

Safety of Infliximab in Crohn's Disease: A Large Single-center Experience

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Background: The aim of this study was to evaluate the short- and long-term safety experience of infliximab treatment in patients with Crohn's disease (CD) in clinical practice.

Methods: The medical records of 297 consecutive patients with CD treated with infliximab at the Beth Israel Deaconess Medical Center were reviewed for demographic features and adverse events.

Results: The 297 patients received a total of 1794 infusions. Patients received a median of four infusions and had a median follow-up of 14.3 months. Forty-four patients (15%) experienced a serious adverse event, requiring the infusion to be stopped in 33 patients (11%). Acute infusion reactions occurred in 18 patients (6%) including respiratory problems in 10 patients (3%) and an anaphylactoid reaction in 1 patient (0.3%). Serum sickness-like disease occurred in one patient (0.3%) and three patients (1%) developed drug-induced lupus. One patient developed a probable new demyelination disorder. Eight patients (2.7%), all of whom were on concurrent immunosuppressants, developed a serious infection, one resulting in fatal sepsis. Six patients (2%) developed malignancies including two lymphomas and two skin cancers. A total of four (1.3%) deaths were observed (median age 72.5 years); two due to gastrointestinal bleeding, one due to sepsis, and one due to malignancy.

Conclusions: While short- and long-term infliximab therapy was generally well tolerated, serious adverse events occurred in 15% of patients including drug-induced lupus, fatal sepsis, and malignancy. Concomitant immunosuppressants were significantly associated with infections and deaths, particularly among elderly patients.

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Infliximab is a chimeric IgG1 α monoclonal anti-TNF- α antibody consisting of human constant and murine variable regions.¹ Infliximab has potent antiinflammatory effects and has been approved by the US Food and Drug Administration (FDA) for the treatment of Crohn's disease (CD) and ulcerative colitis, as well as rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.¹ It is indicated for the induction and maintenance of clinical remission in patients with moderate to severe active CD refractory to conventional therapies.^{2,3} Infliximab is also indicated for fistulizing CD.^{4,5} Following two large randomized controlled trials, ACT1 and ACT2, infliximab is the only biologic currently approved in ulcerative colitis.⁶

Since its FDA approval for CD in 1998 almost one million patients have been treated with infliximab worldwide, including over 300,000 patients with inflammatory bowel disease (IBD).⁷ While the reported efficacy in clinical practice during relatively short-term follow-up has been comparable with data reported in controlled clinical trials,^{8–10} the wide use of infliximab has raised concerns about the short- and long-term toxicity of the drug. Infusion reactions, autoimmune disorders, serious infections including reactivation of tuberculosis, opportunistic infections, and malignancies have been reported with the use of infliximab.^{11–17} Colombel et al¹⁸ recently reported a retrospective cohort study regarding the safety data of 500 patients with CD treated with infliximab at the Mayo Clinic. While the Mayo group found that short- and long-term infliximab was generally well tolerated, over 8% of patients experienced a serious adverse event. There were five deaths (1%) observed in that study, three of which were deemed by the authors as being possibly related to infliximab. Safety information regarding short- and long-term infliximab therapy in clinical practice is limited, with few data from less-selected patient populations in single centers than that reported in larger multicenter clinical trials. The purpose of this study was to evaluate the safety profile of infliximab in clinical practice in patients with CD attending a single center.

