Infliximab for Crohn's Disease: More Than 13 Years of Real-world Experience

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Background: The purpose of this study was to compare the long-term safety of infliximab and nonbiologic agents as Crohn's disease (CD) therapy.

Methods: Patients with CD were prospectively evaluated in this large, observational registry.

Results: Patients (n = 6273) participated in this observational registry from July 1999 through March 2012; 3440 (54.8%) received infliximab (20,971 patient-years), and 2833 (45.2%) received other treatments only (14,806 patient-years). Overall, 59,875 infliximab infusions were

administered (80%, 5 mg/kg); 3006 (89.9%) patients received ≥2 infusions. Adverse events (AEs), most commonly those related to CD (eg, abdominal pain, diarrhea), and serious AEs occurred at a higher rate among infliximab-treated patients. Mortality (0.57/100 patient-years, 0.67/100 patient-years) and malignancy rates (0.69/100 patient-years, 0.71/100 patient-years) for infliximab-treated and other-treatments-only patients, respectively, were generally similar. Serious infection rates were higher for infliximab-treated (2.15/100 patient-years) than other-treatments-only patients (0.86/100 patient-years). Infliximab dose was not associated with mortality or serious infection. An increased risk of serious infection was observed with age (>52 years vs ≤30 years) when examined in infliximab-treated patients. Nonserious cerebrovascular accidents (13 events, 0.06/100 patient-years; 5 events, 0.03/100 patient-years) and pulmonary embolisms (11 events, 0.05/100 patient-years; 4 events 0.03/100 patient-years) also occurred at higher rates among infliximab-treated patients than other-treatments-only patients.

Conclusions: Through more than 13 years of registry experience and an overall median duration of patient follow-up >6 years, mortality was similar between the infliximab-treated and other-treatments-only groups. These final cumulative results are representative of real-world experience among infliximab-treated patients with CD and are consistent with the known risks of disease activity and tumor necrosis factor antagonist therapy.

Key Words: safety profile, infusion reaction, real-world evidence, TREAT Registry

INTRODUCTION

Registries provide important information about the safety of new drugs to healthcare professionals and researchers. Specifically, their relatively large size and long duration allow more precise estimates of the occurrence of adverse events (AEs) that are not obtainable from short-term randomized controlled trials. Upon the marketing authorization of infliximab in 1998, the Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT™; ClinicalTrials.gov NCT00553176) Registry was initiated to evaluate the long-term safety outcomes of infliximab and standard-of-care treatment regimens used in the management of Crohn's disease (CD).[1] This North American registry was observational and not protocol driven; patient care was administered at the discretion of the treating physician.

Initial safety findings from the registry were previously published after an average follow-up of 2 years, and again after more than 5 years per patient.[1, 2] These initial assessments were similar and indicated that mortality risk was comparable between patients with CD who were receiving infliximab or other treatments only. Importantly, an increased risk of serious infection with infliximab use was observed, although CD severity and prednisone or narcotic analgesic use were also independent risk factors.[2]

An assessment of malignancy risk using data from the registry indicated that age, disease duration, and smoking were independently associated with an increased risk of malignancy; infliximab use was not.[3]

The registry was discontinued in May 2012, and data collection continued until final database closure in September 2012. Results of mortality, serious infection, and neoplasms, including malignancies, reflecting the cumulative safety experience of patients with CD receiving therapy in the registry are reported herein.

METHODS

Study Design

The TREAT Registry was initiated in July 1999 to assess the long-term safety of infliximab, the first tumor necrosis factor alpha (TNFα) antagonist approved to treat patients with moderate to severe CD who had failed or were intolerant to conventional therapy. Details of the design have been reported previously.[1, 2] This observational, multicenter, long-term North American registry of patients with CD evaluated the long-term safety outcomes of infliximab use and local standard of care treatment regimens for the management of patients with CD. Gastroenterologists were to be recruited from either community-based or academic practice settings, and collectively were to enroll at least 5000 patients.

Enrolled patients must have had a diagnosis of CD and could not be participating in any clinical trial.

Registry Evaluations

Data were collected at enrollment and semi-annually (approximately every January and July) thereafter. Registry patients were to be followed for at least 5 years. Data collected at enrollment included: demographics (eg, age, race), medication use in the year before enrollment, and physicians' assessments of overall patient health and disease severity according to American College of Gastroenterology guidelines.[4] Data collected semi-annually included AEs, medication use, and the date and outcome of each infliximab infusion. Adverse events specific to this final report include infusion reactions and serious infections within 91 days of infliximab exposure among infliximab-treated patients. A serious infection was defined as any event in the Medical Dictionary for Regulatory Activities System–Organ Class "Infections and Infestations" that was reported as "serious" by the investigator or met the standard criteria for a serious adverse event (SAE), including any event that required hospitalization or prolonged hospitalization, resulted in persistent or significant disability/incapacity or congenital anomaly/birth defect, or was fatal. Further details of AE reporting have been previously reported.[2]

Data Analysis

This final report includes cumulative data collected through the final data extraction in September 2012. Most registry data are summarized by descriptive statistics. Hypothesis

testing was performed; however, given that all end points were safety related and given the retrospective nature of data analyses, no adjustments were made for multiple comparisons. All statistical analyses employed SAS software, version 8.02 or higher (SAS System for Windows, SAS Institute Inc., Cary, NC, USA).

