CLINICAL–ALIMENTARY TRACT

The Safety Profile of Infliximab in Patients With Crohn's Disease: The Mayo Clinic Experience in 500 Patients

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Background & Aims: **The aim of this study was to evaluate the short- and long-term safety of infliximab in patients with Crohn's disease in clinical practice.** ***Methods:*** **The medical records of 500 consecutive patients treated with infliximab at the Mayo Clinic were reviewed and abstracted for demographic features and adverse events. The likelihood of a causal relationship to infliximab for each adverse event was determined by calculating an intrinsic likelihood (imputability) score.** ***Results:*** **The 500 patients received a median of 3 infusions and had a median follow-up of 17 months. Forty-three patients (8.6%) experienced a serious adverse event, of which 30 (6%) were related to infliximab. Acute infusion reactions occurred in 19 of 500 patients (3.8%). Serum sickness–like disease occurred in 19 of 500 patients and was attributed to infliximab in 14 (2.8%). Three patients developed drug-induced lupus. One patient developed a new demyelination disorder. Forty-eight patients had an infectious event, of which 41 (8.2%) were attributed to infliximab. Twenty patients had a serious infection: 2 had fatal sepsis, 8 had pneumonia (of which 2 cases were fatal), 6 had viral infections, 2 had abdominal abscesses requiring surgery, one had arm cellulitis, and one had histoplasmosis. Nine patients had a malignant disorder, 3 of which were possibly related to infliximab. A total of 10 deaths were observed. For 5 of these patients (1%), the events leading to death were possibly related to infliximab.** ***Conclusions:*** **Short- and long-term infliximab therapy is generally well tolerated. However, clinicians must be vigilant for the occurrence of infrequent but serious events, including serum sickness–like reaction, opportunistic infection and sepsis, and autoimmune disorders.**

Anti–tumor necrosis factor therapy is an important therapeutic addition in the treatment of patients with active Crohn's disease (CD). Controlled trials have confirmed the efficacy of infliximab in active CD.[1,2] In responding patients, complete clinical remission can be induced in about one third of patients who did not respond to standard treatment. A new indication is the long-term maintenance treatment of chronic refractory and fistulizing CD.[3,4] More than 150,000 patients with CD have been treated with infliximab, and in large centers the reported efficacy during relatively short-term follow-up has been comparable with data reported in controlled clinical trials.[5–8]

On the other hand, infrequent but serious toxicities related to tumor necrosis factor–neutralizing therapies have emerged. The most concerning are infectious complications, autoimmune disorders, and the theoretical risk of cancer and lymphoma. The available safety data on infliximab are from clinical trials (which represent patient populations selected to meet specific exclusion criteria, thus excluding patients with short-bowel syndrome, patients with stomas, hospitalized patients, patients with severe comorbidities, and so on), case reports, and postmarketing surveillance (which is susceptible to significant underreporting). Information regarding the safety of long-term therapy with infliximab in clinical practice in less-selected patient populations is limited. The purpose of this study was to evaluate the safety profile of infliximab in clinical practice in patients with CD.

Patients and Methods

This study is a retrospective cohort study. Eligible patients were patients with CD who were treated with infliximab at the Mayo Clinic in Rochester, Minnesota, between October 1998 and October 2002. All infusions of infliximab were administered to hospital inpatients or in-hospital outpatient infusion centers at 2 Mayo Clinic hospitals. The hospital pharmacy records from these hospitals were used to identify all patients with CD treated with infliximab during the study

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period. The diagnosis of CD was based on the final diagnosis of the attending physician using criteria that in general follow those used by Loftus et al.[9] Patients with ulcerative colitis and indeterminate colitis are not treated with infliximab at our institution outside of clinical trials. The medical records of these patients (including physician and hospital visits, telephone calls to patients, and telephone calls and written correspondence with other physicians and hospitals) were reviewed, and a computer spreadsheet was created to systematically record the following information for every patient: age, sex, duration of CD, body weight, anatomic extent of CD, concomitant use of corticosteroids, concomitant use of immunosuppressive agents (azathioprine, 6-mercaptopurine, methotrexate, mycophenolate mofetil), indication(s) for infliximab treatment, number of infliximab infusions, time on infliximab, infliximab administration strategy (induction therapy only, maintenance on demand, systematically scheduled maintenance, systematically scheduled maintenance with dose or interval escalation), any cancer or dysplasia (and any association with Epstein–Barr virus, human papilloma virus, or herpes simplex virus), any severe or opportunistic infections (including septic shock, bacteremia, pneumonia, tuberculosis, mycobacterium infections, histoplasmosis, listeriosis, legionellosis, hemorrhagic colitis due to *Escherichia coli*, aspergillosis, *Candida* infection, cytomegalovirus infections, and varicella and herpes zoster infections), specific autoimmune disorders (including delayed hypersensitivity-like reactions, drug-induced lupus, and demyelination/multiple sclerosis), and cardiovascular complications. The short-term follow-up of the first 100 of these patients with CD has been reported previously.[6] This study was approved by the Institutional Review Board of the Mayo Foundation.

Infliximab (Remicade; Centocor Inc., Malvern, PA) was administered initially at a dose of 5 mg/kg as a 2-hour intravenous infusion. Patients with fistulizing disease received 1–3 doses of infliximab over 8 weeks as induction therapy. Similarly, patients with inflammatory disease received 1–2 infusions over 8 weeks as induction therapy. Subsequently, the patients received different numbers of infusions depending on the treatment indication, clinical response, and preferences of each treating physician. Maintenance schedules were individually tailored by treating physicians because of a lack of published data and regulatory approval defining the optimal maintenance treatment regimen before the summer of 2002. Patients were classified into one of 4 groups according to how infliximab was administered: (1) induction therapy only, (2) induction therapy followed by on-demand maintenance therapy, (3) induction therapy followed by scheduled maintenance therapy every 8 weeks, and (4) induction therapy followed by scheduled maintenance therapy with escalation of dose and/or shortened dosing intervals.

