bronchitis with recurrent septicemia</td>
<td></td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; UC, ulcerative colitis; NK, natural killer; GCS, glucocorticosteroids; TNF-α, tumour necrosis factor α.


table 3

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age</th>
<th>Sex</th>
<th>Concomitant medication</th>
<th>No of infusions</th>
<th>Surgery</th>
<th>Complications</th>
<th>Specific comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>35 F</td>
<td></td>
<td></td>
<td>1</td>
<td>Resection</td>
<td>Anastomosis leakage and sepsicaemia</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>35 F</td>
<td></td>
<td>GCS + 5-ASA</td>
<td>6</td>
<td>Proctectomy</td>
<td>Impaired wound healing</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>47 F</td>
<td></td>
<td></td>
<td>1</td>
<td>Colectomy</td>
<td>Pelvic abscess</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>36 M</td>
<td></td>
<td>Azathioprine + metronidazole</td>
<td>6</td>
<td>Fistula</td>
<td>Small bowel obstruction</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>26 M</td>
<td></td>
<td>Azathioprine + GCS + 5-ASA</td>
<td>2</td>
<td>Colectomy</td>
<td>Haematuria</td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>31 M</td>
<td></td>
<td>Azathioprine</td>
<td>3</td>
<td>Proctectomy</td>
<td>Impaired healing</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>38 F</td>
<td></td>
<td>Azathioprine + 5-ASA</td>
<td>1</td>
<td>Colon resection</td>
<td>Deep venous thrombosis</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>67 M</td>
<td></td>
<td>GCS</td>
<td>1</td>
<td>Colectomy</td>
<td>Septicaemia</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>73 M</td>
<td></td>
<td>GCS</td>
<td>1</td>
<td>Colectomy</td>
<td>Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>20 M</td>
<td></td>
<td>Azathioprine + GCS + 5-ASA</td>
<td>1</td>
<td>Colectomy</td>
<td>Pelvic abscess</td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>27 M</td>
<td></td>
<td>GCS + 5-ASA</td>
<td>3</td>
<td>Colectomy</td>
<td>Deep venous thrombosis</td>
<td></td>
</tr>
</tbody>
</table>

CD, Crohn’s disease; UC, ulcerative colitis; GCS, glucocorticosteroids; 5-ASA, 5-aminosalicylic acid.
patients had received a single dose (5 mg/kg) of infliximab. The annual mortality rate among IBD patients in Stockholm County has been historically low, with a standardised mortality ratio of 1.51 for CD and 1.37 for UC.\(^2\) Two of the fatalities occurred postoperatively, giving a mortality rate of 4.9%, which is higher than that previously reported from St Mark’s Hospital\(^3\) in patients operated on for UC, and sixfold greater compared with contemporary material from Stockholm County comprising 381 patients with CD operated on between 1985 and 1994 (Lapidus, personal communication).

A 2.8% mortality rate during a two year follow up of a Scandinavian cohort of IBD patients is exceptional and has not been reported previously.\(^3,\)\(^4\)

Three patients developed lymphoma, two of which were fatal. In view of the young mean age of our study population, the number of lymphomas appears to be high. However, as our study population lacked a strictly matched control group (that is, with a similar disease pattern, duration, medication, etc), no definite conclusions can be drawn from the lymphoma cases that developed in the infliximab cohort. However, the annual overall incidence of non-Hodgkin-type lymphomas in Stockholm County was 0.015% in 2001 compared with the >100 times increased annual incidence of 1.5% in our cohort study. An age matched comparison results in a >1000-fold increase, as the occurrence of lymphomas in the 20–30 year old group of Swedish citizens is extremely rare.

However, controversy remains regarding the risk of lymphoma in IBD. Earlier reports from referral or hospital based IBD patients have demonstrated an increased baseline risk of lymphoma.\(^2,\)\(^3\)\(^5\) Recent epidemiological studies from Sweden, Canada, and Italy are all suggestive of a low risk.\(^1,\)\(^2\)\(^12\)–\(^15\) Although patients in our study were recruited from a population based cohort, hospital or referral bias may have influenced the underlying risk of lymphoma. In one of the lymphoma patients, a 25 year old woman with CD, there was a very short time span between infliximab infusion and the diagnosis of malignant disease. Normally, this would suggest a lower probability of a causal relationship between malignancy and the study drug. However, we know little of the possible effects and temporal relations of infliximab in IBD patients prone to develop lympho- or myeloproliferative disease. Anti-TNF-\(\alpha\) blocking compounds may exert hitherto poorly understood effects that could facilitate the promotion of lymphoma development. This could imply that a short time frame between drug exposure and the diagnosis of lymphoma does not necessarily exclude a potential relationship. One of the other three lymphoma cases in this study was a 25 year old male who received one 5 mg/kg infusion and was diagnosed with a natural killer cell-type of lymphoma in the spleen one year later. This patient has previously been reported in the ACCENT I trial.\(^6\) He succumbed six months after diagnosis despite having received several courses of anti-lymphoma cytotoxic drugs.

In patients with a high risk of infection, immunosuppressants should only be used after thorough consideration of the risk versus benefit ratio. Previous studies indicate that inhibition of TNF-\(\alpha\) with infliximab may lead to specific rather than generalised immune suppression.\(^2\)\(^9\)\(^10\) which theoretically would give infliximab a better risk-benefit profile compared with azathioprine/6-MP or cyclosporin. However, 101 cases of tuberculosis have been reported after infliximab therapy, and an association between this treatment and reactivation of tuberculosis has been deemed plausible.\(^7\)\(^11\) In the light of this, labelling of infliximab has been adjusted accordingly both in Europe and in the USA.

Considering the previously reported case of aspergillosis\(^5\) and our cases of fatal Pneumocystis carinii and life threatening Listeria meningitis, it is reasonable to suspect that treatment with infliximab leads to an increased risk of potentially severe opportunistic infections. Whether or not infliximab treatment contributed to fatal septicemia in the two elderly men in our study is difficult to ascertain as both men were at high risk of contracting infection. In the ACCENT I trial, two deaths from septicemia were reported. One case was probably not associated with infliximab treatment but the other case, a 35 year old woman, died from sepsis following bowel resection after infliximab treatment.\(^6\)

Overall, the variety of severe events associated with the use of infliximab for IBD in this study mirrors that reported recently from the Mayo Clinic. In that retrospective study, 500 patients received between one and 46 infusions and they reported three patients with malignancy, 41 patients with infectious events, and five deaths possibly related to infliximab.\(^12\)

The efficacy of infliximab treatment in our study closely resembles the results of earlier controlled trials\(^1,\)\(^2\)\(^4\) and those reported in other large open studies.\(^18\)\(^20\) We did not encounter significant efficacy differences between the IBD subgroups. Our off label experience in UC correlates well with previous small studies\(^13\)\(^16\) but preliminary results from a randomised placebo controlled study of infliximab in GCS refractory UC were found to be negative.\(^5\)\(^6\)

In conclusion, our study shows that the efficacy of infliximab, as demonstrated in controlled trials, is reproducible in a population based IBD cohort comprising mainly CD patients. However, a 3% mortality rate in association with infliximab treatment implies that vigilance in drug surveillance needs to be emphasised, particularly with regard to opportunistic infections and development of lymphoma. In light of the observed severe adverse events, off label use of infliximab in UC cannot be recommended until prospective randomised trials have proven that the drug is appropriate for this indication.

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