The infliximab-treated group included patients who received the drug within 12 weeks before enrollment or at some point during registry participation. Patients categorized as other-treatments-only were those who did not receive infliximab, but received systemic corticosteroids therapy (ie, prednisone or equivalent) or immunosuppressives (ie, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]) during registry participation.

The temporal relationship to infliximab dosing is critical to the evaluation of causality. Pharmacokinetic studies have demonstrated that infliximab is generally eliminated from the body by 3 months after an infusion. Accordingly, the TREAT Registry Advisory Board prespecified that infections occurring within 3 months (91 days) of an infliximab infusion were considered potentially related to infliximab, whereas infections occurring after 3 months were considered unrelated to infliximab. Malignancies occurring in infliximab-treated patients were considered potentially related to infliximab regardless of temporal association.

Rates of AEs per 100 patient-years (/100 patient-years) of follow-up were summarized. Rates of mortality, serious infections, and overall serious adverse events were compared between infliximab-treated patients and patients receiving other treatments only by calculating relative risk (RR) ratios and corresponding 95% confidence intervals (CIs). The RR ratios were determined using univariate Poisson regression accounting for within-patient correlations, and *P* values were derived from generalized estimating equation methods. For other variables, the Student *t* test and χ^2 test were used to assess equality of means between treatment groups and evaluate the association between treatment group and categorical variables, respectively.

A Cox proportional hazards model with time-varying covariates was used to determine the relative contribution (in the form of hazard ratios [HRs] and 95% CIs) of different factors to the occurrence of death and serious infection. Factors assessed included age at registry enrollment, sex, race, diseased segment(s), disease duration at registry enrollment, disease severity, and CD medication use (infliximab, prednisone, immunosuppressives, and narcotic analgesics). For mortality and serious infection analyses, data for CD medications were obtained from 6-month data collection periods (January–June and July–December) occurring between enrollment and the time of the event. Data for medication use during the period in which a death occurred were included in this analysis. CD medication "ever used" was obtained from all available 6-month periods that occurred from enrollment through the period before the onset of the serious infection, and it was included in the analysis. Other medication use during the

period in which a serious infection occurred was not included because medication start and stop dates were only collected for infliximab.

Additionally, we retrospectively evaluated patient demographics (including age groups), disease characteristics, and medication regimens (infliximab, prednisone, immunomodulators, narcotic analgesics) associated with the time to first serious infection using a multivariate Cox proportional hazards regression model and a univariate model just for age. Patients were stratified by age groups based on age quartiles as follows: ≤30 years (n = 1480), 31 to 41 years (n = 1669), 42 to 52 years (n = 1535), and >52 years (n = 1552); 37 had age missing.

Ethical Considerations

Modifications to the registry design and data collection instruments were approved by participating institutional review boards, and all patients provided written informed consent.

RESULTS

Patient Disposition and Baseline Characteristics

This final report describes the cumulative safety experience for 6273 patients with CD followed in the registry (3440 infliximab-treated, 2833 other-treatments-only) with a median duration of patient follow-up exceeding 6 years.

At final database closure, infliximab-treated patients were followed for 20,971 patient-years, and patients receiving other treatments were followed for 14,806 patient-years. Cumulative data from both active and discontinued patients were summarized, including 2085 active patients (33% of total enrolled) with an average follow-up of 9.61 years, representing a subgroup of patients with established CD. Notably, 20 patients who had previously received other treatments only received infliximab for their CD since the last TREAT report[2] and are now analyzed as infliximab-treated patients (Fig. 1).

Within 1 year of enrollment, infliximab-treated patients were more likely to have received prednisone (47.6% vs 31.5%), immunosuppressives (51.9% vs 32.2%), antibiotics (31.9% vs 23.5%), narcotic analgesics (17.2% vs 9.2%), or antidepressants (13.4% vs 8.3%) than patients receiving other treatments only (*P* < 0.001 for all comparisons) (Table 1). Patients who received infliximab also differed significantly from patients who received other treatments only regarding intestinal segment(s) affected by disease, disease severity, and health resource utilization in the year before enrollment. These differences are consistent with the notion that infliximab-treated patients had more severe disease than those receiving other treatments only.