Potential complications of infliximab included infusion reactions, serum sickness–like reactions, drug-induced lupus and other autoimmune diseases, cardiovascular complications, serious infections, cancers, and death. Serious adverse events were defined as those leading to or prolonging hospitalization, those that were fatal or life threatening, or those that resulted in significant disability. Serious infections were defined as those leading to or prolonging hospitalization, those that were fatal or life threatening or that resulting in significant disability, and opportunistic infections. Acute infusion reactions were defined as any significant adverse experience that occurred during or within 1 hour after infusion. Serum sickness–like reactions were defined clinically as the occurrence of at least one of the following cluster of features occurring 1–14 days after reinfusion of infliximab: myalgias, arthralgias, fever, or rash.[10,11] Although serum sickness–like reactions have been associated with the rapid formation of high-titer human antichimeric antibodies,[10,11] the ability to measure high-titer human antichimeric antibodies was not commercially available in the United States until 2002[12] and it was therefore not possible to measure high-titer human antichimeric antibodies in those patients suspected of having a serum sickness–like reaction. The diagnosis of drug-induced lupus was based on the presence of at least one of the following clinical symptoms (muscle and joint pain and swelling, flu-like symptoms, and fever) associated with the presence of antinuclear antibodies and either anti–double-stranded DNA or antihistone antibodies.

The likelihood of a causal relationship for each adverse event was determined with a method derived from Begaud et al. with 7 criteria divided into 2 groups: chronologic and clinical.[13] Chronologic criteria were time elapsed between a dose and adverse event, evolution of the adverse event when the therapy was discontinued, and evolution if the therapy was resumed. Clinical criteria were clinical signs, any existing favorable conditions (due to an underlying disease or state or to a drug interaction), evidence of another cause contributing to the clinical signs, and results of a reliable specific additional assay. Intrinsic likelihood (imputability) of a causal relationship was rated on a scale of 0–4 using the 7 criteria: 0, not related; 1, doubtful; 2, possible; 3, likely; 4, definite. Intrinsic likelihood scores ≥ 2 were considered to be at least possibly related to infliximab. The overall proportion of patients with adverse events was calculated irrespective of the length of their follow-up.

Data Analysis

Descriptive statistics were calculated as percentages reported for discrete data and medians (range) for continuous data. The cumulative probability of an infectious complication as a function of the cumulative number of infusions was estimated using the Kaplan–Meier survival method. It should be noted that this approach does not take into account the number of months on infliximab or the dose of infliximab. In particular, the underlying hazard rate for infections is thus a function of number of infusions, not time of observation. A stratified χ^2 analysis (Cochran–Mantel–Haenszel method) was used to assess the association of serious infection events in patients with CD treated with infliximab (serious infection and no serious infection). Each potential risk factor was examined in separate analyses. The individual potential risk factors of

Table 1. Baseline Characteristics of Patients

Median age, *yr* (range)	37 (5–85)
Male sex (%)	219 (44)
Median duration of disease, *yr* (range)	8 (0–60)
Disease location (%)	
Small bowel	124 (25)
Colon	164 (33)
Small bowel and colon	184 (37)
Pouch	28 (6)
Perianal disease	184 (37)
Indication for infliximab (%)	
Active inflammatory disease	323 (65)
Active fistulizing disease	120 (24)
Pouch failure	30 (6)
Others	27 (5)
Concomitant medication (%)	
Corticosteroids	156 (31)
Azathioprine/6-mercaptopurine	374 (75)
Methotrexate	53 (11)
Corticosteroids and either azathioprine, 6-mercaptopurine, or methotrexate	111 (22)
No immunosuppressant treatment[a]	37 (7)

[a]Indicates no corticosteroids, azathioprine, 6-mercaptopurine, or methotrexate.

interest included sex; age at time of first infliximab infusion; concomitant therapy with corticosteroids but not azathioprine, 6-mecaptopurine, or methotrexate; concomitant therapy with azathioprine, 6-mercaptopurine, or methotrexate but not corticosteroids; and concomitant therapy with both corticosteroids and azathioprine, 6-mercaptopurine, or methotrexate. Patients were stratified by number of infusions (1–5, 6–10, 11–15, 16–20, and ≥21), and the Cochran–Mantel–Haenszel test for general association across all strata was used to assess the association between each potential risk factor and occurrence of a serious infection. A multivariable analysis that simultaneously examined multiple risk factors was not performed because of the limited number of patients (n = 15) in the "serious infection" category.

Results

Patient Characteristics

A total of 512 consecutive patients met the eligibility criteria for the study. Twelve patients refused authorization for review of their medical records for research purposes, leaving a study cohort of 500 patients (98%) who were both eligible and gave written authorization for review of their medical records. A total of 219 male patients and 281 female patients with a median age of 37 years (range, 5–85 years) were included in the study. Twenty-eight of the 500 patients (6%) were children or adolescents (age 17 years or younger). Table 1 shows the demographic characteristics, duration of CD, disease location, and indications for infliximab treatment. The median follow-up was 17 months (range, 0–48 months), with only 38 patients (7.6%) having <4 weeks of follow-up. A total of 202 patients were followed up for 0–12 months, 121 patients were followed up for 13–24 months, 114 patients were followed up for 25–36 months, and 63 patients were followed up for 37–48 months.

Treatment With Infliximab

A total of 2211 infusions were administered. Patients received a mean ± SD of 4 ± 5 infusions (median number of infusions, 3; range, 1–46). The primary indication for treatment with infliximab was inflammatory luminal disease in 323 (65%), fistulizing disease in 120 (24%), CD of the ileoanal pouch in 30 (6%), and others, including extraintestinal manifestations, growth failure, or postoperative maintenance of remission in 27 (5%). A total of 245 patients (49%) received infliximab as induction therapy only, 159 (32%) received induction therapy followed by on-demand maintenance therapy, 75 (15%) received induction therapy followed by scheduled maintenance therapy every 8 weeks, and 21 (4%) received induction therapy followed by scheduled maintenance therapy requiring escalation of dose and/or shortened dosing intervals.

Serious Adverse Events

Forty-three patients (8.6%) experienced a serious adverse event (Table 2), of which 30 (6.0%) were considered at least possibly related, including 15 serious infections, 2 severe infusion reactions, 5 serum sickness–like reactions, 3 cases of drug-induced lupus, 2 cases of solid tumors, one case of non-Hodgkin's lymphoma, and one new demyelination syndrome. Finally, a 63-year-old woman with a 3-year history of Crohn's colitis with perianal complications and a 12-year history of cardiomyopathy received infliximab as maintenance therapy every 8 weeks in combination with methotrexate. She experienced worsening of heart failure after 14 infusions. Interruption of infusions and placement of a pacemaker were associated with cardiac improvement, and the event was judged possibly related to infliximab. This patient was treated before recent reports indicating that infliximab therapy is contraindicated in patients with congestive heart failure.[14,15]

Infusion reactions. Acute infusion reactions occurred in 19 of 500 patients (3.8%), leading to discontinuation of the infusion in 9 of 19 (Table 3). Two of the infusion reactions were potentially life-threatening cardiopulmonary symptoms that required treatment with epinephrine (see the first 2 patients in Table 3). Most infusion reactions (14 of 19) occurred after the second infusion, and the median time since last infusion was 1

