ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (12): 1135-1144
0114-5916/08/0012-1135/$48.00/0

Serious Events with Infliximab in Patients with Inflammatory Bowel Disease

A 9-Year Cohort Study in the Netherlands

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Abstract

Background: The tumour necrosis factor-α inhibitor infliximab is incorporated in the treatment guidelines for patients with inflammatory bowel disease (IBD). However, concerns about serious adverse events such as infections, malignancies and death do exist.

Objective: To evaluate the occurrence of serious events of infliximab during 9 years in a single-centre cohort of patients with IBD.

Methods: Consecutive patients (>18 years) with a proven diagnosis of IBD who started treatment for IBD with infliximab at our referral centre in the Netherlands, from June 1999 to October 2007, were included. Infusion data were collected prospectively and medical records were reviewed retrospectively. All serious events were recorded and scored in the following categories: events leading to hospitalization, infections, malignancies and death. Severity and relationship to the use of infliximab were assessed for every serious event.

Results: 147 patients (33% male, mean age at first infusion 38 years, standard deviation = 12) received a total number of 1924 infusions (median per patient = 10, range 1–70). A total of 89 patients (61%) were hospitalized during follow-up, involving a total of 300 hospitalizations. Of these, 60 hospitalizations (20%) were considered at least possibly related to the use of infliximab. In 21 hospitalizations, the occurrence of a serious infection was considered at least possibly related to infliximab. Of all hospitalized patients, 70 patients (79%) underwent 139 surgical procedures, of which 70 surgeries (50%) were gastrointestinal related. Nine patients (6%) developed malignancies during follow-up: four colorectal carcinomas, one carcinoid tumour with another primary signet-ring cell carcinoma of the small bowel, one breast cancer, two skin cancers and one superficial melanoma. During follow-up, eight patients (5%) died: six as a result of malignancies, one patient as a result of a complication of short bowel syndrome and one patient due to unknown reasons. Patients who developed malignancies tended to have a longer disease duration than those who did not.

Conclusion: Clinicians prescribing biological therapies should be aware of the development of serious events in their patients. Thorough follow-up of all patients during treatment with infliximab is warranted. If infliximab is considered in

patients with IBD not responding to conventional treatment, efforts to exclude other possible underlying causes for worsening of symptoms should be made. Careful prescribing and monitoring during follow-up remains necessary.

Background

Inflammatory bowel disease (IBD) affects the lives of millions of people in developed countries. The two major types of IBD are Crohn's disease (CD) and ulcerative colitis (UC). It is commonly thought that IBD is caused by an exaggerated immune response to commensal bacteria in genetically susceptible individuals.[1,2] Therefore, targeting this immune response plays an important role in the therapy of IBD.

The chimeric (partly human, partly murine) monoclonal antibody infliximab, which targets tumour necrosis factor (TNF)-α is incorporated in the treatment guidelines for patients with IBD, based on positive results in randomized clinical trials.[3-5] In short, patients who are unable to remain in remission despite adequate treatment with immunosuppressive drugs, patients with intolerance to conventional treatment (i.e. corticosteroids and immunosuppressants) and patients with enterocutaneous fistulas not responding to conventional therapies are eligible for treatment with infliximab.[6] Besides being prescribed for IBD, infliximab is prescribed for patients with other auto-inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis.

Despite the fact that infliximab has benefit in a certain population of patients with IBD not responding to conventional therapies, concerns about serious and potentially severe adverse effects do exist. Adverse effects of infliximab in the short term, such as (acute) infusion reactions and infections, are known from clinical trials and cohort studies.[7] Clinical evidence is now emerging on the long-term safety and efficacy of infliximab. The use of infliximab is clearly associated with an increased risk of infection. Serious opportunistic infections such as mycobacterium infections,[8,9] *Pneumocystis jiroveci* (*carinii*) pneumonia,[10] pulmonary actinomycosis[11] and others have been described following the use of infliximab, as a result of suppression of T-cell-mediated immunity.