PATIENTS AND METHODS

We performed a retrospective cohort study of 297 consecutive patients with CD treated with infliximab at

TABLE 1. Characteristics of Study Patients

Characteristics of Patients	All Pts	Infliximab without Immunosuppressants	Infliximab with Immunosuppressants	<i>P</i> (Unpaired <i>t</i> -test)
Number of patients	297	160	137	
Mean age yr (range)	40 (19–84)	41.1 (21–84)	43.6 (19–81)	0.11
Female sex (%)	178 (60)	97 (60)	75 (56)	0.32
Median duration of disease (years)	13.9 (1–48)	13.8 (1–48)	14.2 (1–39)	0.81
Median follow-up (months)	14.3 (1–86)	11.9 (1–70)	9.5 (1–86)	0.07
Total follow-up (patient-years)	261	157	104	0.08
Disease localization				
Small bowel	27 (9)	16 (10)	11 (8)	0.62
Colon	110 (37)	61 (38)	49 (36)	0.77
Ileocolitis	148 (50)	76 (48)	72 (53)	0.57
Others	12 (4)	7 (4)	5 (4)	0.9
Indications for infliximab (%)				
Active luminal disease	175 (59)	93 (58)	82 (60)	0.77
Active fistulizing disease	107 (36)	57 (36)	50 (36)	1.0
Others	15 (5)	10 (6)	5 (4)	0.52
Concomitant meds at start (%)	137 (46)			
6-MP/AZA only			61 (45)	
Corticosteroids only			50 (36)	
Combined immunosuppressants (6MP/AZA/corticosteroids)			25 (18)	
Methotrexate only			1 (0.7)	

Beth Israel Deaconess Medical Center between October 1998 and January 2005. The study was approved by the hospital's Institutional Review Board committee. The diagnosis of CD was confirmed in all cases by review of patient's medical, endoscopic, radiological, and pathological records. The following information was recorded for every patient and entered in a database: age, sex, indication for infliximab treatment, disease duration, age of disease onset, location of disease, smoking habits, extraintestinal manifestations, history of previous surgery, concomitant medication use at start of treatment, concomitant medication use during the treatment, premedication before infusions, number of infusions, intervals between infusions, and the ability to taper corticosteroid dosage with infliximab. Medical records were reviewed for safety data. Serious adverse events were defined as effects causing life-threatening conditions, with a significant change in patient's vital signs, discontinuation of infusion, or leading to hospitalization or death. Reactions during or within 2 hours of infusions were defined as acute infusion reactions. All potential complications of infliximab included infusion reactions, serum-sickness-like reactions, drug-induced lupus and other autoimmune diseases, serious infections, malignancies, and deaths were documented.

All patients received premedication with diphenhydramine 12.5–25 mg orally and acetaminophen 650 mg orally before infusions. Premedication with hydrocortisone 200 mg intravenously (IV) were given to patients with a history of a serious infusion reactions. Concurrent immunosuppressive therapy included either prednisone, azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate, or cyclosporine.

Statistical Analysis

Comparison of characteristics between groups was performed by unpaired *t*-test and comparison of side effects was performed by Fisher's exact test. A *P*-value less than 0.05 was considered statistically significant. SPSS 14.0 software (Chicago, IL) was used for statistical analysis.

RESULTS

Patients Characteristics

As outlined in Table 1, 297 patients were evaluated in the study, 178 of them female and 119 of them male with a mean age of 40 years (range 19–84 years). The median duration of CD at first infliximab infusion was 13.9 years (range 1–49 years). The disease was confined to the

colon in 110 patients (37%), the small bowel in 27 patients (9%), and involved the small bowel and colon in 148 patients (50%). Twelve patients (4%) had disease involving the upper gastrointestinal tract including esophagus, stomach, and duodenum. Active luminal disease was the indication for infliximab treatment in 175 patients (59%), fistulous disease the indication in 107 patients (36%), while active IBD-associated arthritis or spondyloarthritis was the indication in 15 patients (5%). The median follow-up was 14.3 months (range 1–86 months) with 110 patients having ≤ 1 month of follow-up. A total of 155 patients were followed for 0–12 months, 62 patients for 13–24 months, 47 patients for 25–36 months, 18 patients for 37–48 months, 7 patients for 49–60 months, 4 patients for 61–72 months, and 3 patients for 73–86 months. Our 297 patients were followed up for a total of 261 patient years. In all, 152 patients (51%) had prior bowel resection for CD.