Table 2. Summary of Serious Adverse Events

Intrinsic likelihood (imputability) score		
Score ≥2 points (n = 30)	Score <2 points (n = 13)	Total (n = 43)
Serious infections: n = 15 (4 with associated death) Infusion reactions: n = 2 Serum sickness–like disease: n = 5 Drug-induced lupus: n = 3 Cancer: n = 2 (one with associated death) Non-Hodgkin's lymphoma: n = 1 Demyelination: n = 1 Worsening of heart failure: n = 1	Serious infections: n = 3 Cancer: n = 5 (2) (one with associated death) Hodgkin's lymphoma: n = 1 Deaths of other origin: n = 4	Serious infections: n = 18 (4 with associated death) Infusion reactions: n = 2 Serum sickness–like disease: n = 5 Drug-induced lupus: n = 3 Cancer: n = 7 (2 with associated death) Non-Hodgkin's lymphoma: n = 1 Hodgkin's lymphoma: n = 1 Demyelination: n = 1 Worsening of heart failure: n = 1 Deaths of other origin: n = 4

month (range, 0.5–12 months). Infusion reactions occurred despite the use of concomitant corticosteroids or immunosuppressive medications in 17 of 19 patients and were associated with the subsequent occurrence of a serum sickness–like reaction in the following days in 2 cases. Only 3 of 11 patients were successfully reinfused. In the other 8 patients in whom reinfusion was attempted, a subsequent infusion was followed by the occurrence of a new infusion reaction and in 2 cases a serum sickness–like disease despite premedication with corticosteroids and/or diphenhydramine and acetaminophen. One patient who had already experienced 2 infusion reactions at a 10-month interval was successfully reinfused 1 month later following premedication with methylprednisolone, diphenhydramine, and acetaminophen.

Serum sickness–like disease. Serum sickness–like disease occurred in 19 of 500 patients and was considered at least possibly related to infliximab in 14 (2.8%) (Table 4). Five of these cases met the criteria of a serious adverse event, of which one has been reported in detail elsewhere.[16] A 33-year-old white man presented with an exacerbation of CD and was treated with his second infusion of infliximab 15 months after the first infusion. Within 7 days, he developed arthralgias, myalgias, and fever followed by respiratory failure. He required intubation and mechanical ventilation. An open lung biopsy specimen showed eosinophilic pneumonia. Human antichimeric antibodies were present at high concentrations. An extensive investigation for infectious etiologies was negative. The patient was treated with intravenous corticosteroids and fully recovered after a prolonged hospitalization. Most of the serum sickness–like reactions (11 of 15) occurred after the second infusion, and the median time from the last infusion was 10.5 months (range, 0.5–23 months). Serum sickness–like disease occurred despite the use of concomitant immunosuppressive medications in 12 of 14 patients. Patients were generally treated with a short course of corticosteroids. Among 3 patients who were subsequently reinfused, one who had developed an infusion reaction and serum sickness–like disease after a second infusion had a new infusion reaction after a third infusion. No follow-up was available for the other 2 patients. Four patients overall experienced both an infusion reaction and serum sickness–like disease during infliximab therapy.

Drug-induced lupus and other autoimmune diseases. Three patients developed clinical symptoms consistent with drug-induced lupus after 5, 10, and 19 infusions. All patients had antinuclear antibodies, 2 had anti–double-stranded DNA antibodies, and 2 had antihistone antibodies. One patient was successfully reinfused 22 months later; in another patient, a new infusion of infliximab 5 months later led to the recurrence of symptoms.

A 19-year-old woman with Crohn's ileocolitis developed numbness of the right arm and leg as well as weakness of the right hand 4 weeks after the initiation of infliximab therapy. Neurologic examination confirmed upper and lower right extremity sensory and motor deficits. Magnetic resonance imaging examination of the head and thoracic cord showed multiple gadolinium-enhancing lesions with distribution and configuration most suggestive of multiple sclerosis or other demyelinating process. Treatment with infliximab was immediately stopped, and follow-up at 8 weeks showed partial symptomatic but not radiographic improvement. This case is reported in detail elsewhere.[17]

Infections. Forty-eight patients had an infectious event, of which 41 (8.2%) were considered at least possibly related to infliximab (Table 5). Fifteen patients had a serious infection: 2 had fatal sepsis, 8 had pneumonia (of which 2 cases were fatal; one of these patients also had *Candida* esophagitis), one had severe viral gastroenteritis

Table 3. Summary of Infusion Reactions

Sex/age (*yr*)	Serious adverse event	Infusions (n)	Time since last infusion	Concomitant treatment	Chronologic criteria score	Clinical criteria score	Intrinsic likelihood (imputability) score	Short-term consequence of infliximab treatment	Follow-up
F/39	Yes	3	1 mo	Prednisone 20 mg, AZA 150 mg	3	3	4	Infusion stopped, patient treated with epinephrine[a]	No reinfusion since
F/20	Yes	2	1 mo	AZA 100 mg	3	3	4	Infusion stopped, patient treated with epinephrine[a]	No reinfusion since
F/25	No	2	1 mo	AZA 100 mg	3	3	4	10% of the dose infused	Third infusion with prednisone 2 months later: mild IR + SSLR, treatment stopped
F/21	No	2	3 mo	Methotrexate 25 mg	3	3	4	Infusion completed with S,A,D	SSLR following second infusion: third infusion 2 months later with S,A,D; new IR, treatment stopped
F/18	No	2	15 days	AZA 125 mg	3	1[b]	3	Infusion stopped	Successful reinfusion 6 months later with S,A,D, 13 infusions since
F/19	No	4	1 mo	6-MP 50 mg	3	3	4	Infusion stopped	No reinfusion since
F/31	No	2	15 days	AZA 125 mg	3	3	4	Not known	Reinfusion of 4 more doses; new IR at sixth dose despite A,D
F/29	No	12	1 mo	6-MP 100 mg	3	3	4	Infusion stopped	No reinfusion since
F/41	No	2	2 mo	—	3	3	4	Not known	No reinfusion since
F/26	No	2	5 mo	AZA 200 mg	3	3	4	Infusion stopped	Reinfusion 1 month later leading to new IR despite S,A,D
F/39	No	2	1 yr	6-MP 50 mg	3	3	4	Infusion completed	SSLR following the same injection; no reinfusion since
M/14	No	2	15 days	Prednisone 10 mg, 6-MP 50 mg	3	3	4	Infusion stopped	Reinfusion 2 months later leading to new IR despite prednisone and D
F/20	No	3	4 wk	AZA 125 mg	3	3	4	Infusion completed with D	Reinfusion 2 months later leading to IR despite S,A,D Reinfusion 16 months later leading to SSLR despite S,A,D
F/17	No	2	4 wk	Prednisone 40 mg	3	2	3	Infusion stopped	No reinfusion since
M/36	No	2	3 wk	Prednisone 20 mg	3	3	4	Not known	Successful reinfusion 13 months later with S,A,D
F/28	No	2	2 mo	AZA 150 mg	3	3	4	Infusion stopped	Reinfusion 3 months later leading to IR despite D
M/33	No	2	6 mo	AZA 200 mg	3	3	4	Not known	No reinfusion since
F/23	No	2	15 days	Prednisone 20 mg	3	1	3	Infusion completed	Reinfusion 10 months later leading to IR despite A,D; infusion completed; successful reinfusion 1 month later with S,A,D