More infliximab-treated (2124/3440, 61.7%) than other-treatments-only patients (342/2833, 12.1%) had received infliximab within 1 year of enrollment. Thus, approximately one-third of infliximab-treated patients received their initial dose during registry participation. Most infliximab-treated
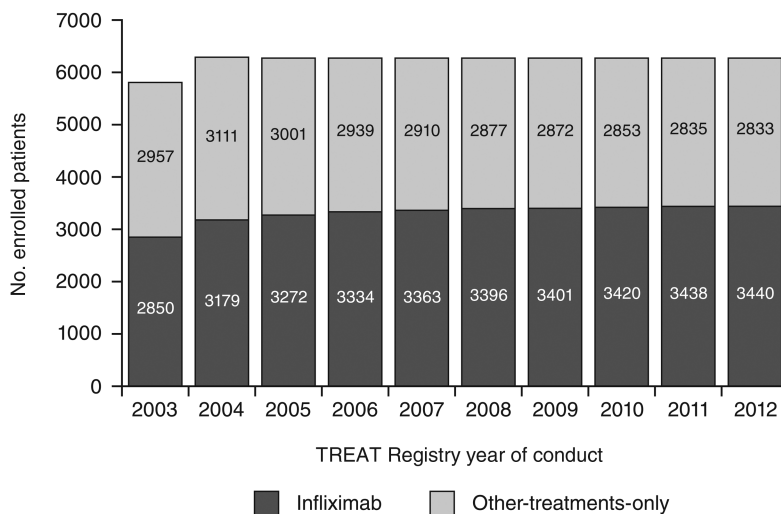
FIGURE 1. Patient enrollment history.

patients (3006, 89.9%) had received at least 2 infusions, and most (47,914/59,875, 80.0%) received the 5-mg/kg dose (Supplementary Table 1).

Overall TREAT Registry Safety Experience

All adverse events

The adverse events most commonly reported in the registry were abdominal pain, CD (eg, disease exacerbation), and diarrhea (Table 2). These AEs were most frequently reported in the infliximab-treated group. Among infliximab-treated patients, more AEs classified as infection/infestations were considered to be related to infliximab (53.7%, 1000/1864) than not (46.4%, 864/1864). Notably, nonserious cerebrovascular accidents (13 events, 0.06/100 patient-years; 5 events, 0.03/100 patient-years) and pulmonary embolisms (11 events, 0.05/100 patient-years; 4 events 0.03/100 patient-years) also occurred at higher rates among infliximab-treated patients. Uncommon nonserious adverse events such as congestive heart failure (3 events, 0.01/100 patient-years; 3 events 0.02/100 patient-years), interstitial lung disease (1 event, 0.00/100 patient-years; 0 events 0.00/100 patient-years), and psoriaform lesions (1 event, 0.00/100 patient-years; 0 events 0.00/100 patient-years) occurred at higher rates among infliximab-treated patients (Table 2).

Sensitivity analysis including data through February 2012 evaluated whether the AE rates in both groups were affected by exposure after the initiation of treatment with other biologic agents. The incidence of all AEs in the infliximab-treated and other-treatments-only groups were similar when data after the initiation of other biologic therapies were excluded (Supplementary Table 2). Additionally, AE rates in infliximab-treated patients were consistent with rates observed for patients receiving other biologic treatments.

Serious adverse events

Deaths.   Overall, 232 (3.7%) of the 6273 registry patients died during the registry (Supplementary Table 3). Unadjusted mortality rates were similar between the infliximab-treated (128, 0.57/100 patient-years) and other-treatments-only groups (104, 0.67/100 patient-years) ($P = 0.22$) (Supplementary Table 4), yielding an RR of 0.85 (95% CI, 0.66–1.10). Mortality rates were also similar between the infliximab dose groups ($P = 0.78$) (Supplementary Table 4). Infliximab dose (10 mg/kg vs 5 mg/kg or unknown dose) did not predict mortality risk (Supplementary Table 5). Among all patients, age ($P < 0.001$), ileal disease ($P = 0.050$), prednisone use ($P < 0.001$), and narcotic analgesic use ($P = 0.016$) were significant independent predictors of mortality.

Malignancies.   During the registry, 306 neoplasms, including 249 malignancies, were reported (Table 2). The proportion of patients who developed any neoplasm was similar between infliximab-treated (0.84/100 patient-years) and other-treatments-only (0.87/100 patient-years) patients. The proportion of patients who developed any malignancy was also similar between infliximab-treated (0.69/100 patient-years) and other-treatments-only patients (0.71/100 patient-years). The most common malignancies occurred in the solid tumor category, with the highest rates in breast, lung, prostate, and melanoma cancers and malignancies of the large intestine (Supplementary Table 6). Basal and squamous cell skin cancers were also commonly reported. As reported previously,[3] 1 case of hepatosplenic T-cell lymphoma was observed in the registry in a patient who received a single dose of infliximab 3 years before the cancer diagnosis and had received thiopurines for at least 3 years during registry participation, and an unspecified amount of time before registry entry. Fifty-nine deaths were related to malignancies (26 infliximab-treated and 33 other-treatments-only) (Supplementary Table 3).