Infliximab Treatment

In all, 121 patients (42%) received induction infliximab 5 mg/kg at 0, 2, and 6 weeks only but no subsequent infliximab infusions; 48 patients (16%) had induction and subsequent on-demand infliximab 5 mg/kg infusions thereafter. A further 128 patients (43%) had induction and subsequent scheduled maintenance 5 mg/kg infusions every 8 weeks, of whom 29 patients (23%) required either a dose escalation to 10 mg/kg or a shortening of the infusion interval because of poor response. A total of 1794 infliximab infusions were administered. Forty-nine (17%) patients received hydrocortisone 200 mg IV as premedication. A total of 137 patients (46%) were on concomitant immunosuppressive drugs. As outlined in Table 1, there was no significant difference in patient or disease characteristics between those patients who received Infliximab without immunosuppressants and those who received concomitant immunosuppressants. Sixty-one patients (21%) were receiving 6-MP or AZA, 50 (17%) were on corticosteroids, and one patient (0.3%) was on methotrexate. Twenty-five patients (8%) were receiving a combination of 6-MP, AZA, and/or corticosteroids drugs at the beginning of their infliximab treatment (Table 1).

Global Safety

A total number of 99 (33%) possibly related adverse events were recorded during the study period, 44 (14%) of which were deemed serious. Because of the serious adverse events, 33 patients (11%) had to abort their infliximab treatment. Four patients died during the study period, all of whom were also receiving concomitant immunosuppressive therapies (Table 2).

TABLE 2. Summary of Adverse Events Associated with Infliximab Infusions

Adverse Events	<i>n</i>	%
Any adverse events	99	33
Serious adverse events	44	14
Treatment aborted	33	11
Death	4	1.3

Serious Adverse Events

Forty-four patients (15%) experienced a serious adverse event, requiring the infusion to be stopped in 33 patients (11%). Severe infusion reactions occurred in 18 patients (6%), one of which was characterized by an anaphylactoid reaction (0.35%) which was treated successfully with medical intervention. One patient experienced severe back pain as an immediate infusion reaction and two patients had severe hypotension which required their infusions to be discontinued. One patient had severe delayed hypersensitivity reaction after the third infliximab infusion, which was 104 weeks after their second infusion, and required hospitalization and steroid therapy. Six patients (2.1%) developed a malignancy during treatment. There were eight severe infections and one of them resulted in septicemia and death. Table 3 summarizes all serious adverse events including deaths associated with infliximab infusions with respect to the presence or absence of concomitant immunosuppressants. Concomitant immunosuppressants were significantly associated with all infections, including serious infections and deaths. The rate of serious adverse events was further analyzed among patients on concomitant immunosuppressants with respect to concomitant 6-MP/AZA therapy ($n = 61$ patients), concomitant corticosteroids ($n = 50$ patients), and concomitant 6-MP, AZA, and corticosteroid therapy. There were no significant differences in serious adverse events between patients receiving only concomitant 6-MP/AZA therapy and those receiving only concomitant corticosteroids.

Infusion Reactions/Delayed Reactions

The most common reaction was rash and urticaria, which occurred in 21 patients and was successfully treated with conventional medical therapy. No patients developed atypical, eczematous, or psoriatic skin reactions. Ten patients suffered shortness of breath during or shortly after infusions. Other infusion reactions comprised anaphylaxis, back pain, and hypotension. A total of 32 patients had delayed infusion reactions. Four of the delayed reactions were severe and required hospitalization. There was no difference in the rate of all or severe infusion reactions (immediate and delayed) between patients who received