AZA, azathioprine; IR, infusion reaction; SSLR, serum sickness–like reaction; S, 6-methylprednisolone; A, acetaminophen; D, diphenhydramine; 6-MP, 6-mercaptopurine.

[a]Anaphylactic reaction with potentially life-threatening cardiopulmonary symptoms.

[b]Patient has previously received rituximab for the treatment of B-cell lymphoma.

with dehydration requiring hospitalization, 2 had abdominal abscesses requiring surgery, and one had arm cellulitis. Finally, a 73-year-old man with ankylosing spondylitis and CD had infusions of infliximab 5 mg/kg every 2 months added to azathioprine 150 mg/day for postoperative maintenance of remission following a third ileal resection. He subsequently developed a right submandibular lymphoid mass that progressively enlarged. Histoplasmosis was diagnosed by excisional biopsy. Three patients had varicella-zoster virus infections that were not serious but probably represent opportunistic infections. Most infections occurred after a few infusions. The cumulative probability of an infectious complication relative to the cumulative number of

Table 4. Summary of Serum Sickness–Like Reactions

Sex/age (*yr*)	Serious adverse event	Infusions (n)	Time since last infusion	Concomitant treatment	Clinical symptoms	Chronologic criteria score	Clinical criteria score	Intrinsic likelihood (imputability) score	Treatment	Follow-up
M/33	Yes	2	15 mo	AZA 125 mg	Arthralgias, myalgias, acute respiratory distress syndrome[a]	3	3	4	See results in text	No reinfusion since
F/57	Yes	2	1 mo	AZA 250 mg	Arthralgias, myalgias, headache	3	2	3	S	No reinfusion since
M/43	Yes	2	21 mo	AZA 200 mg	Arthralgias, myalgias, fever	3	3	4	Morphine, prednisone 40 mg/10 days	No reinfusion since
F/68	Yes	4	12 mo	AZA 175 mg	Facial edema, esophageal discomfort	3	1	3	?	Reinfusion 1 month later, no follow up
F/21	Yes	2	6 wk	—	Fever	2	2	2	Prednisone 60 mg/ 2 weeks	No reinfusion since
F/63	No	2	9 mo	MTX 15 mg	Myalgias	3	2	3	Prednisone 30 mg; D 50 mg × 2 doses; A 1000 mg × 2 doses over 4 days	No reinfusion since
F/21	No	2	2 mo	MTX 25 mg	Myalgias, arthralgias	3	2	3	Six-day course tapering prednisone starting at 60 mg	Third infusion 2 mo later with S,A,D, new infusion reaction, treatment stopped[b]
F/30	No	2	23 mo	6-MP 75 mg	Rash	3	3	4	Prednisone 60 mg first day and 40 mg the day after	No reinfusion since
F/34	No	2	19 mo	6-MP 75 mg	Arthralgias, myalgias	3	3	4	Ten-day course tapering prednisone starting at 60 mg + D	No reinfusion since
F/20	No	5	16 mo	AZA 125 mg, tacrolimus	Severe jaw, shoulder, and leg stiffness	3	2	3	Prednisone 40 mg	No reinfusion since[b]
F/39	No	2	1 yr	6-MP 50 mg	Myalgias, fever	2	3	3	Prednisone 40 mg	No reinfusion since[b]
F/43	No	2	15 days	AZA 150 mg	Fever, "flu-like" symptoms	3	1	3	No	Reinfusion 1 month later, no follow-up available
F/25	No	3	2 mo	AZA 100 mg	Ankle swelling	2	2	2	Prednisone, D	No reinfusion since[b]
F/52	No	2	1 mo	AZA 100 mg	Rash	2	2	2	D	No reinfusion since
F/29	No	4[c]	8 mo	—	Rash	2	2	2	D, A	No reinfusion since
F/53	No	2	15 days	AZA 75 mg	Fatigue, jaw pain	2	1	1	No	Reinfusion 1 month later followed by numbness, tingling, and heaviness in chest
M/46	No	2	12 mo	MTX 25 mg	Arthralgias	2	1	1	Prednisone for 2 wk	Successful reinfusion 6 months later with S,A,D
F/42	No	2	3 mo	—	Rash	1[d]	3	1	No	No reinfusion since
F/44	No	4	4 mo	6-MP 100 mg	Pruritus	2	1	1	D	No reinfusion since
F/43	No	3	7 mo	MTX 25 mg	Arthralgias	2	1	1	Five-day course of prednisone 40 mg	No reinfusion since

AZA, azathioprine; MTX, methotrexate; D, diphenhydramine; A, acetaminophen; S, 6-methylprednisolone; 6-MP, 6-mercaptopurine.
[a]This case is reported in detail by Hanaver et al.[10]
[b]Infusion reaction and serum sickness–like reaction in the same patient.
[c]Patient previously treated with humanized immunoglobinG1 monoclonal antibody to tumor necrosis factor (CDP571); 3 blinded study infusions and one unblinded infusion 6 weeks before infusion of infliximab.
[d]Symptoms occurred 6 weeks after second infusion.