Another point of concern regarding the use of biologicals in IBD is the development of malignancies, especially lymphomas. In 2006, Bongartz et al.[12] published a meta-analysis on the risk of malignancies in patients with rheumatoid arthritis treated with infliximab in randomized clinical trials. The outcome of this analysis was a dose-related increased risk for the development of malignancies. Furthermore, the development of hepatosplenic T-cell lymphoma, a very rare subtype of peripheral T-cell non-Hodgkin's lymphoma, has been described in paediatric and young adult patients treated with infliximab.[13] Although it is unclear if infliximab plays a role in the pathogenesis of this lymphoma, clinicians prescribing infliximab in paediatric patients have been warned by the manufacturer to pay attention to a possible development of this very rare lymphoma in their patients.

In this single-centre cohort study we evaluated the occurrence of serious events after the onset of infliximab treatment in patients with IBD, with a follow-up of 9 years.

Methods

Patients

Consecutive patients (aged >18 years) with a proven diagnosis of IBD who started treatment with infliximab between June 1999 and October 2007 at our centre were included in our study cohort. Our centre, the Department of Gastroenterology and Hepatology of the Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, is an IBD referral centre. Referred patients and paediatric patients who had already received infliximab outside our medical centre at the time of first infusion were excluded. The dose of infliximab administered was based on a patient's weight and adjusted to

a dose of 5 mg/kg bodyweight, given as a 2-hour intravenous infusion. Indications for treatment with infliximab were based on Dutch treatment algorithms that were available at the time.[14,15]

Serious Events with Infliximab

Infusion and dose data and were collected prospectively and complete medical records were reviewed retrospectively over the study period. The following variables related to infliximab were recorded: indication for infliximab, dose, duration and co-medication (corticosteroids and immunosuppressants) and the treatment strategy (on-demand vs scheduled maintenance treatment). At the time of starting administration of infliximab, most patients were on an 'on-demand' schedule. However, when evidence became available indicating that an on-demand strategy was associated with the development of antibodies to infliximab,[16] patients switched to a maintenance strategy. Furthermore, the phenotype according to the Montreal Classification,[17] sex, age at start of infliximab treatment and prior use of medication for a period of at least 3 months in the year prior to infliximab administration were abstracted.

Acute infusion reactions were defined as any adverse event occurring during infusion or within a period of 2 hours after infusion, and delayed infusion reactions as reactions occurring from 24 hours to 14 days after treatment with infliximab, according to Cheifetz et al.[18] A serious event was defined as any unfavourable event since the start of infliximab, from one of the following categories: infections, malignancies and death. Hospitalizations, length of stay and surgical procedures were assessed from medical records and electronic patient records, subdivided into gastrointestinal related and other. Furthermore, events were scored for severity and likelihood of relationship to infliximab; grading of adverse events was performed by adapting the grading of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)[19] [table I] and assessment of causality was performed by using a modified WHO-Uppsala Monitoring Centre (UMC) scale of case causality assessment[20] (table II). Scoring was performed by an experienced gastroenterologist (DJ) blinded for information that could lead to a patient's identity.

All events during follow-up were graded by the NCI CTCAE, and defined as related to the use of infliximab if causality was scored 3 (possible) or 4 (probable), following the modified WHO-UMC scale of case causality assessment as described in table II.

Table I. Grading system of adverse events adapted from the National Cancer Institute Common Terminology Criteria for Adverse Events[19]

Grade	Description	No. of events	Events related to infliximab use [n (%)][a]
0	No adverse event (absent) or within normal limits	NA	NA
1	Mild adverse event (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance)	1	0 (0)
2	Moderate adverse event (minimal intervention; local intervention; noninvasive intervention)	73	18 (25)
3	Severe and undesirable adverse event (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)	216	46 (21)
4	Life-threatening or disabling adverse event (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, haemorrhage, sepsis. Life-threatening physiological consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation)	23	18 (78)
5	Death related to adverse event	7	6 (86)

a Events are defined related to the use of infliximab if causality was scored 3 (possible) or 4 (probable), following the modified WHO-Uppsala Monitoring Centre scale of case causality assessment as described in table II.