TABLE 1: Demographic and Disease Characteristics at Enrollment

Parameters	Infliximab-Treated[a] (n = 3440)	Other-Treatments-Only (n = 2833)	*P* Value[b]	All Patients (n = 6273)
Age at enrollment,[c] No.	3424	2812	<0.0001	6236
Mean ± SD, y	40.5 ± 14.0	44.9 ± 15.3		42.5 ± 14.7
Sex, No. (%)	3392	2771	0.42	6163
Male	1389 (40.9)	1163 (42.0)		2552 (41.4)
Female	2003 (59.1)	1608 (58.0)		3611 (58.6)
Baseline body mass index, No.	3200	2622	0.93	5822
Mean ± SD	25.8 ± 5.6	25.8 ± 5.4		25.8 ± 5.5
Race/ethnicity, No. (%)	3388	2765	0.62	6153
Caucasian	3062 (90.4)	2524 (91.3)		5586 (90.8)
Black	245 (7.2)	175 (6.3)		420 (6.8)
Asian	15 (0.4)	9 (0.3)		24 (0.4)
Hispanic	44 (1.3)	37 (1.3)		81 (1.3)
Other	22 (0.6)	20 (0.7)		42 (0.7)
Years between diagnosis and enrollment, No.	3361	2744	0.26	6105
Mean ± SD	11.2 ± 9.8	11.5 ± 10.7		11.3 ± 10.2
Disease severity, No. (%)	3300	2699	<0.001	5999
Remission[d]	471 (14.3)	1057 (39.2)		1528 (25.5)
Mild–moderate[e]	1741 (52.8)	1335 (49.5)		3076 (51.3)
Moderate–severe[f]	1005 (30.5)	291 (10.8)		1296 (21.6)
Severe–fulminant[g]	83 (2.5)	16 (0.6)		99 (1.7)
Involved intestinal area, No. (%)	3328	2706	<0.001	6034
Ileum only	875 (26.3)	926 (34.2)		1801 (29.8)
Colon only	976 (29.3)	788 (29.1)		1764 (29.2)
Ileum and colon	1477 (44.4)	992 (36.7)		2469 (40.9)
Health resource utilization in year before enrollment, No. (%)				
Any admission	931 (27.1)	538 (19.0)	<0.001	1469 (23.4)
Surgical admission	597 (17.4)	386 (13.6)	<0.001	983 (15.7)
Medical admission	485 (14.1)	251 (8.9)	<0.001	736 (11.7)
Medication use in year before enrollment, No. (%)				
Antibiotics	1096 (31.9)	667 (23.5)	<0.001	1763 (28.1)
Antidepressants	462 (13.4)	236 (8.3)	<0.001	698 (11.1)
Immunosuppressives[h]	1784 (51.9)	912 (32.2)	<0.001	2696 (43.0)
Infliximab[i]	2124 (61.7)	342 (12.1)	ND	2466 (39.3)
Narcotic Analgesics	593 (17.2)	260 (9.2)	<0.001	853 (13.6)
Prednisone	1639 (47.6)	891 (31.5)	<0.001	2530 (40.3)

[a]Infliximab-treated patients are those patients who received infliximab within 12 weeks before enrollment or who received infliximab at some other time during the registry.

[b]*P* value from *t* test (continuous variables) or chi-square test (categorical variables).

[c]Note that 80 patients who were younger than age 18 years were enrolled into the registry and then subsequently discontinued when the registry entrance criteria were amended to include only patients age 18 years or older.

[d]Remission refers to patients who are asymptomatic or without inflammatory sequelae and refers to patients who have responded to acute medical intervention or have undergone surgical resection without evidence of residual disease. Patients requiring corticosteroids to maintain well-being are considered "steroid-dependent" and are not "in remission."

[e]Mild–moderate disease applies to ambulatory patients who are able to tolerate oral alimentation without manifestations of dehydration, toxicity (high fevers, rigors, prostration), abdominal tenderness, painful mass, obstruction, or >10% weight loss.

[f]Moderate–severe disease applies to patients who have failed to respond to treatment for mild–moderate disease or those with more prominent symptoms of fevers, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.

[g]Severe–fulminant disease applies to patients with persistent symptoms despite the introduction of corticosteroids or individuals presenting with high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.

[h]Immunosuppressives at baseline include azathioprine, cyclosporine, 6-mercaptopurine, and methotrexate.

[i]By definition, patients categorized as other-treatments-only received infliximab more than 12 weeks before enrollment.

Abbreviation: ND, not done.

