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Safety Aspects of Infliximab in Inflammatory Bowel Disease Patients

A Retrospective Cohort Study in 100 Patients of a German University Hospital

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Key Words

Infliximab · Inflammatory bowel disease Safety · Crohn's disease

Abstract

Background: Infliximab, a chimeric anti-tumour necrosis factor monoclonal antibody with potent anti-inflammatory effects, represents an effective treatment option in patients with severe inflammatory bowel disease (IBD). Serious side-effects of such an immunomodulating therapy are speculated and therefore we reviewed our clinical experience in a retrospective safety study looking upon a single cohort of 100 IBD patients from a large German University Hospital. ***Methods:*** 100 patients with severe Crohn's disease (n = 92), ulcerative colitis (n = 7) or indeterminate colitis (n = 1) treated with infliximab (5 mg/kg) from January 2000 to December 2003 were retrospectively analysed for acute and subacute adverse events by chart review. ***Results:*** Overall, infliximab therapy was generally well tolerated. No fatal complications, malignancies, autoimmune diseases, neurologic or cardiovascular complications were observed in the cohort during the study period. Overall, adverse events were observed in 10 patients: 2 patients showed an acute infusion reaction, 1 patient a serum sickness-like reaction, in 4 patients a bacterial or viral infection occurred, in 1 patient pancytopenia and 2 patients developed surgical complications. Only 6 patients with adverse events required admission to hospital. A case of tuberculosis after infliximab was not found. The lack of adverse side-effects was associated with young median age and infrequent comorbidities of the cohort. ***Conclusion:*** Regarding its strong immunomodulating capacity, infliximab appears to be an efficient and relatively safe therapeutic option for patients with severe IBD. However, the use of infliximab requires careful screening and close patient monitoring to identify patients at risk and the infrequent, but sometimes serious complications of infliximab.

Introduction

Infliximab is a chimeric monoclonal antibody comprised of 75% human and 25% murine sequences, binding with a high specificity and affinity to tumour necrosis factor (TNF)-α and thereby neutralising its immunological effects. TNF-α plays a pivotal role in the pathogenesis of mucosal inflammation in inflammatory bowel disease (IBD) [1]. The clinical efficacy of infliximab in the treatment of moderate to severe Crohn's disease, fistulae or steroid-refractory patients has been shown in several controlled clinical trials [2–6]. Furthermore, a major benefit

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for quality of life [7] and extra-intestinal manifestations in Crohn's disease [8–10] has been described.

Since TNF-α represents an important cytokine in the inflammatory response, the consequences of pharmacologically blocking its physiological functions raise serious concerns. Potential side-effects are tuberculosis [11], infections or hypersensitivity reactions [12, 13], malignancy or autoimmune disease [14]. Thus, the safety aspects of infliximab are of special interest. Although infliximab showed an acceptable safety profile in both premarketing and large clinical trials [2, 3, 15–21], there is an obvious need for further investigator publications on safety aspects resulting from growing experience in practice. We therefore performed a retrospective safety study on a single cohort of 100 IBD patients treated by us with infliximab. The patients were treated in our IBD out-patient clinic situated in a large academic setting.

Methods

Our survey included 100 IBD patients treated with infliximab at the Department of Internal Medicine II, Klinikum Grosshadern, University of Munich, Munich, Germany, between January 2000 and December 2003. Medical records of every patient in this study were reviewed for the following information: sex, age, diagnosis, duration of disease, previous medical history (including data on cardiovascular or pulmonary disease, neurologic disorders, autoimmune disease, cancer, dysplasia and infections), anatomic location of Crohn's disease or ulcerative colitis, endoscopic and laboratory results, previous treatment strategies, concomitant medication (corticosteroids, azathioprine, 6-mercaptopurine, methotrexate, mesasalazine), indication for infliximab administration and time and number of infliximab infusions. Complete medical files were available for all patients. Summary statistics for categorical variables were expressed as number (+ percentage); summary statistics for continuous variables were expressed as mean (+ range) where appropriate.

In all patients, a careful patient interview and examination were performed prior to treatment by a senior gastroenterologist. Our screening protocol was prompted by recommendations from the literature [17–20]. According to safety recommendations, patients with underlying infection or neoplasia, heart or lung disease or neurologic disorders were excluded from infliximab therapy. Our screening protocol further included a tuberculosis skin testing (0.1 ml s.c.) and an obligatory chest X-ray in order to exclude previous or present tuberculosis before starting the treatment. In addition, all patients with abdominal pain, elevated white blood cell count or C-reactive protein level underwent a CT or MRI of the abdomen excluding an intra-abdominal abscess formation. Infection with *Clostridium difficile* was excluded by stool microbiology. Female patients at birth-giving age were informed about the need of birth control.