Table 5. Summary of Infectious Events

Type of infection	Sex/age (*yr*)	Infusions (n)	Time since last infusion	Concomitant treatment	Clinical presentation	Infectious agent	Serious adverse event (death)
Sepsis	F/35	1	Cellulitis: 1 wk Abscess: 7 wk Death: 12 wk	—	Cellulitis, intra-abdominal abscess, sepsis, respiratory failure	*Staphylococcus* in blood	Yes (yes)
	M/73	2	Pneumonia: 1 wk Multiple organ failure and death: 8 wk	Prednisone 20 mg/day	Cirrhosis with liver failure, renal insufficiency, and diabetes mellitus Peptic ulcer disease	?	Yes (yes)
Pneumonia	M/79	2	Pneumonia and death: 1 mo	Prednisone 40 mg/day	Lewy body dementia, anemia, bilateral pneumonia, respiratory failure	?	Yes (yes)
	M/74	2	Pneumonia and death: 8 wk	Prednisone 40 mg/day	Pneumonia, esophagitis	? *Candida albicans*	Yes (yes)
	F/47	6	2 wk	6-MP 75 mg/day	Pneumonia	*Streptococcus pneumoniae*	Yes (no)
	F/34	2	2 mo	6-MP 75 mg/day	Pneumonia	?	Yes (no)
	M/71	2	15 days	MTX 7.5 mg/wk	Pneumonia	?	Yes (no)
	F/32	11	1 mo	MTX 25 mg/wk	Pneumonia	?	Yes (no)
	F/52	1	1 mo	AZA 175 mg/day	Pneumonia	?	Yes (no)
	M/63	6	1 mo	MTX 12.5 mg/wk	Pneumonia, diarrhea	*Clostridium difficile* in stools	Yes (no)
Histoplasmosis	M/73	15	1 wk	AZA 150 mg/day	Swelling of the mandibular angle area	*Histoplasma capsulatum* in lymph node	Yes (no)
Viral infections	F/45	1	1 mo	AZA 150 mg/day Prednisone 15 mg/day	Shingles	Varicella-zoster virus	No (no)
	F/25	3	2 wk	AZA 100 mg/day	Chicken pox	Varicella-zoster virus	No (no)
	F/17	2	15 days	AZA 100 mg/day Prednisone 4 mg/day	Shingles	Varicella-zoster virus	No (no)
	F/49	1	1 mo	—	Genital herpes	Herpes simplex virus	No (no)
	F/15	6	6 wk	6-MP 50 mg/day	Mononucleosis	Epstein–Barr virus	No (no)
	F/42	3	1 mo	AZA 100 mg/day	Severe viral gastroenteritis with dehydration	?	Yes (no)
Abscesses	F/28	3	3 mo	AZA 150 mg/day	Abdominal abscess	*Enterococcus* *Candida albicans*	Yes (no)
	F/47	2	2 wk	—	Abdominal abscess	?	Yes (no)
	F/79	11	1 mo	—	Peristomal abscess	?	No (no)
	M/71	2	1 mo	Prednisone 40 mg/day AZA 100 mg/day	Postoperative cutaneous abscess	?	No (no)
	M/59	3	1 mo	AZA 200 mg/day	Perianal abscess	?	No (no)
	M/51	4	1 mo	AZA 100 mg/day	Perianal abscess	?	No (no)
	M/43	3	1 mo	AZA 150 mg/day	Perianal abscess	?	No (no)
	F/28	5	2 mo	AZA 175 mg/day	Perianal abscess	?	No (no)
	F/15	4	1 mo	MTX 15 mg/wk	Perianal abscess	?	No (no)
	F/36	2	1 mo	6-MP 150 mg/day	Perianal abscess	?	No (no)
Cutaneous infections	M/43	3	3 mo	Prednisone 20 mg/day	Arm cellulitis	?	Yes (no)
	F/53	4	1 wk	AZA 125 mg/day	Onychomycosis	*Candida albicans*	No (no)
	F/15	1	2 wk	—	Ulcerated lesion on surgical scar	*Serratia marcescens*	No (no)
	M/32	6	1 mo	AZA 250 mg/day	Leg cellulitis	?	No (no)
	F/48	2	3 mo	AZA 100 mg/day	Perioral pustules and scales	*Haemophilus* *Candida albicans*	No (no)
Upper respiratory tract infections	F/34	2	2 wk	MTX 25 mg/wk	Bronchitis	?	No (no)
	M/47	1	1 mo	AZA 200 mg/day	Bronchitis	?	No (no)
	F/26	2	6 wk	AZA 125 mg/day	Sinusitis	?	No (no)
	F/39	1	1 wk	AZA 100 mg/day	Pharyngitis	?	No (no)
	M/16	3	1 mo	6-MP 75 mg/day	Sinusitis	?	No (no)
	M/40	19	1 mo	AZA 100 mg/day	Sinusitis	?	No (no)
	M/37	2	1 wk	Prednisone 40 mg/day	Bronchitis	?	No (no)
	M/39	3	2 wk	AZA 200 mg/day	Bronchitis	?	No (no)
	M/37	2	1 mo	AZA 200 mg/day	Sinusitis	?	No (no)
Urinary tract infection	F/55	20	2 wk	AZA 175 mg/day	Pyuria	?	No (no)
Catheter infection	F/24	2	1 mo	Prednisone 20 mg/day	Fever	*Staphylococcus*	No (no)

6-MP, 6-mercaptopurine; MTX, methotrexate; AZA, azathioprine.

infliximab infusions is shown in Figure 1. The Cochran–Mantel–Haenszel analysis did not detect an association between serious infections and sex; age at time of first infliximab infusion; concomitant therapy with corticosteroids but not azathioprine, 6-mercaptopurine, or methotrexate; concomitant therapy with azathioprine, 6-mercaptopurine, or methotrexate but not corticosteroids; and concomitant therapy with both corticosteroids and azathioprine, 6-mercaptopurine, or methotrexate (Table 6).

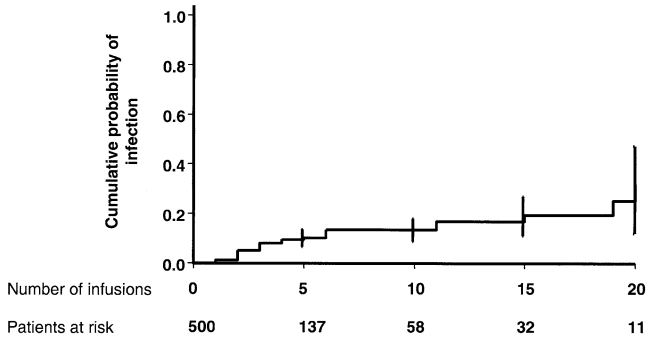

Figure 1. The cumulative probability of an infectious complication relative to the number of infliximab infusions in 500 patients.