TABLE 2: Adverse Event Rates Per 100 Patient-Years of Follow-Up

Adverse Event Category Preferred Term Rate/100 Patient-Years (No. Events)[a]	Infliximab-Treated[b] (n = 3440)	Other-Treatments-Only (n = 2833)	All Patients (n = 6273)
Patient-years of follow-up	20,971	14,806	35,777
Average years of follow-up	6.1	5.2	5.7
Adverse events	118.63 (24,878)	65.89 (9756)	96.80 (34,634)
Common adverse events[c]			
Abdominal pain	15.70 (3293)	10.19 (1509)	13.42 (4802)
Diarrhea	12.52 (2626)	8.10 (1199)	10.69 (3825)
Crohn's disease	12.88 (2702)	6.77 (1003)	10.36 (3705)
Nausea	5.21 (1093)	3.03 (449)	4.31 (1542)
Anemia	5.33 (1118)	2.84 (421)	4.30 (1539)
Arthritis	5.10 (1069)	2.27 (336)	3.93 (1405)
Fistula	4.97 (1043)	1.74 (257)	3.63 (1300)
Vomiting	2.97 (622)	1.82 (270)	2.49 (892)
Bacterial infection[d]	2.69 (577)	0.93 (143)	1.95 (720)
Constipation	1.66 (348)	1.24 (184)	1.49 (532)
Headache	2.08 (436)	0.63 (93)	1.48 (529)
Rash	1.79 (375)	0.43 (64)	1.23 (439)
Pyrexia	1.61 (338)	0.65 (96)	1.21 (434)
Depression	1.25 (262)	0.94 (139)	1.12 (401)
Back pain	1.34 (282)	0.68 (100)	1.07 (382)
Pain	1.15 (242)	0.53 (78)	0.89 (320)
Muscle spasms	1.12 (235)	0.42 (62)	0.83 (297)
Sinusitis[d]	1.03 (222)	0.40 (62)	0.77 (284)
Serious adverse events	13.17 (2762)	7.20 (1066)	10.70 (3828)
Serious adverse event, SOC of interest			
Cardiac disorders	0.21 (44)	0.28 (41)	0.24 (85)
Respiratory disorders	0.23 (49)	0.17 (25)	0.21 (74)
Embolic and thrombotic events	0.16 (34)	0.10 (15)	0.14 (49)
Female disorders	0.10 (22)	0.12 (18)	0.11 (40)
Cerebrovascular disorders	0.11 (23)	0.07 (10)	0.09 (33)
Adverse events of interest			
Infections[d]	8.73 (1876)	3.67 (563)	6.62 (2439)
Bacterial infection	2.69 (577)	0.93 (143)	1.95 (720)
Viral infection	0.97 (208)	0.38 (59)	0.72 (267)
Sinusitis	1.03 (222)	0.40 (62)	0.77 (284)
Bronchitis	0.82 (177)	0.27 (41)	0.59 (218)
Fungal infection	0.40 (87)	0.18 (28)	0.31 (115)
Pneumonia	0.21 (45)	0.12 (18)	0.17 (63)
Urinary tract infection	0.20 (43)	0.13 (20)	0.17 (63)
Pharyngitis	0.23 (49)	0.08 (12)	0.17 (61)
Upper respiratory tract infection	0.17 (37)	0.10 (16)	0.14 (53)
Herpes zoster	0.10 (21)	0.05 (7)	0.08 (28)
Clostridial infection	0.02 (5)	0.01 (2)	0.02 (7)
Clostridium difficile colitis	0.01 (3)	0.00 (0)	0.01 (3)
Tuberculosis	0.01 (3)	0.01 (1)	0.01 (4)
Herpes zoster disseminated	0.00 (1)	0.00 (0)	0.00 (1)
Hepatitis C	0.00 (0)	0.01 (1)	0.00 (1)
Serious infections	2.15 (450)	0.86 (127)	1.61 (577)
Pneumonia	0.22 (47)	0.09 (13)	0.17 (60)

(Continued)

TABLE 2: Continued

Adverse Event Category Preferred Term Rate/100 Patient-Years (No. Events)[a]	Infliximab-Treated[b] (n = 3440)	Other-Treatments-Only (n = 2833)	All Patients (n = 6273)
Adverse events of interest (cont.)			
Sepsis	0.10 (21)	0.05 (7)	0.08 (28)
Herpes zoster	0.03 (6)	0.00 (0)	0.02 (6)
Bronchitis	0.02 (4)	0.00 (0)	0.01 (4)
Sinusitis	0.01 (3)	0.00 (0)	0.01 (3)
Tuberculosis	0.01 (2)	0.00 (0)	0.01 (2)
Histoplasmosis	0.00 (1)	0.00 (0)	0.00 (1)
Histoplasmosis, disseminated	0.00 (1)	0.00 (0)	0.00 (1)
Pharyngitis	0.00 (1)	0.00 (0)	0.00 (1)
Neoplasms, benign, malignant, and unspecified (including cysts and polyps)[e]	0.84 (177)	0.87 (129)	0.86 (306)
Neoplasm, benign	0.16 (33)	0.16 (24)	0.16 (57)
Malignancies	0.69 (144)	0.71 (105)	0.70 (249)
Neoplasms, malignancy, solid tumor	0.45 (94)	0.44 (65)	0.44 (159)
Melanoma	0.04 (9)	0.03 (4)	0.04 (13)
Neoplasms, malignancy, nonmelanoma skin cancer[e]	0.20 (41)	0.20 (29)	0.20 (70)
Neoplasms, malignancy, lymphoma[e,f]	0.04 (8)	0.04 (7)	0.04 (15)
Neoplasms, malignancy, hematologic[e]	0.00 (1)	0.03 (4)	0.01 (5)
Hepatobiliary disorders			
Hepatitis	0.00 (1)	0.00 (0)	0.00 (1)
Hepatotoxicity			
Alanine aminotransferase increased	0.00 (1)	0.02 (3)	0.01 (4)
Liver function test abnormal	0.00 (1)	0.01 (2)	0.01 (3)
Jaundice	0.01 (2)	0.01 (1)	0.01 (3)
Heart failure			
Cardiac failure congestive	0.01 (3)	0.02 (3)	0.02 (6)
Cardiac failure	0.00 (0)	0.01 (1)	0.00 (1)
Congestive cardiomyopathy	0.00 (0)	0.01 (1)	0.00 (1)
Hematologic reactions			
Leukopenia	0.73 (153)	0.61 (91)	0.68 (244)
Thrombocytopenia	0.19 (39)	0.11 (17)	0.16 (56)
Pancytopenia	0.01 (2)	0.00 (0)	0.01 (2)
Hypersensitivity			
Anaphylactic reaction	0.15 (32)	0.01 (1)	0.09 (33)
Hypersensitivity	0.13 (27)	0.01 (2)	0.08 (29)
Drug hypersensitivity	0.01 (3)	0.01 (2)	0.01 (5)
Serum sickness	0.02 (5)	0.00 (0)	0.01 (5)
Anaphylactic shock	0.00 (1)	0.00 (0)	0.00 (1)
Neurologic reactions			
Peripheral neuropathy	0.22 (47)	0.09 (13)	0.17 (60)
Optic neuritis	0.02 (5)	0.01 (1)	0.02 (6)
Demyelination	0.02 (4)	0.00 (0)	0.01 (4)
Multiple sclerosis	0.01 (3)	0.04 (6)	0.03 (9)
Relapsing-remitting multiple sclerosis	0.00 (0)	0.01 (2)	0.01 (2)
Vasculitis cerebral	0.00 (1)	0.00 (0)	0.00 (1)
Autoimmunity			
Lupus-like syndrome	0.14 (31)	0.00 (0)	0.08 (31)
Cutaneous lupus erythematosus	0.00 (1)	0.00 (0)	0.00 (1)