Infliximab (Remicade; Centocor Inc., Malvern, Pa., USA) was administered in patients with active fistulizing Crohn's disease, active luminal Crohn's disease refractory to conservative treatment or in a rescue approach in patients with severe steroid-refractory ulcerative colitis or indeterminate colitis in a 2-hour intravenous infusion at a dose of 5 mg/kg. All infusions of infliximab were administered to hospital in-patients or out-patients at the Department of Internal Medicine II, Grosshadern, University of Munich. The staff is fully trained in the administration of infliximab infusions. During the infusion, vital parameters were checked every 30 min. In case of an adverse event, a senior gastroenterologist was called and the event and the action taken were documented in the medical file.

All patients in the out-patient clinic stayed for 2 h after the infusion with repeated controls of vital parameters. They reported to the physician 48 h after infusion by telephone. For follow-up, patients were seen and examined in the out-patient department and lab controls were performed on a regular base in order to assess efficacy and long-term safety. Clinical remission for patients with Crohn's disease was defined as a Crohn's disease activity index of ≤ 150 in patients with steroid-refractory active Crohn's disease or as closure of draining fistulae at week 8.

Results

Patient Characteristics

A total of 100 patients met the eligibility criteria for this retrospective cohort study. The study population consisted of 54 male and 46 female patients at the median age of 36 (range 18–65), in which Crohn's disease (n = 92), ulcerative colitis (n = 7) or indeterminate colitis (n = 1) was diagnosed by clinical parameters, laboratory results and endoscopic/histologic findings (table 1). No children or adolescents under the age of 18 were included. The median follow-up after the last infliximab infusion was 26 months (range 3–48 months) with only 3 patients (3%) having <6 weeks of follow-up. Eighty-two of 100 patients received concomitant immunosuppressive medication (azathioprine, n = 64; 6-mercaptopurine, n = 18), mesasalazine (n = 10) or corticosteroids (n = 42).

Results of Patient Screening

As a result of our intensified safety protocol prior to treatment, 2 patients were shown to have positive test results for tuberculosis skin tests and were therefore excluded from infliximab therapy. Fourteen patients were shown to have an intra-abdominal abscess or an intestinal stenosis in CT or MRI and therefore had to undergo surgery or antibiotic treatment. All these patients showed an elevated C-reactive protein level or white blood cell count and a significant clinical history of abdominal pain or fever. Of the 14 patients initially excluded from infusion therapy, 6 patients received infliximab in their further medical course after completion of surgical or antibiotic treatment. In all 6 patients, no complications were observed.

Infliximab Therapy

Infliximab was given to patients with active fistulizing Crohn's disease or active luminal Crohn's disease refractory to conservative treatment, intolerant to immunosuppressive therapy or with contraindications to steroids (n = 92; table 1). In addition, our cohort included a small number of patients with severe steroid-refractory ulcerative colitis (n = 7) or indeterminate colitis (n = 1). Overall, a total of 322 infusions was given in 100 patients (median number of infusions 3, range 1–7). Ninety-two patients received an infliximab infusion at weeks 0, 2 and 6 following the three-dose induction regimen, 8 patients only had a single infusion for induction. Eighty-six of the 100 patients treated (86%) were shown to be in clinical remission after induction therapy (week 8). Fifteen patients required repeated infliximab infusions in an on-demand maintenance therapy regimen (4–7 times); 71 patients stayed in remission on immunosuppressive medication (azathioprine or 6-mercaptopurine). Reduction or cessation of steroids was possible in 38 patients.

Adverse Events

Overall, infliximab therapy was well-tolerated in 90 of 100 patients (90%). Serious adverse events were infrequent. In our cohort, no fatal complication, malignancy or neurologic or cardiovascular complication was noted during the observation period; furthermore, no new onset of autoimmune disease was diagnosed. Adverse events documented in the observation period occurred in 10 of 100 patients (10%), including 2 patients with acute infusion reactions (2%), 1 patient with a mild serum sickness-like reaction (1%), 4 patients with bacterial or viral infections (4%), 2 patient with surgical complications (2%) and 1 patient with pancytopenia (1%) (table 2). However, 5 adverse events reported below in detail (5%) have to be critically reviewed in their relation to infliximab analysing parameters like the time interval between therapy and the onset of side-effects or concomitant medication. Overall, 6 events were classified as serious adverse events requiring admission to hospital (6%). All adverse events were successfully managed with medication and without sequelae.