NA = not applicable.

Table II. Modified WHO-Uppsala Monitoring Centre scale of case causality assessment[20]

Grade	Description
1	Unrelated: a causal relationship can be definitively excluded and another documented cause of the event is most plausible
2	Unlikely: a causal relationship is improbable and another documented cause of the adverse event is most plausible
3	Possible: a causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the adverse event and administration of infliximab
4	Probable: a causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the adverse event and administration of infliximab and there is a reasonable response on withdrawal

Statistics

Frequency tables were compiled describing characteristics of the included patients at the time of their first infusion with infliximab. The number of hospitalizations were analysed on a patient level, and defined as related to the use of infliximab if causality was scored 3 or 4. This procedure was repeated for both serious infection and surgery as the reason for hospitalization. All patients who were hospitalized, whether or not the occurrence of a serious infection was the main reason, were compared with regard to the treatment strategy (on demand vs scheduled maintenance) and the use of co-medication, which was defined as use over a period of at least 6 months.

Patients that developed malignancies during follow-up were compared with the remaining patients for disease severity (defined as presence of fistulas), duration of disease, cumulative dose of infliximab and the use of concomitant medication using Student's t-test and Pearson's chi-squared test.

The annual mortality and infection rate was calculated by dividing the number of deceased patients or patients with infection by the duration of follow-up in years. All calculations were performed using SAS software (version 8.2; SAS Institute Inc., Cary, NC, USA). All p-values calculated were two-tailed and the alpha level of significance was set at 0.05.

Results

Patients

A total of 147 patients (33% male) were included; baseline characteristics at time of first infusion with infliximab are given in table III. At baseline, mean age was 38 years (standard deviation = 12) with a mean disease duration of 16 years. Primary indication for treatment was luminal CD in 55 patients (37%), fistulizing disease in 80 patients (54%), UC in 9 patients (6%) and indeterminate colitis in 3 patients (2%). Involvement of different parts of the intestinal tract was scored using the

Table III. Baseline characteristics of 147 patients with inflammatory bowel disease at start of infliximab treatment

Characteristic	No of patients
Mean age, y (SD)	38 (±12)
Male sex (%)	49 (33)
Mean disease duration, y (range)	16 (0–41)
Indication for infliximab treatment (%)	
luminal CD	55 (37)
fistulizing CD	80 (54)
UC	9 (6)
indeterminate colitis	3 (2)
Montreal classification CD (%)	
ileum	26 (18)
colon	42 (29)
ileocolonic	63 (43)
ileum + isolated upper disease	1 (1)
colon + isolated upper disease	1 (1)
ileocolonic + isolated upper disease	4 (3)
only perianal disease	1 (1)
Montreal classification UC (%)	
ulcerative proctitis	1 (1)
left-sided	3 (2)
pancolitis (extensive colitis)	5 (3)
Prior medication (%)[a]	
5-aminosalicylic acid	66 (45)
corticosteroids	113 (77)
antibacterials	15 (10)
immunosuppressants	90 (61)
Concomitant medication at first infusion (%)	
corticosteroids	102 (69)
immunosuppressants	93 (63)

a Medication had to be used over a period of at least 3 mo during the previous year.

CD = Crohn's disease; **UC** = ulcerative colitis.

Montreal classification: in patients with CD it was limited to the small bowel in 26 patients (18%), ileocolonic in 63 patients (43%) and colonic in 42 patients (29%).

A total number of 1924 infusions were given with a median per patient of 10 (range 1–70), over a median follow-up of 59 months (range 1–99). Patients were followed for a total of 674 patient years. Twenty-eight patients (20%) received infliximab for less than 6 months.