(Continued)

TABLE 2: Continued

Adverse Event Category Preferred Term Rate/100 Patient-Years (No. Events)[a]	Infliximab-Treated[b] (n = 3440)	Other-Treatments-Only (n = 2833)	All Patients (n = 6273)
Other adverse events			
Erythema nodosum	0.28 (59)	0.16 (23)	0.23 (82)
Pruritus	0.96 (199)	0.09 (13)	0.60 (212)
Pyoderma gangrenosum	0.22 (46)	0.06 (9)	0.16 (55)
Cerebrovascular accident	0.06 (13)	0.03 (5)	0.05 (18)
Psoriasis	0.06 (12)	0.02 (3)	0.04 (15)
Pulmonary embolism	0.05 (11)	0.03 (4)	0.04 (15)
Eczema	0.02 (5)	0.03 (4)	0.03 (9)
Interstitial lung disease	0.00 (1)	0.00 (0)	0.00 (1)
Pulmonary fibrosis	0.00 (1)	0.00 (0)	0.00 (1)
Erythema multiforme	0.00 (1)	0.00 (0)	0.00 (1)
Cholestasis	0.00 (0)	0.01 (1)	0.00 (1)
Psoriaform dermatitis	0.00 (1)	0.00 (0)	0.00 (1)

[a]The incidence of adverse events (AEs) is reported as the rate of AEs per 100 patient-years. Patient-years is defined as the number of years from baseline or January 1, 2002 (if registered before then), until discontinuation or May 12, 2013 (patient-years calculated as number of days enrolled in registry/365.25). There are 12 AEs that were reported in 2001 that are not included in this Table. Prior to 2002, the TREAT Registry collected less detailed information on events than when the program expanded the collection of safety data in January 2002. In the interest of full disclosure, the events reported were (1) infliximab-treated: 3 Cushingoid syndrome (1.28 events/100 patient-years), 2 solid tumor malignancies (0.85 events/100 patient-years), 6 infections requiring hospitalization (2.55 events/100 patient-years); and (2) other treatments only: 1 Cushingoid syndrome (0.57 events/100 patient-years).

[b]"Infliximab-treated" indicates patients who received infliximab at any point before event onset, including the year before registration.

[c]Common adverse events are those reported at a rate of 1.00 events per 100 patient-years of follow-up in either group and listed by decreasing order for all patients.

[d]Patient-years used for the adverse event category of infections; preferred terms of bacterial infection and sinusitis were infliximab-treated, 21,486; other-treatments-only, 15,348; all patients, 36,834.

[e]Adverse events in the MeDRA System Organ Class "Neoplasms, benign, malignant, and unspecified (incl. cysts and polyps)" have been classified into 5 malignancy categories: Benign, Nonmelanoma skin cancer, Solid tumors, Hematologic, and Lymphoma. In the Solid tumors category, the MedDRA preferred term has been replaced with tumor location.

[f]Includes 1 patient in the other-treatments-only group who developed hepatosplenic T-cell lymphoma.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class.

Serious infections and infections of interest

Overall, 577 (9.2%) of the 6273 registry patients had serious infections during the registry, including 450 who received infliximab (2.15/100 patient-years) and 127 who received other treatments only (0.86/100 patient-years) (Table 2), yielding an unadjusted RR of 2.46 (95% CI, 1.80–3.36); pneumonia occurred most frequently.