Infusion Reactions and Serum Sickness-Like Disease

In our cohort, we observed 2 patients with acute infusion reactions and 1 patient with serum sickness-like disease associated with infliximab therapy, leading to discontinuation of the infusion in 2 patients. None of the events was life-threatening, epinephrine did not have to be administered and the use of treatment protocols (see below for details) resulted in a rapid resolution of all acute reactions to infliximab. In both patients with infusion reactions, the event had occurred despite being on concomitant immunosuppressive medication (azathioprine) for >6 months.

A 29-year-old male patient with Crohn's disease had a mild acute infusion reaction with urticaria during the second infusion of infliximab (week 2 of three-dose induction regimen), which resolved after symptomatic treatment (diphenhydramine). The infusion was continued without complications and no hospital admission was required. The patient was successfully reinfused in week 6, administrating premedication with corticosteroids.

A 30-year-old female patient with severe fistulizing Crohn's disease developed a moderate acute hypersensitivity reaction with flush, urticaria and pruritus during the 6th infusion of infliximab; the infusion was immediately stopped and the patient recovered soon after out-

Table 1. Patient characteristics (n = 100)

Male/female	54/46
Median age	36 (18–65)
Duration of IBD, years	8.4 (1–24)
IBD subtype	
Crohn's disease	92 (92%)
Ulcerative colitis	7 (7%)
Indeterminate colitis	1 (1%)
Disease location of Crohn's disease	
Terminal ileum only	65
+ Colon	18
+ Oesophageus/stomach	9
Disease location of ulcerative colitis	
Rectum only	3
Left-sided colitis	2
Pancolitis	2
Indication for infliximab therapy	
Refractory Crohn's disease	72
Intolerance to immunosuppression	4
Contraindications to steroids	16
Steroid-refractory ulcerative colitis	7
Steroid-refractory indeterminate colitis	1
Median follow-up after the last infliximab infusion, months	26 (3–48)
Concomitant medication at time of first infliximab infusion	
Azathioprine	64
6-Mercaptopurine	18
Mesasalazine	10
Corticosteroids	42

Table 2. Patients with side-effects of infliximab therapy

Patient No.	Sex	Age	Diagnosis	Adverse event	Time interval	Infusions	Concomitant medication
1	m	29	CD	acute infusion reaction	minutes	2	azathioprine
2	f	30	CD	acute infusion reaction	minutes	6	azathioprine
3	f	21	CD	serum sickness-like reaction	5 days	3	10 mg prednisone
4	m	22	CD	varicella-zoster infection	1 week	1	azathioprine
5	m	51	CD	bacterial pneumonia	3 weeks	2	6-mercaptopurine
6	m	45	CD	acute pyelonephritis	6 months	4	azathioprine
7	f	30	CD	tonsillar abscess/sepsis	3 months	1	azathioprine
8	m	54	CD	surgical complications	3 weeks	3	30 mg prednisone
9	f	40	CD	surgical complications	2 weeks	1	20 mg prednisone
10	f	32	IC	pancytopenia	6 days	1	antibiotics, 50 mg prednisone

CD = Crohn's disease; IC = indeterminate colitis.

patient treatment with corticosteroids and diphenhydramine. This patient had never experienced any infusion reactions before; the time since the last infusion was 4 years. So far, no reinfusion of infliximab has been administered in this patient due to safety issues.

In addition, a 21-year-old female patient with active luminal Crohn's disease developed a serum sickness-like disease 5 days after the third infliximab infusion (week 6 of induction regimen) with pruritus, rash and myalgia, which resolved after symptomatic treatment in the out-patient department (corticosteroids) and no hospital admission was required. The patient refused reinfusion of infliximab.

Infections

Overall, we observed 4 events with bacterial or viral infections in our study population (4%). None of the infectious complications described were fatal. In the cohort, no intra-abdominal abscess, opportunistic infection or cutaneous infection was observed.

A 22-year-old male patient with Crohn's disease developed for the first time in his life a generalized infection with varicella-zoster virus 1 week after the first infusion of infliximab. After symptomatic treatment for pruritus in the out-patient clinic, the patient soon recovered without further complications.

A 51-year-old male patient with Crohn's disease showed an acute onset of bacterial uncomplicated pneumonia 3 weeks after the second infusion of infliximab (week 2 of induction regimen), which resolved soon after antibiotic treatment in the hospital.

A 45-year-old male patient with severe fistulizing Crohn's disease and a known enterovesicular fistula was found to have acute pyelonephritis *(Escherichia coli)* 6 months after the 4th infliximab infusion requiring long-standing antibiotic treatment. The patient had been on concomitant immunosuppressive therapy with azathioprine for 18 months.