TABLE 3. Summary of Serious Adverse Events Associated with Infliximab Infusions

Adverse Events	All Pts	Infliximab w/o Immunosupp	Infliximab + All Immunosupp	Infliximab + AZA/6MP	Infliximab + Steroids	Infliximab + AZA/6MP + Steroids	P
Number of patients	297	160	137	61	50	25	
Severe infusion reaction	18 (6.1%)	10 (6.3%) ^a	8 (5.8%) ^a	4 (6.6%)	3 (6%)	1 (4%)	N.S. ^a
Severe delayed reaction	4 (1.3%)	2 (1.3%) ^b	2 (1.5%) ^b	1 (1.6%)	1 (2%)	0	N.S. ^b
Serious infections	8 (3%)	0 ^c	8 (5.8%) ^c	3 (4.9%)	4 (8%)	1 (4%)	0.009 ^c
Others**	8 (3%)	2 (1.3%) ^d	6 (4.4%) ^d	4 (6.6%)	2 (4%)	0	N.S. ^d
Malignancy	6 (2%)	2 (1.3%) ^e	4 (2.9%) ^e	2 (3.3%)	0	2 (8%)	N.S. ^e
Deaths	4 (1.3%)	0 ^f	4 (2.9%) ^f	1 (1.6%)	0	3 (12%)	0.04 ^f

Two-sided Fisher Exact Test.

Others includes patients with serum sickness reactions and auto-immune diseases.

^aNumber of patients with severe infusion reactions who received infliximab treatment w/o immunosuppressives versus infliximab with all immunosuppressives.^bNumber of patients with severe delayed reactions who received infliximab treatment w/o immunosuppressives versus infliximab with all immunosuppressives.^cNumber of patients with serious infections who received infliximab treatment w/o immunosuppressives versus infliximab with all immunosuppressives.^dNumber of patients with serum sickness reactions and auto-immune diseases who received infliximab treatment w/o immunosuppressives versus infliximab with all immunosuppressives.^eNumber of patients with malignancy who received infliximab treatment w/o immunosuppressives versus infliximab with all immunosuppressives.^fNumber of died patients who received infliximab treatment w/o immunosuppressives versus infliximab with all immunosuppressives.

concomitant immunosuppressants or corticosteroids and those who did not; 22% versus 18%, respectively, $P > 0.05$ (Fig. 1).

Autoimmune Disorders

Three patients (1%) had lupus-like disease with arthritis, fever, and elevated antinuclear factor titers. One patient (0.3%) who was on concomitant 6-MP and ciprofloxacin was diagnosed as having possible multiple sclerosis on brain magnetic resonance imaging (MRI), and one patient had serum sickness-like disease (0.3%).

Infections

A total of 34 patients developed infections on infliximab therapy, eight of which were reported as severe. Two patients developed septicemia, one of whom, an 81-year-old man with active luminal CD who was also on 6-MP, died as a result of overwhelming Gram-negative sepsis. Three patients developed abdominal abscesses, two had bronchitis, and one developed a pneumonia. Another patient developed a lung abscess complicating a necrotizing pseudomonal pneumonia. Upper respiratory tract infections ($n = 10$) were the most common of type of infection during infliximab therapy and all were successfully treated with antibiotics. Most of the infections were mild and occurred after several infliximab infusions; four herpes simplex, two vaginitis, one varicella zoster, four fungal infections, two urinary tract infections, and one pilonidal sinus infection. The mean age of the patients with infections was 38 and did not differ significantly from patients who had

not experienced infections ($P > 0.05$). Patients receiving concomitant immunosuppressants experienced more infections compared to the patients not receiving concomitant immunosuppressants; 13% versus 2.9%, respectively, $P < 0.05$ (Fig. 1). Patients receiving concomitant immunosuppressants had significantly more serious infections compared to the patients not receiving concomitant immunosuppressants; 5.8% versus 0%, respectively, $P = 0.009$ (Table 3). While the rate of serious infections was higher