Specifically, 3 cases of tuberculosis were reported; 2 patients who received infliximab (0.01/100 patient-years) and 1 who received other treatments only (0.01/100 patient-years). Before initiating infliximab therapy, patients were screened for tuberculosis and treated for latent infection, if necessary, according to local clinical practice. Fungal infections were reported among 115 patients, 87 who received infliximab (0.40/100 patient-years) and 28 (0.18/100 patient-years) among patients who received other treatments only. Histoplasmosis (1 event, 0.00/100 patient-years) and disseminated histoplasmosis (1 event, 0.00/100 patient-years) were reported in patients who received infliximab in northwestern Texas and western North Carolina, respectively. One case of hepatitis C was reported in the other-treatments-only group (1 event, 0.01/100 patient-years).

Among all patients, age; use of prednisone, narcotic analgesics, or infliximab; moderate/severe disease; colonic disease; and disease duration at enrollment (all $P \leq 0.049$) were significant independent predictors of serious infection (Supplementary Table 5). Infliximab dose (10 mg/kg vs 5 mg/kg or unknown dose) did not predict serious infection risk (Supplementary Table 4). There was no evidence of an increase in the occurrence of serious infections with receipt of 2 or more infliximab infusions. Specifically, the incidences of serious infections were 2.62, 2.25, 1.82, and 1.87/100 patient-years in association with receipt of 1–3, 4–9, 10–24, and ≥25 infliximab infusions, respectively (data not shown). Cumulative dose of infliximab did not predict infectious complications.

At the close of the registry, unadjusted incidence rates of serious infections were 1.50, 2.10, and 1.88/100 patient-years for patients receiving no infliximab in past 91 days, infliximab 5 mg/kg (or unknown dose), and infliximab 10 mg/kg ($P = 0.62$) (Supplementary Table 4). Thirty-two deaths were attributed to

TABLE 3: Predictors of Time to First Serious Infection—All Patients (Using Exposure Any Time After Registration)

Risk Factors	Adjusted Hazard Ratios (95% CI)	P Value*
Age 31 to ≤41 vs ≤30 y	0.704 (0.482–1.028)	0.069
42 to vs ≤30 y	0.861 (0.591–1.255)	0.437
>52 vs ≤30 y	1.316 (0.907–1.910)	0.148
Sex: female vs male/unknown	1.020 (0.802–1.299)	0.870
Race: Caucasian vs other/unknown	0.735 (0.495–1.091)	0.126
Diseased area:[a] ileum only vs ileum and colon	0.845 (0.637–1.120)	0.241
Diseased area:[a] colon only vs ileum and colon	0.760 (0.559–1.032)	0.079
Diseased area:[a] unknown vs ileum and colon	1.341 (0.487–3.691)	0.570
Years between diagnosis and enrollment	1.020 (1.008–1.032)	0.001
Severity:[b] mild vs remission	0.980 (0.736–1.304)	0.889
Severity:[b] moderate/severe vs remission	2.182 (1.531–3.109)	<0.001
Severity:[b] unknown vs remission	0.000 (0.000–8E222)	0.967
Infliximab vs no infliximab[c]	1.456 (1.131–1.874)	0.004
Prednisone vs no prednisone[c]	1.569 (1.175–2.097)	0.002
Immunomodulators vs no immunomodulators[c]	1.199 (0.941–1.528)	0.141
Narcotic analgesics vs no narcotic analgesics[c]	1.977 (1.435–2.723)	<0.001

The outcome of this analysis is time to first event. Immunomodulators are defined as azathioprine, methotrexate, and 6-mercaptopurine.
*P value from Wald chi-square test.
[a]This represents diseased area at baseline, as disease area is not collected longitudinally.
[b]This represents time-varying severity in the data collection period before the event or censoring.
[c]This represents time-varying medication use and is defined as any use between enrollment and the 6-month data collection period before the event or censoring.
Abbreviation: CI, confidence interval.

TABLE 4: Age Quartiles as Predictors of Time to First Serious Infections—All Patients (Using Exposure in the Period Prior to the Event)

Risk Factor Age Quartiles, y	Adjusted Hazard Ratios (95% CI)	P Value*
Infliximab-treated		
31 to ≤41 vs ≤30	0.936 (0.647–1.354)	0.726
42 to vs ≤30	1.229 (0.862–1.751)	0.254
>52 vs ≤30	1.600 (1.152–2.223)	0.005
Other-treatments-only		
31 to ≤41 vs ≤30	0.822 (0.429–1.575)	0.554
42 to vs ≤30	0.486 (0.230–1.028)	0.059
>52 vs ≤30	0.774 (0.391–1.532)	0.462
All patients		
31 to ≤41 vs ≤30	0.797 (0.578–1.098)	0.164
42 to vs ≤30	0.866 (0.630–1.191)	0.377
>52 vs ≤30	1.266 (0.943–1.700)	0.117

Patients were eligible for this analysis if they contributed data in 2002 or beyond, had nonmissing baseline covariates, and had at least 1 period of data collection beyond baseline. Data on serious infections were available beginning in 2002. The event must have occurred on or after registration or January 1, 2002 (if registered before then), and on or before December 31, 2011, to contribute to this analysis. The outcome of this analysis in time to first event.
*P value from Wald chi-square test.
Abbreviation: CI, confidence interval.

infections (23 infliximab-treated and 9 other-treatments-only) (Supplementary Table 3).