Infusion Reactions

A total number of 16 acute infusion reactions were seen in 12 patients (8%). When patients developed acute infusion reactions, infusion was discontinued and patients received intravenous corticosteroids and a selective histamine H_1 receptor antagonist (clemastine). Based on the clinical response to these agents, infliximab was re-administered at a slower infusion rate and discontinued if symptoms reoccurred. The majority of acute infusion reactions occurred during the fifth and sixth infusions and most patients who developed acute infusion reactions were receiving scheduled maintenance therapy (figure 1). There were 12 delayed infusion reactions, occurring in ten patients (7%).

Hospitalization

A total of 89 patients (61%) were hospitalized during follow-up involving a total of 300 hospitalizations. Of these hospitalizations, 60 (20%) were considered to be at least possibly related to the use of infliximab (a score of ≥3 on the modified WHO-UMC scale of case causality assessment). The overall median number of hospitalizations per patient was 2, ranging from 1 to 19. Of the hospitalizations at least possibly related to infliximab, the median number per patient was 1 (range 1–6). Overall median length of stay was 7 days (range 1–70) and in the group with hospitalization at least possibly related to infliximab, it was 8 days (range 1–48).

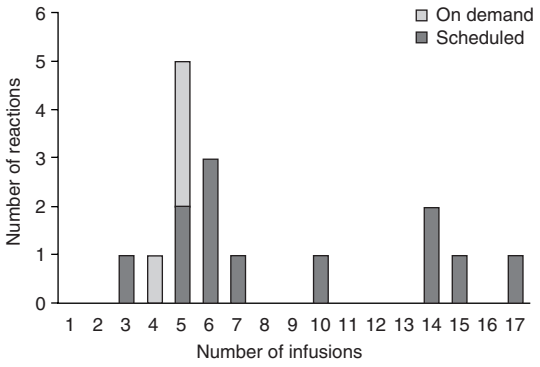

Fig. 1. Acute infusion reactions to infliximab. Patients were stratified according to their treatment regimen (on demand vs scheduled).

In 57 hospitalizations (involving 36 patients), the occurrence of a serious infection was the main reason for hospitalization; in 21 patients (24%) this was considered at least possibly related to infliximab. The following infections were recorded: abscess (58%), gastroenteritis (16%), urinary tract infection (11%), pneumonia (5%), sepsis (9%) and not categorizable (5%). It should be noted that some patients had multiple types of infection. The annual infection rate was 5%. Of all 89 hospitalized patients, 70 (79%) underwent 139 surgical procedures of which 70 (50%) were gastrointestinal related.

Most patients were hospitalized because of their disease. No significant differences were found regarding different treatment schedules (on demand vs scheduled) and between the different groups of comedication, i.e. corticosteroids, immunosuppressants or both (table IV).

Malignancies

During follow-up, nine patients (6%) developed malignancies (table V). Four colorectal carcinomas, one carcinoid tumour with another primary signet-ring cell carcinoma of the small intestine, one breast cancer, one basal cell carcinoma, one squamous cell carcinoma of the skin and one superficial melanoma were seen. All malignancies except one were judged at least possibly related to the use of infliximab (table V). The relationship is unlikely in the case of a 56-year-old man with a 14-year history of CD, who was hospitalized because of general deterioration, dyspnoea, diarrhoea and fatigue. Besides his CD, he had a history of ankylosing spondylitis and a Dukes BII colon tumour, which had been complete-

Table IV. Summary of concomitant medication and treatment strategy regarding hospitalization and infection