A 30-year-old female patient with Crohn's disease was admitted to hospital due to a severe generalized sepsis 3 months after the first infusion of infliximab, requiring intensive care treatment with intubation. The focus of the sepsis was a tonsillar abscess and the patient recovered on antibiotic treatment without further complications. The patient had been on concomitant immunosuppressive therapy with azathioprine for 12 months.

Surgical Complications

A 54-year-old male patient (Crohn's disease) of the cohort underwent surgery (ileocoecal resection) 3 weeks after the 3rd infusion of infliximab and showed marked insufficiency of the surgical anastomosis requiring two surgical revisions. The patient had been on concomitant steroids (30 mg prednisone/day).

A 40-year-old female patient (Crohn's disease) underwent ileocoecal resection 2 weeks after the 1st infusion of infliximab. The patient, who was on concomitant steroids (20 mg prednisone/day) at the time of surgery, required two surgical revisions due to repeated surgical insufficiency.

Bone Marrow Toxicity

In a 32-year-old female patient with indeterminate colitis who received one infusion with infliximab in a rescue approach, we observed marked pancytopenia over 2 weeks, requiring blood transfusions and G-CSF. The patient recovered after 3 weeks and underwent total colectomy without complication. The pancytopenia retrospectively started 6 days after the infliximab infusion; however, the patient also received 2 different intravenous antibiotics of which one was started 2 days before the pancytopenia occurred. In summary, it remains unclear whether the infliximab therapy or antibiotic treatment has caused this serious complication. Investigations for viral infection or malignancy showed no pathological finding; furthermore, no antinuclear antibodies, anti-double-stranded DNA or parameters of hemolysis were found.

Additional Information

No onset of autoimmune disease, malignancy or death was observed during the observation period. None of the patients in our cohort became pregnant during the observation period.

Evaluation of Risk Factors

Regarding the potential need of developing a risk profile predicting adverse events, data like gender, age, concomitant medication, duration of disease, number of infliximab infusions, time interval between infliximab infusions, allergies in the medical history and level of antinuclear antibodies were evaluated. Analysing our patient cohort, none of the risk factors evaluated was found to be statistically significant due to the limited number of patients with adverse events.

Discussion

The purpose of our retrospective cohort study was to evaluate the safety profile of infliximab in clinical practice in our IBD patients over a time period of 4 years. Our experience demonstrates that infliximab is an effective and safe treatment option in daily clinical practice if careful patient screening and observation is guaranteed.

In comparison to other clinical studies published, it is of note that there were no fatal complications in our cohort and that the overall rate of serious adverse events related to infliximab (6%) was remarkably low [2, 17–20]. Reviewing data from different academic settings, reporting a mortality rate of up to 1% and higher incidences of serious adverse events [2, 17], the careful patient screening and thorough exclusion criteria of our centre may have prevented complications to a higher rate than published before. In addition, it has to be emphasized that patients in our cohort were younger (similar median, but different range, with no patient being >65 years) and carefully selected for comorbidities, which are known to be contributing risk factors for mortality. Analysing reports of IBD patients dying after infliximab therapy published so far [2, 17], comorbidites and old age are a major risk factor. This fact stresses the importance of special caution in infliximab therapy in elderly persons or patients with associated medical problems and may implicate improved criteria for patient selection. An additional explanation for the small number of adverse events in our cohort may also be the limited number of patients on maintenance infliximab therapy (n = 15).

Also, there have been ongoing concerns about infliximab and its risk of inducing lymphoproliferative disorders or other malignancies on a long-term base. In our study on safety data summarizing 4 years of follow-up, no signs or parameters suggestive of neoplasia or lymphoproliferative disorder have been observed. These data are in line with results of large controlled trials, in which no increased incidence of malignancy in individuals treated with infliximab had been found [21]. Although these results are definitively reassuring, more data on long-term safety are clearly required.

Regarding the significant risk of tuberculosis after infliximab therapy documented in previous studies and reviews on patients with Crohn's disease or rheumatoid arthritis [11, 22], it is of note that there was no onset of tuberculosis in our cohort. Although this study was performed in a regional area with a low incidence of tuberculosis [23], 2 patients were found to have positive tuberculosis test results by screening prior to treatment and were excluded from infliximab therapy. Since tuberculin tests may produce false-negative results in patients on immunosuppressive medication, a careful risk assessment and appropriate patient screening for tuberculosis (skin test with 0.1 ml s.c. and chest X-ray) should be routinely taken into consideration in the approach towards patients with Crohn's disease prior to infliximab infusion.