Malignant disorder. Nine patients had a malignant disorder (Table 7). In 3 patients, the malignancy was judged as possibly related to infliximab. A 66-year-old female smoker with a 4-year history of CD and no concomitant treatment reported increasing fatigue 2 months after a third infusion of infliximab. She did not report any shortness of breath or chest pain. Her computed tomographic scan showed a right pulmonary lower lobe mass with metastasis of the liver. Bronchoscopy was not diagnostic. An ultrasound-guided liver biopsy specimen showed adenocarcinoma with lung primary. The event was judged as possibly related to infliximab because of the temporal association of the new diagnosis of lung cancer to the initiation of infliximab in a patient who was asymptomatic before treatment. A 65-year-old male smoker with a 16-year history of CD and treated with azathioprine 75 mg/day for 6 years was diagnosed with metastatic lung cancer 2 months after a ninth infusion of infliximab. Again, the event was judged as possibly related to infliximab because of the occurrence of a new diagnosis of lung cancer within 1.5 years of initiating infliximab therapy in a patient who was asymptomatic before treatment. A 70-year-old man underwent evaluation in October 2000 for a 7-year history of CD with colonic and perianal involvement, including abscess. Pelvic lymphadenopathy had been noted previously on magnetic resonance imaging and attributed to CD. He underwent incision and drainage of a perianal abscess and was treated with 3 infusions of infliximab and started on azathioprine 200 mg daily. Five months later, he reported malaise, worsening recurrent drenching night sweats, fever, and anorexia. He had massive splenomegaly and hepatomegaly. Biopsy of the bone marrow and right inguinal lymph node confirmed follicular non-Hodgkin's lymphoma stage IVB. The event was judged as possibly related to infliximab because of rapid progression from pelvic lymphadenopathy to stage IVB disease over 5 months (assuming that the baseline pelvic lymphadenopathy represented a preexisting lymphoma).

Deaths. A total of 10 deaths were observed (Table 8). For 5 of these patients (0.8%), the events leading to death were judged as either likely related or possibly related to infliximab. A 35-year-old woman with a 10-year history of CD developed an abdominal abscess that was drained surgically. She developed a postoperative abscess and fistula that required radiologic percutaneous drainage. Two months later, a sinogram was performed that showed persistence of the abscess cavity. The patient received one infusion of infliximab. She had not been on long-term medication for her CD. One week later, she developed cellulitis at the site of the percutaneous drain. Seven weeks after the infusion, she underwent an exploratory laparotomy for acute abdomen with debridement of an abscess cavity and right lower quadrant abdominal wall and repair of bladder fistula. She developed respiratory failure 5 days after surgery and died from sepsis 12 weeks after the infusion. A 73-year-old man with a 21-year history of CD received 2 infusions of infliximab within a 15-day interval. He was treated with prednisone 20 mg/day for 2 months. Two days after the second infusion, he appeared lethargic and disoriented and was hospitalized. A diagnosis of hepatic encephalopathy with

Table 6. Summary of Cochran–Mantel–Haenszel Analyses of Each Potential Risk Factor for Serious Infection

Variables	*P*	Odds ratio (95% confidence interval)
Male sex (reference is females)	0.82	0.89 (0.33–2.40)
Greater than median age at time of first infliximab infusion (reference is age less than or equal to median)	0.05	0.35 (0.12–1.05)
Concomitant corticosteroids but not azathioprine, 6-mercaptopurine, or methotrexate (reference is no corticosteroids and no azathioprine, 6-mercaptopurine, or methotrexate)	0.37	0.38 (0.04–3.43)
Concomitant azathioprine, 6-mercaptopurine, or methotrexate but not corticosteroids (reference is no corticosteroids and no azathioprine, 6-mercaptopurine, or methotrexate)	0.94	0.92 (0.12–7.14)
Concomitant corticosteroids and azathioprine, 6-mercaptopurine, or methotrexate (reference is no corticosteroids and no azathioprine, 6-mercaptopurine, or methotrexate)	0.74	1.50 (0.14–15.98)

NOTE. Cochran–Mantel–Haenszel analysis for serious infection versus no serious infection. An odds ratio >1 represents an increased risk for infection (see Patients and Methods for details). Significance is defined as $P < 0.05$.

Table 7. Summary of Malignant Disorders

Sex/age (*yr*)	Infusions (n)	Delay since last infusion	Associated treatment	Length of associated treatment	Clinical presentation	Chronologic criteria score	Clinical criteria score	Intrinsic likelihood (imputability) score
F/66	3	2 mo	—	—	Lung cancer	1	2	2
M/65	9	2 mo	Azathioprine	6 yr	Metastatic lung cancer	2	2	2
M/70	3	5 mo	Azathioprine	5 mo	Non-Hodgkin's lymphoma, *B*-cell phenotype, Epstein–Barr virus status unknown	2	2	2
M/51	4	6 mo	Azathioprine	6 yr	Hodgkin's lymphoma	1	1	1
F/51	1	1 wk	—	—	Abdominal carcinomatosis	0	1	0
M/63	4	1 mo	Azathioprine	18 mo	Squamous cell carcinoma	1	2	1
M/57	3	5 mo	Azathioprine	1 yr	Basal cell carcinoma	1	2	1
F/45	2	15 mo	Azathioprine	4 yr	Squamous cell carcinoma	0	1	0
F/45	3	11 mo	—	—	Basal cell carcinoma	0	2	0

liver failure most likely due to previously undiagnosed alcoholic liver cirrhosis was made. Pneumonia was detected. His condition progressively worsened, with appearance of renal insufficiency and diabetes mellitus. Five weeks after the second infusion, he underwent an operation for a perforated duodenal ulcer. His liver and kidney function continued to deteriorate, and he died from multiple organ failure 3 weeks later. Although

Table 8. Summary of Deaths

Gender/age (*yr*)	Cause	Infusions (n)	Time since last infusion	Associated treatment (duration)	Clinical presentation	Intrinsic likelihood (imputability) score
F/35	Sepsis	1	Cellulitis: 1 wk Abscess: 7 wk Death: 12 wk	—	Cellulitis, intra-abdominal abscess, sepsis, respiratory failure	3
M/73	Multiple organ failure	2	Pneumonia: 1 wk Multiple organ failure and death: 8 wk	Prednisone 20 mg (2 mo)	Pneumonia, multiple organ failure; associated conditions; cirrhosis with liver failure, renal insufficiency and diabetes mellitus, peptic ulcer disease	3
M/79	Respiratory failure	2	Pneumonia and death: 1 mo	Prednisone 40 mg (26 yr)	Bilateral pneumonia, respiratory failure; associated conditions: Lewy body dementia, anemia	2
M/74	Pneumonia	2	*Candida* esophagitis: 1 mo Death: 8 wk	Prednisone 10 mg (5 mo)	Associated conditions: history of azathioprine-associated pancreatitis with pseudocysts, type 1 diabetes mellitus	2
F/66	Lung cancer	3	2 mo	—	Lung cancer with metastasis	2
F/51	Abdominal carcinomatosis	1	1 wk	—	Abdominal carcinomatosis discovered at surgery	1
M/86	Unknown	2	4 mo	Prednisone 15 mg, total parenteral nutrition (4 mo)	*Staphylococcus* septicemia, recurrent *Clostridium difficile* infection	0
F/68	Unknown	3	2 yr	Azathioprine 150 mg (2 yr)	Associated conditions: short-bowel syndrome, coronary heart disease, renal failure	0
F/58	Unknown	1	2 days	—	Associated conditions: hypertension, obesity, cryptogenic cirrhosis with portal hypertension, aortic stenosis	0
M/32	Unknown	8	2 mo	Prednisone 50 mg, methotrexate 25 mg (8 mo)	Associated conditions: mesenteric vein thrombosis, central vein catheter infection, Graves' disease	0