Medication	Hospitalizations			Infections		
	no. of events (n = 300)	no. of patients (n = 89)	median no. of events per patient	no. of events (n = 57)	no. of patients (n = 36)	median no. of events per patient
No concomitant medication	6	3	2	4	3	1
Corticosteroids	33	10	3	5	4	1
Immunosuppressants	57	16	2	7	4	1
Combination	136	31	3	28	14	1
Unknown	2	1	2	1	1	1
<6 Mo of infliximab	66	28	2	12	10	1
Infliximab						
on demand	177	44	2	38	20	1
scheduled	123	45	2	19	16	1

ly removed 14 years earlier. During his hospitalization he received three infusions with infliximab. Six days after being discharged, he was re-admitted to the hospital because of a massive gastrointestinal bleeding and died during an emergency operation. At autopsy, an adenocarcinoma was seen in the ileorectal region, with invasion of the iliac vessels.

Three patients continued infliximab after the diagnosis of malignancy. Besides patients with basal cell carcinoma and superficial melanoma, there was one patient with metastatic breast cancer. This 52-year-old woman had had a history of severe fistulizing perianal CD for 26 years and was responding well to infliximab. When diagnosed with breast cancer, her treating physicians strongly advised her to stop further treatment. Despite that, she decided to continue treatment with infliximab with the argument that she would rather have a few good months with limited CD activity and a potentially reduced life expectancy, than having a few more months with both active perianal CD and breast cancer.

Patients who developed malignancies were compared with patients who did not develop malignancies; no significant differences were found in age of onset, concomitant medication and existence of fistulae. Patients who developed malignancies had received a median number of 17 infusions with infliximab, compared with a median number of 10 infusions in patients who did not. The cumulative dose of infliximab received, which has been associated with the development of malignancies, did not show significant differences either; the mean dose in the group with malignancies was 1540 mg (600–35 000 mg) versus a mean of 2500 mg (300–21 940 mg). However, a significant difference was seen in duration of disease ($p < 0.01$); patients with malignancies had a mean duration of disease of 29 years (±7.3 years), compared with a mean duration of disease of 15 years (±8.6 years) in patients who did not develop malignancies.

Deaths

During follow-up, eight patients (5%) died: six as a result of malignancies (all patients with colorectal carcinomas, breast cancer or primary signet-ring cell carcinoma of the small intestine), one patient as a result of a complication of short bowel syndrome and for one patient the reason was unknown. The annual mortality was 1.2%.

Discussion

In our 9 years of single-centre experience, a total of 147 patients with IBD received nearly 2000 infusions with infliximab. In 12 patients (8%), an acute infusion reaction was seen and 10 patients (7%) developed delayed infusion reactions. Our rate of acute infusion reactions on a patient level is comparable with reported rates in other studies.[18] With regard to the development of acute infusion reactions, most treatment algorithms state that vital signs should be monitored during infusion.[18,21] We recently showed that scheduled monitoring of vital

Table V. Characteristics of patients who developed malignancies

Sex/ age (y)	Disease	Disease duration (y)	No. of infusions	Cumulative dose received (mg)	Time since last infusion	Concomitant medication	Type of malignancy	Follow-up	Likelihood score[a]
M/56	CD[b]	31	4	1 600	32 mo	Azathioprine	Colorectal cancer	Patient died 5 mo after diagnosis	3 (Possible)
F/48	CD[b]	32	4	1 200	7 wk	Corticosteroids, 5-ASA	Colorectal cancer	Patient underwent surgery and received radiation therapy and died 19 mo after diagnosis	3 (Possible)
M/63	CD[b]	37	3	900	26 mo	Mesalazine	Colorectal cancer	Patient died nearly 6 mo after diagnosis	3 (Possible)
F/44	CD[b]	21	9	3 400	6 wk	Corticosteroids, azathioprine, 5-ASA	Basal cell carcinomas	Basal cell carcinomas could be removed completely and infliximab was readministered	3 (Possible)
F/52	CD[b]	31	47	23 500	2 wk	5-ASA, azathioprine (later followed by methotrexate)	Melanoma	Melanoma could be removed completely and infliximab was continued	4 (Probable)
M/56	CD	14	3	900	6 d	Corticosteroids, azathioprine	Colorectal cancer	Patient died during an emergency operation because of massive bleeding caused by a tumour in the ileorectal region that had grown into the iliac vessels	2 (Unlikely)
F/45	CD	18	29	11 600	2 mo	5-ASA, azathioprine	Carcinoid tumour,[c] lymphangitis carcinomatosa	Patient received chemotherapy and died nearly 7 mo after diagnosis	3 (Possible)
F/52	CD[b]	26	12	4 348	2 mo	Corticosteroids, 5-ASA (only during first year of treatment), 3 mo of methotrexate	Breast cancer	Patient underwent surgery and received another ten infusions with infliximab and died 28 mo after diagnosis	3 (Possible)
F/52	CD	18	2	600	17 mo	Azathioprine	Squamous cell carcinoma	Squamous cell carcinoma could be removed completely	3 (Possible)