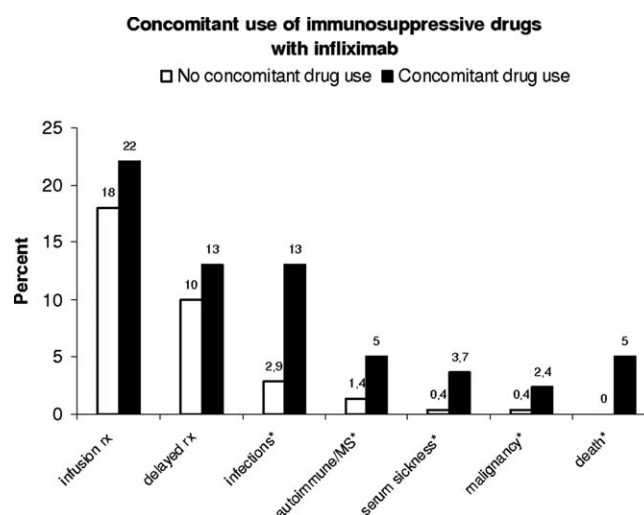


FIGURE 1. Frequency of adverse events in patients receiving infliximab therapy with concomitant drug (AZA, 6-MP, MTX, or corticosteroids, $n = 79$) and those not receiving concomitant drugs ($n = 203$) * $P < 0.05$.

TABLE 4. Clinical Characteristics, Treatment Details, and WHO Causality Categories of the Patients with Malignant Disorders

Sex/ Age	Infusions	Duration of Infusions	Concomitant Immunomodulator	Duration of Immunomodulator Therapy	Type of Malignancy	WHO Causality Categories
F/81	3	2 mo	6-MP, steroid	6 mo	Anaplastic large cell NHL	Possible
M/62	5	11 mo	6-MP	2 years	Cardia adenocarcinoma	Unrelated
F/29	5	2 years	—	—	Melanoma in situ	Possible
F/50	2	6 mo	6-MP	13 years	Lung MALT Lymphoma	Possible
M/63	3	6 mo	—	2 mo	Basal cell skin carcinoma	Possible
M/63	2	2 mo	6-MP, MTX	One year	Infiltrating ductal breast carcinoma	Possible

among those patients receiving concomitant corticosteroids compared to those receiving concomitant 6-MP or AZA, the difference was not significant: 8% versus 4.9%, respectively, $P = 0.7$ (Table 3).

Malignancy

Malignancy was diagnosed in six patients during the study period which comprised a skin basal cell carcinoma, melanoma in-situ, gastric adenocarcinoma, lung MALT lymphoma, anaplastic large cell non-Hodgkin lymphoma, and an infiltrating ductal breast cancer (Table 4). The two patients with skin basal cell carcinoma and melanoma in-situ were treated with only infliximab, whereas the other four patients with malignancy were on concomitant 6-MP. While the patient with gastric adenocarcinoma was on 6-MP for 2 years at the time of his gastric cancer diagnosis, chronic acid reflux may have been a significant contributing factor, as this patient had long-standing Barrett's esophagus and this cancer originated in the cardia. The patient with lung MALT lymphoma was on 6-MP for 13

years for active Crohn's ileocolitis and had received two infliximab infusions in the 6-month period prior to the cancer diagnosis. An 81-year-old patient on concomitant 6-MP and corticosteroids presented with anaplastic large cell non-Hodgkin's lymphoma while on infliximab and died as a result of massive gastrointestinal bleeding. There was no evidence of association between Epstein-Barr virus and either the MALT or non-Hodgkin's lymphoma. A 63-year-old man who developed intraductal infiltrating breast cancer was treated with 6-MP and methotrexate 9 years before the diagnosis of cancer and received two infliximab infusions 3 years beforehand. Using the WHO definitions of causality (Table 5),¹⁹ we attributed five of six malignancies as possibly related to infliximab therapy and one case involving a 62-year-old man with long-standing Barrett's esophagus and acid reflux symptoms who developed adenocarcinoma of his cardia as being unrelated to infliximab therapy. The mean age of the six patients who developed malignancy was 54 years, which was significantly higher than those patients who did not develop malignancy (41 years, $P < 0.005$).

TABLE 5. Adapted from Original WHO Categories, Available at <http://www.who-umc.org/index2.html>

WHO Categories for Causality

Very likely/certain: A clinical event with a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals.