Intensified patient screening by radiologic imaging was of high value in patients with abdominal pain, fever or elevated white blood cell/C-reactive protein level, in which a CT or MRI was performed as part of our safety protocol. Overall, 14 patients had to be excluded from infliximab therapy due to an abscess or intestinal stenosis diagnosed by careful screening; 6 of these 14 patients

received infliximab after successful surgical drainage and antibiotic treatment without further complications. As a result, none of the 100 patients analysed in our retrospective study showed an adverse event due to an intra-abdominal abscess or related complications. Previous data from other cohort studies reported on patients with intra-abdominal abscesses or small bowel obstructions who were even dying after infliximab therapy [2, 17]. Based upon our data, we propose that careful medical screening and radiologic imaging is of high value in such patients with suspected intra-abdominal abscess or intestinal stenosis.

In our study population, viral or bacterial infections occurred in 4%. This is a remarkably low frequency compared to data from the ACCENT I trial where 32% of patients had infections requiring antibiotic treatment [2]. In addition, we did not observe any clinically relevant opportunistic infections like candida, listeriosis, histoplasmosis, aspergillosis or pneumocystis carinii pneumonia in contrast to previous trials [11]. This fact might also well be explained by our patient demographics (age, comorbidities) and the intensified safety protocol. Impressed by the 45-year-old male patient with severe fistulizing disease and developing acute pyelonephritis, we underline that enterovesicular fistulae are a risk factor in infliximab therapy. Still in this case, infliximab was probably not the proven cause. In Crohn's disease patients with known moderate to severe enterovesicular fistulae, regular urine analysis and prophylactic antibiotic treatment should be considered as a standard in the infliximab safety protocol.

Acute infusion reactions occurred in 2% of all patients (n = 2), representing a lower frequency than observed in other clinical studies. This might also be related to the fact that only a small number of patients of our cohort received infliximab as a maintenance therapy. Both events reported were classified as mild to moderate and as not life-threatening complication. Given the high number of patients in our cohort on concomitant long-term immunosuppressive therapy started prior or at the time of infliximab therapy, this result is consistent with data from clinical studies indicating that a concomitant immunosuppressive therapy is proven to reduce the risk of infusion reactions [24–26]. However, given the fact that both patients in whom infusion reactions occurred had been on long-standing azathioprine medication, coadministration of immunosuppressive therapy may lower but not completely prevent the risk of infusion reactions. Regarding the 30-year-old female patient who had a moderate infusion reaction, the long time interval since the last infliximab infusion (4 years) might be considered as a risk factor for developing infusion reactions. Although there are reports of successful readministration of infliximab in patients with a history of infusion reactions [27], the patient had no reinfusion due to safety reasons.

Serum sickness-like reactions classified as a mild adverse event occurred in 1 patient (1%), reporting pruritus, rash and myalgias, which soon resolved after symptomatic treatment. This percentage is in line with the incidence observed in large clinical trials (2% in the ACCENT I trial) [2]; however, in our study, there might be a tendency of patients to underreport mild symptoms like myalgias or arthralgias to their physicians so that further studies on the frequency and risk factors of serum sickness-like disease after infliximab therapy are required.

A 32-year-old female patient with indeterminate colitis who received infliximab developed marked pancytopenia which resolved after 3 weeks. In the ACCENT I maintenance trial and postmarketing surveillance data, there were no similar reports [2, 17–20]. However, case reports from 2 patients with rheumatoid arthritis or scleroderma have shown serious pancytopenia after infliximab infusion [28, 29]. Although it will remain unclear whether the concomitant antibiotic therapy or the underlying inflammatory disease itself has caused this adverse event [30, 31], further investigations on bone marrow toxicity caused by infliximab therapy are required. This adverse event also points to the need of further controlled clinical studies on infliximab in the therapy of indeterminate colitis.

Regarding the 2 patients with complications after surgery, the concomitant use of high doses of steroids most likely seems to have caused these adverse events. However, further controlled clinical trials on the effect of infliximab therapy on the outcome of surgical interventions in IBD patients are required.

Conclusion

The results of this retrospective single cohort study show that infliximab is an effective and relatively well-tolerated treatment option for patients with active luminal or fistulizing Crohn's disease with an acceptable short-term and long-term safety profile. Our data confirm that careful patient screening and selection as well as a vigilant approach towards theoretical risks are required in using this promising therapy. In conclusion, our study provides more data on safety aspects using infliximab in IBD patients and valuable information for improving screening protocols.

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