a Likelihood of malignancy being related to the use of infliximab (Modified WHO-Uppsala Monitoring Centre of causality assessment as described in table II).

b CD patients with fistula.

c This patient developed a carcinoid tumour with another primary signet-ring cell carcinoma (linitis plastica type) and lymphangitis carcinomatosa.

5-ASA = 5-aminosalicylic acid; **CD** = Crohn's disease; **F** = female; **M** = male.

signs during infusion neither indicated nor predicted development of acute infusion reactions.[22] Sixty-one percent of all patients were hospitalized after the start of infliximab treatment during follow-up. In 14% of all patients, the main reason for hospitalization was an infection that was considered at least possibly related to the use of infliximab. Nine patients developed malignancies and subgroup analysis, comparing patients with and without malignancies, showed a significant difference in duration of disease. During follow-up, eight patients died, the majority as a result of malignancies.

In large, controlled clinical trials of maintenance therapy with infliximab in patients with CD, the annual rate of serious infection with infliximab ranged from 4% to 4.6%.[3,23] Our annual infection rate is comparable to these studies, but slightly higher than demonstrated by follow-up data from clinical practice, which showed an annual incidence of serious infections of 1.2–2.1%.[24,25] The TREAT (The Crohn's Therapy, Resource, Evaluation and Assessment Tool) registry, a large-scale, ongoing, observational registry of patients treated for CD, showed no significant differences in rates of serious infection between patients treated with infliximab and patients not treated with infliximab in the latest published evaluation.[26] However, a recent case-control study showed that immunosuppressive medication such as corticosteroids, azathioprine/mercaptopurine and infliximab, especially when used in combination, is associated with an increased risk of opportunistic infections in patients with IBD.[27]

In our cohort, only those infections for which hospitalization was required were registered. As a consequence, we underestimated the true rate of infections in patients treated with infliximab. Furthermore, patients could be treated for less severe infections by their general practitioner. Since we reviewed the medical charts retrospectively, this information could not be reliably retrieved.

Concerns do exist about the development of lymphomas in patients treated with infliximab. In our cohort, only solid tumours were found, with the majority being colorectal cancer. Patients with IBD, especially patients with UC and, to a lesser degree, patients with CD, are at greater risk of developing colorectal cancer, depending on risk factors such as duration and severity of disease and simultaneous primary sclerosing cholangitis.[28] In our subgroup analysis comparing patients with and without malignancies (patients with malignancies being the group who contributed most to the number of patients who died during follow-up), only duration of disease was significantly different. Duration of colitis is a significant contributor in the development of colorectal cancer in patients with IBD.[28] Besides patients with UC, patients with CD have an increased risk of developing colorectal cancer.[29,30] A general consensus exists that the same contributing factors for colorectal cancer in patients with UC apply for patients with CD.[30] In our cohort, a causal relationship between the use of infliximab and the development of solid tumours cannot be made; the malignancies seem to be more related to underlying disease than to the use of infliximab. However, these malignancies developed at a relatively young age. This indicates that careful monitoring of patients with IBD for signs that could be attributable to a malignancy is necessary to detect serious events at an early stage.