Probable: A clinical event with a reasonable time relationship to drug administration and is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Possible: A clinical event with a reasonable time relationship to drug administration but which could also be explained by concurrent disease or other drugs or chemicals.

Unlikely: A clinical event whose time relationship to drug administration makes a causal connection improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals.

Unrelated: A clinical event with an incompatible time relationship to drug administration and which could be explained by underlying disease or other drugs or chemicals.

Unclassifiable: A clinical event with insufficient information to permit assessment and identification of the cause.

Mortality

Four patients (1.3%) died during the follow-up period. The mean age was for these four patients was 64 years (range 61–84 years). One patient died from Gram-negative septicemia, one from duodenal ulcer bleeding, one from massive gastrointestinal bleeding complicating non-Hodgkin's lymphoma, and one from metastatic gastric adenocarcinoma. All four patients who died were on concomitant immunosuppressants, 6-MP and corticosteroids in three patients and 6-MP monotherapy in one patient. The mean age of the four patients who died was 64 years, which was significantly higher than the mean age for the group (40 years, $P < 0.00001$). Mortality was significantly higher among patients who were on concomitant immunosuppressants compared to patients not on concomitant immunosuppressants (2.9% versus 0%; $P = 0.04$) (Fig. 1).

DISCUSSION

The present study reports the safety data in a single center of a cohort of patients with CD who received infliximab. While the rate of all adverse events was found to be 33%, a total of 14% of them were deemed serious. Four patients (1.3%) died during the study period, all of whom were receiving concomitant immunosuppressant therapies and of note all four deaths occurred in relatively old patients.

The TREAT registry, which is a prospective, multicenter, and long-term infliximab registry of North American patients with CD, has provided valuable safety data regarding the therapy. Although the risk of serious infections observed with infliximab treatment was found to be increased in the registry, mortality rates were similar between infliximab and noninfliximab receiving groups.²⁰ In our study the majority of infections were mild and resolved with medical treatment. The rate of severe infections was 3% in our study, one of whom died with sepsis. In a case-control study from the Mayo Clinic, the odds ratio for opportunistic infections associated with the use of corticosteroids, AZA/6-MP, or infliximab was 2.6 (95% confidence interval [CI] 1.4–4.7), and increased to 12.9 (95% CI 4.5–37.0) when two or more drugs were used.²¹ There was a 4-fold increase in infections among patients receiving concomitant immunosuppressants compared to the patients receiving infliximab without concomitant immunosuppressants in our study group. While concomitant corticosteroids was significantly associated with an increased infection rate, the frequency of infections was similar throughout the range of infusions, with no association seen between infections and first infusions.

In our study, all adverse events except acute infusion reactions and delayed reactions were significantly higher among patients taking concomitant immunosuppressants (Fig. 1). While previous data have shown that coadminis-

tration of immunosuppressive drugs can reduce infusion reactions, our results did not support these observations, possibly limited by the relatively small number of infusion reactions in our study.^{22,23} Only one patient experienced an anaphylactoid reaction during their infusion but was successfully treated and 8 weeks later was able to tolerate reinfusion after desensitization, as has been reported previously.²⁴

Analysis of randomized controlled trials reveals an infusion reaction rate of $\approx 22\%$ among patients receiving infliximab infusion compared to 9% in placebo groups.^{1–6} Seventeen percent of our patients developed infusion reactions, which were severe in 6% of patients. Severe delayed reactions were seen in 1.3% of patients, a number of whom required hospitalization. The majority of infusion reactions were experienced during induction rather than maintenance therapy and when expressed as a percentage of the total number of infusions only 1% of the 1794 infusions administered were associated with infusion reactions. However, even this low infusion reaction rate probably does not justify home administration of infliximab because of the potentially life-threatening nature of severe infusion reactions.