there were multiple factors that contributed to this patient's death, the temporal association between the infusions of infliximab and the development of pneumonia make it impossible to exclude the possibility that infliximab caused or contributed to his death. A 79-year-old patient with a 26-year history of CD received 2 infusions of infliximab within an 8-week interval for active disease despite the use of prednisone 40 mg/day that he received almost continuously for 26 years. He was chronically debilitated with coronary artery disease, Lewy body dementia, failure to thrive, and weight loss. He was hospitalized for bilateral pneumonia 1 month after the second infusion and died from respiratory failure. A 73-year-old patient with a 15-year history of CD died from pneumonia 8 weeks after a third infusion of infliximab. He had chronic pancreatitis complicated by a pseudocyst and pancreatic endocrine and exocrine insufficiency. An upper endoscopy 1 month before death showed ulcerations within the lower esophagus with *Candida* infection. The final patient's death was related to lung cancer.

The median age of the 10 deceased patients was 67 years (range, 31–85 years); 6 of the 10 had a severe comorbidity associated with CD: liver cirrhosis in 2, dementia, type 1 diabetes mellitus, coronary heart disease, and mesenteric thrombosis. In addition, one of the 10 had a contraindication to treatment (persistent abdominal abscess).

Discussion

The safety profile of infliximab is a timely issue because its use and indications are rapidly increasing. Safety data in CD are available from controlled trials of up to 1 year in duration that included 1057 carefully selected patients: 102 of 108 patients with luminal CD received 1–2 induction doses of infliximab over 12 weeks, of whom 37 of 73 were retreated with 1–4 maintenance doses over 36 weeks[1,18]; 63 of 94 patients with fistulizing CD received 3 induction doses over 18 weeks[2]; 573 patients with luminal CD received 1–8 induction and maintenance doses over 54 weeks (mean ± SD of 5.3 ± 2.9 doses); and 282 patients with fistulizing CD received 3–8 induction and maintenance doses over 54 weeks.[4] In addition, there are reports of adverse events from postmarketing surveillance[11,14,19–23]; these postmarketing surveillance reports are probably incomplete due to the highly variable and relatively low level of reporting. There are no published data regarding the use of infliximab for more than 1 year or more than 8 doses in patients with CD. The present study for the first time provides a point estimate of adverse events associated with short-term and long-term use of infliximab in a large consecutive group of unselected patients with CD treated in clinical practice, including patients treated for more than 1 year with more than 8 doses. The relatively low number of median infusions (3) in our study reflects the lack of published data and regulatory approval before the summer of 2002 that specified a 3-dose induction regimen over 6 weeks followed by systematic maintenance dosing every 8 weeks. Our data confirm that infliximab is generally well tolerated. The 6% rate of serious adverse events reasonably related to the drug is consistent with the rate of 7% observed in the 573 patients with CD treated with infliximab for up to 1 year in the ACCENT I maintenance trial.[3] Nevertheless, our results also point to the occurrence of rare but severe side effects that must be anticipated and recognized by the clinicians.

Acute infusion reactions occurred in <4% of patients. This percentage is lower than the result observed in clinical trials (22%)[11] and in previous uncontrolled series (5%–19%).[5,6,24] The first explanation is that we only recorded clinically important reactions. More than half of our reported infusion reactions, representing 1.8% of the total, led to the permanent discontinuation of the infusion. In the combined safety data from all clinical trials with infliximab, 2.6% of patients had infusion reactions leading to discontinuation,[11] which is comparable to our results. The low incidence of acute infusion reactions in our study is also consistent with previous observations that concomitant treatment with immune modifiers may also reduce the frequency of infusion reactions,[12,25] because nearly 90% of our patients were receiving concomitant immunosuppressive medications started either before or at the time that they received their first infusion of infliximab. Nevertheless, this coadministration of immunosuppressive medications clearly does not completely abolish the risk because 17 of 19 reactions occurred in patients treated with corticosteroids or azathioprine, 6-mercaptopurine, or methotrexate. Two infusion reactions were life threatening and required treatment with epinephrine. Severe anaphylactic or anaphylactic-like reactions with clinical symptoms including hypotension, laryngeal/pharyngeal edema, and severe bronchospasm have already been reported during infliximab infusion.[26–28] This underscores the fact that clinicians should be prepared to manage patients experiencing severe infusion reactions and that home-care administration of infliximab should only be undertaken with great caution, if at all. In clinical trials, there has been little long-term effect of acute infusion reactions on short-term responses. However, in our experience, severe infusion reactions clearly impact on the use of infliximab because only a minority of patients was successfully reinfused. Several means have been proposed to reduce the

frequency of infusion reactions (by reducing the development of antibodies to infliximab) such as systematic repeated infusions at 0, 2, and 6 weeks; use of immunosuppressive medications; and pretreatment with a high dose of intravenous corticosteroids before initial infusion.[12,25]

Serum sickness–like disease, characterized by myalgias, arthralgias, fever, and rash occurring within 1–14 days of infusion, was seen in 14 patients (2.8%). Five of 14 met the criteria of a serious adverse event. One case that was particularly severe, leading to an acute respiratory distress syndrome, was an unusually severe delayed hypersensitivity reaction to infliximab.[16] There are limited data characterizing the rate of systemic reactions after retreatment with infliximab. Serum sickness–like reactions were uncommon (2% of patients) in the ACCENT I trial, in which patients received scheduled infusions.[3] On the other hand, in an uncontrolled series, delayed systemic reactions occurred in 9% (8 of 86) of the total CD population treated with infliximab and accounted for three fourths of the severe adverse reactions encountered in retreated patients.[29] As in our experience, reactions occurred after a prolonged interval before drug reinfusion and despite the use of concomitant immunosuppressive medications in most patients. Only a minority of patients in our study who experienced serum sickness–like reactions subsequently underwent retreatment with infliximab. In other disease settings, such as when γ-globulin is administered, serum sickness–like reactions are easily retreated with premedication with corticosteroids and diphenhydramine.