One patient was treated with infliximab for worsening of gastrointestinal symptoms, which, on retrospective investigation, were found to be caused by colorectal cancer. Since IBD-related symptoms may have other causes such as malignancy, clinicians should consider a diagnostic work-up before starting treatment with infliximab. We retrospectively checked the medical records of the four patients who developed colorectal cancer with regard to endoscopies performed. None of the colorectal cancers was discovered during a previous colonoscopy or sigmoidoscopy. Three of four patients underwent at least two colonoscopies in the 3-year period before the colorectal cancer was diagnosed.

Another patient, who developed breast cancer, insisted on continuing treatment with infliximab. This is in line with a recent study by Johnson et al.,[31] which revealed that patients with CD are willing to accept an elevated risk of serious adverse

events in exchange for clinical efficacy with regard to their disease.

Our annual mortality rate of 1.2% is in accordance with previous double-blind clinical trials with infliximab and follow-up data from clinical trials, reporting incidences ranging from 0.7% to 1.3%[3,23] and from 1.2% to 1.3%,[24,25] respectively. However, as pointed out by Lichtenstein et al.,[26] this mortality rate is in accordance with published mortality rates in historical cohort studies before infliximab was introduced, with annual mortality rates of 1.3% in patients with CD.[32,33] In the multivariate regression analysis of the TREAT registry, only the use of prednisone was an independent predictor of both serious infection and death.[26] Our study was underpowered to perform such an extensive multivariate analysis.

The use of infliximab in fistulizing CD is associated with a reduced number and length of hospitalizations.[34] In our cohort, a considerable number of patients were hospitalized (61%) and 70 gastrointestinal surgeries were performed during follow-up. In our centre, infliximab given in a conventional 'step-up' approach was administered relatively late in the course of disease. This possibly had consequences for the biological behaviour of the disease, with progression of stricturing and fistula formation. It seems that this approach is not able to substantially change the course of disease, and surgery remained inevitable in a large number of patients.

One limitation of this study is the lack of a comparator, for example, a group of patients with similar disease severity, medication use, duration of disease and number of bowel segments involved but not treated with infliximab. As a consequence we can not report 'higher rates', but only high rates. Furthermore, no risk ratios could be calculated. Other factors such as concomitant use of corticosteroids and immunosuppressants could be likely to contribute to the reported event rate here. Therefore, the reported adverse effects might be caused by conventional medication used together with infliximab. As conventional medication causes serious events as well,[35] it is difficult to differentiate. Another limitation with regard to this retrospective study is that we were not able to differentiate between patients who fully responded to infliximab therapy and those who responded only partially or in whom response was lost, since response to infliximab was not measured prospectively following a standard protocol and definitions.

While long-term data on other TNFα-inhibitors used in the treatment of IBD (e.g. adalimumab) are lacking, infliximab is the only TNFα-inhibitor suitable for a long-term safety analysis at this moment. Therefore, no comparison in long-term safety can be made. Although not studied in head-to-head trials, we would also stress precaution concerning other anti-TNFα agents used in the treatment of IBD.

Conclusion

Although infliximab is of great value in the treatment of IBD, clinicians prescribing biological therapies should be aware of the development of serious events in their patients. There might be an indication for surveillance screening for colorectal cancer in patients who are receiving infliximab treatment. Thorough follow-up of patients during treatment is warranted. If infliximab is considered in patients with IBD not responding to conventional treatment, efforts to exclude other possible underlying causes for worsening of symptoms should be made.

Acknowledgements

No sources of funding were used to assist in the preparation of this study. Dirk J. de Jong has received speaker fees from Abbott, Schering Plough, Dr Falk Pharma GmbH, UCB Pharma and Ferring B.V. The other authors have no conflicts of interest directly relevant to the content of this study to declare.

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