Lupus-like disease with formation of autoantibodies and arthritis and other systemic symptoms occurred in three patients and is similar in frequency to previous studies.¹² One patient was diagnosed as having possible multiple sclerosis during our study. In 1996 van Oosten et al²⁵ showed increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal antitumor necrosis factor (TNF) antibody cA2. Since then several studies have reported demyelinating diseases during infliximab treatment.^{12,26} Interestingly, a recent study by Gupta et al,²⁸ reported that demyelinating diseases occur more frequently among patients with IBD compared to non-IBD patients. Ultimately, more data are required to clarify whether anti-TNF biologic agents result in significantly increased incidence rates of demyelination among IBD patients.

The integrity of the immune system remains very important in controlling tumor antigens, and consequently increased risk of malignancy, in particular lymphoma, is a potential outcome among patients treated with infliximab.¹⁸ Reassuringly, the rate of malignancy among trial patients who are taking infliximab is reported to be similar to that expected for patient populations not receiving infliximab.²⁷ A total of six cancers (2.1%) were seen in our study group, four of whom were receiving 6-MP including both patients who developed lymphoma who were receiving concomitant 6-MP for long periods. Interestingly, while the TREAT registry has reported no significant difference in lymphoma rates among infliximab and noninfliximab patients,²⁰ there are ample data suggesting a slight increased risk of

lymphoma among IBD patients treated with 6-MP or azathioprine.^{28,29} It is well known that malignancy rates increase with aging in normal populations. We cannot directly compare the malignancy rate with the standardized incidence rates reported in population-based studies because of the relatively small sample size of our study.

Recognition that reactivation of latent tuberculosis can complicate infliximab use^{17,30} led to the introduction of guidelines in 2001 recommending PPD skin testing and chest x-ray examinations prior to initiating infliximab therapy.³² Our experience of no cases of tuberculosis is similar to other North American and German infliximab series.^{31,33} In addition to PPD and chest x-ray screening, the lack of tuberculosis reactivation in these studies as in ours could also reflect the relatively low prevalence of tuberculosis among the background population treated in these geographical locations.³³

Mortality rates of $\approx 0.5\%$ – 1.5% has been reported in other large infliximab series²⁰ and is similar to our mortality rate of 1.4%. It is noteworthy that all four deaths that occurred in our study occurred in elderly patients who were also receiving concomitant immunosuppressants. With the exception of one patient who died with advanced gastric adenocarcinoma of the cardia, the remaining three patients who died were on corticosteroids and 6-MP in addition to infliximab. These results support the data from the TREAT registry, which has reported corticosteroid use as an independent risk factor for serious infection and death in patients receiving infliximab.²⁰ Similarly, a retrospective-cohort study evaluating the mortality rate, for the era prior to anti-TNF therapies was done by Lewis et al.³⁵ They reported that IBD patients treated with corticosteroids, but not thiopurines, are at increased risk of death. However, it is important to remember that patients who need more than one medication tend to have more serious and complicated CD. This could cause “bias by indication.”

In conclusion, our single-center experience details the short and long-term safety profile of infliximab in a large group of patients. The relatively long duration of CD makes these data unique. Infliximab was well tolerated in the majority of patients, but serious side effects, particularly serious infections, can occur especially in patients on concomitant immunosuppressants. The rate of serious infections was higher among those patients receiving concomitant corticosteroids compared to those receiving concomitant 6-MP or AZA, but the difference was not significant, which may reflect the relatively smaller number of patients in these subgroups. Malignancy and mortality were significantly higher among elderly patients in our study, while other adverse events including infections showed no difference with respect to age. Furthermore, concomitant immunosuppressants had little protective effect against

infusion reactions in our study, despite several studies claiming that immunosuppressants may decrease infusion reactions.³⁶ While the overall safety experience is reassuring, clinicians should weigh the benefits and risks of anti-TNF therapy in all patients, with particular evidence from our study suggesting that risk of infection and malignancy may outweigh benefits among elderly patients.

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