Three patients developed a lupus-like syndrome. This finding is similar to previous reports. In the ACCENT I maintenance trial, although 34% of patients assigned maintenance treatment developed anti–double-stranded DNA, only 2 patients developed drug-induced lupus.[3] In an open-label clinical experience, 7.2% of 125 patients with CD initiating treatment with infliximab were positive for antinuclear antibody at baseline; the frequency of a positive antinuclear antibody reaction increased to 56.8% after infliximab therapy, with most patients becoming antinuclear antibody positive after one or 2 infusions.[30] Two of 125 patients developed clinical evidence of drug-induced lupus manifested by a butterfly rash and polyarthralgias in conjunction with a positive antinuclear antibody, anti–double-stranded DNA antibody, and antihistone antibody, and one developed autoimmune hemolytic anemia. The case of demyelination that developed shortly after starting therapy with infliximab is more concerning. Limited data have been presented linking anti–tumor necrosis factor α therapy in patients with CD with new-onset multiple sclerosis–like syndromes. Mohan et al. described 20 patients with demyelinating processes during the use of anti–tumor necrosis factor therapy (2 with infliximab and 18 with etanercept) for inflammatory arthritis.[23] Signs and symptoms from these processes included vision changes from optic neuritis, paresthesias, gait changes, confusion, apraxia, ascending paralysis, and facial palsy. The most common symptom was paresthesias, which occurred in 65% of cases. The mean time to symptom onset from initiation of therapy was 5 months but ranged from 1 week to 15 months. In most cases, patients experienced partial or complete resolution of their symptoms following discontinuation of therapy. Physicians should be aware of this adverse effect and should monitor for neurologic symptoms throughout infliximab therapy. Patients who develop new neurologic symptoms should undergo evaluation by magnetic resonance imaging.

The most frequent cause of serious adverse events associated with use of infliximab in this series was infection with sepsis and pneumonia, leading to 4 deaths. Even though almost all patients were treated with concomitant corticosteroids and/or immunosuppressive therapy, the temporal relationship between infusions of infliximab and the occurrence of infections made the causal relationship with the drug likely. In clinical trials, no statistically significant increase in serious infections or sepsis was observed in infliximab-treated patients compared with placebo-treated patients.[11] However, many placebo-treated patients were crossed over to therapy with infliximab, so the duration of observation under placebo is relatively limited. In clinical practice, the use of infliximab has been associated with definite occurrence of unexpected infections. In the postmarketing experience, in 271,000 patients followed up, the rate of pulmonary complications was 0.29%. Recent published data emphasized the risk of tuberculosis associated with infliximab leading to the recommendation that patients undergo purified protein derivative skin testing before infliximab therapy.[21] No case of tuberculosis was observed in this series. This may be due to the low endemic incidence of tuberculosis in the predominant rural population with relatively few migrants treated at our institution. In our study, one case of histoplasmosis (since this study was completed, a second patient in the study cohort developed disseminated histoplasmosis), 3 varicella-zoster virus infections, and one case of *Candida* esophagitis were observed. In postmarketing experience, opportunistic infections including *Pneumocystis carinii* pneumonia, histoplasmosis, listeriosis, aspergillosis, coccidioidomycosis, cytomegalovirus infections, cryptococcosis, and systemic candidiasis have all been described

and in some instances have led to patient death.[11,22,31–36] One of the most interesting findings from this study was that the rate of infectious events did not correlate with the number of infusions. Nearly 70% of infections in our series occurred after 3 or fewer infusions. This is consistent with what has been described regarding the risk of tuberculosis; in the report by Keane et al., 48 of the 70 patients developed tuberculosis after 3 or fewer infusions.[21] Whether this predilection to infection early in the course of treatment with infliximab reflects a worse general status of patients when infliximab is started or an individual predisposition is unknown.[37] Stratified χ^2 analysis for serious infection failed to detect a statistically significant association for any of the potential risk factors.

The 1.5% extracolonic cancer rate possibly related to infliximab observed in our study is similar to the rate of 18 of 1678 (1.1%) of new or recurrent cancers observed in patients who have completed clinical trials with infliximab,[38] including the 1.0% rate observed in the ACCENT I trial.[3] Population-based studies have shown that there is not an overall increased risk of extracolonic malignancies in patients with CD,[39–42] with the possible exceptions of non-Hodgkin's lymphoma[41,42] and squamous skin cancers.[39] The crude rates of extracolonic cancers observed in our study cannot be directly compared with the standardized incidence rates reported in these population-based studies; however, the observed rates and incidences of malignancies in completed clinical trials of infliximab were similar to those expected for the patient populations studied.[38] Thus, our data from a large treated population generally concur with the conclusion that a causal association between infliximab and risk of malignant disease is unlikely.

The 1% mortality rate possibly related to infliximab observed in this large case series is higher than the 1.4 reports per 1000 patients (0.14%) observed in postmarketing surveillance but is generally comparable to the 0.5% rate observed in the ACCENT I trial.[3] The mortality rate in our study is also generally comparable with the expected excess of mortality reported in patients with CD, particularly when considering that infliximab therapy is indicated only for patients with moderate to severe CD who are unresponsive to conventional therapy.[9,43,44] It should be emphasized that 3 of the 5 attributable deaths were associated with a relatively old age of patients (73, 79, and 73 years) and severe comorbidities, both of which are known to be major contributing factors to mortality risk. A fourth patient with a death attributable to infliximab was a 35-year-old patient with a persistent abdominal abscess. Treatment with infliximab is contraindicated in patients with serious infections,[11] and this particular patient should not have been treated with infliximab.

The data for this retrospective cohort study were obtained from patient medical records, which included physician and hospital visits, telephone calls to patients, and telephone calls and written correspondence with other physicians and hospitals. It is possible that some episodes of infliximab-related toxicity occurred that were diagnosed and treated by other health care providers and were not recorded in the Mayo Clinic medial record. Thus, the results of our study may represent an underestimate of the true rate of infliximab-related toxicity.

In conclusion, short-term and long-term infliximab therapy is generally well tolerated. However, clinicians must be vigilant for the occurrence of infrequent but serious events, including serum sickness–like reaction, opportunistic infection and sepsis, and autoimmune disorders. Caution is required when prescribing the drug in elderly patients, especially when comorbidity is associated.

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