We retrospectively evaluated patient demographics (including age groups), disease characteristics, and medication regimens as independent risk factors for serious infections. Baseline demographics and disease characteristics were generally comparable across all 4 age groups (Supplementary Table 7). Duration and severity of disease and prednisone, narcotic, and infliximab use were all identified as significant factors; age group was not (Table 3). A significantly increased risk was observed for time to serious infection for infliximab-treated patients in the age >52 years group vs age ≤30 years group (HR, 1.60; (95% CI, 1.152–2.22; P = 0.005); this observation was not seen in a similar comparison with other-treatments-only patients (HR, 0.774; 95% CI, 0.39–1.53; P = 0.462) (Table 4).

Other SAEs

Overall, SAEs occurred at a higher rate in the infliximab-treated than other-treatments-only group (2762, 13.17/100 patient-years, vs 1066, 7.20/100 patient-years), yielding an unadjusted RR of 1.80 (95% CI, 1.57–2.06) (Table 2; Supplementary Table 4). Cardiovascular system SAEs occurred at a lower rate in the infliximab-treated than other-treatments-only group (44, 0.21/100 patient-years, vs 41, 0.28/100 patient-years) during the registry. Serious cerebrovascular and thromboembolic events

occurred more frequently in the infliximab-treated than other-treatments-only group.

Other adverse events of interest

Congestive heart failure occurred in 6 patients, with 3 events reported in each group (infliximab-treated, 0.01/100 patient-years; other-treatments-only, 0.02/100 patient-years) (Table 2). Notably, SAEs of congestive heart failure occurred in 14 patients, with a lower rate observed in the infliximab-treated group (4 events, 0.02/100 patient-years) than in the other-treatments-only group (10 events, 0.07/100 patient-years; data not shown).

Rates of hypersensitivity (27 events, 0.13/100 patient-years, vs 2 events, 0.01/100 patient-years), anaphylactic reactions (32 events, 0.15/100 patient-years, vs 1 event, 0.01/100 patient-years), and Lupus-like syndrome (31 events, 0.14/100 patient-years, vs 0 events) were higher in the infliximab-treated group than in the other-treatments-only group (Table 2).

Dermatologic events of interest were rash (375 events, 1.79/100 patient-years, vs 64 events, 0.43/100 patient-years), pruritus (199 events, 0.96/100 patient-years, vs 13 events, 0.09/100 patient-years), psoriasis (12 events, 0.06/100 patient-years, vs 3 events, 0.02/100 patient-years), eczema (5 events, 0.02/100 patient-years, vs 4 events, 0.03/100 patient-years), erythema nodosum (59 events, 0.28/100 patient-years, vs 23 events, 0.16/100 patient-years), and pyoderma gangrenosum (46 events, 0.22/100 patient-years, vs 9 events, 0.06/100 patient-years). These events occurred at higher rates in the infliximab-treated group than in the other-treatments-only group (Table 2).

Four events of demyelinating disease (0.02/100 patient-years) were reported in 3 infliximab-treated patients; none were reported in the other-treatments-only group. The rate of peripheral neuropathy was higher in the infliximab-treated group (47 events, 0.22/100 patient-years) than in the other-treatments-only group (13 events, 0.09/100 patient-years). Multiple sclerosis (MS; 3 events, 0.01/100 patient-years; 6 events, 0.04/100 patient-years) and relapsing-remitting MS (0 events, 0.00/100 patient-years; 2 events, 0.01/100 patient-years) occurred at higher rates among patients who received other treatments only (Table 2).

Overall, 2.8% (1648/59,875) of infliximab infusions were associated with an infusion reaction, most commonly headache (0.5%) and arthritis (0.4%) (Supplementary Table 1). The rate of infusions associated with an infusion reaction decreased over time from 5.4% of 11,504 infusions[5] to the present rate of 2.8% of 59,875 infusions.

DISCUSSION

Patient enrollment in TREAT was completed in March 2004, and the registry was closed in May 2012. The use of academic institutions and community-based practices that treated patients according to local clinical practice allowed for broad treatment paradigms among patients with CD of varying duration and severity. This final evaluation of the TREAT experience reflects more than 6 years of follow-up per patient.

Overall, SAEs and AEs occurred at higher rates among infliximab-treated patients; however, this observation must be appraised in the context that patients entering the registry had more severe CD than those receiving other treatments only. The higher incidence of diarrhea and abdominal pain seen in infliximab-treated patients likely reflects the greater disease severity noted for the infliximab group.[4]

Throughout the registry conduct, the risk of mortality has been similar between the infliximab-treated and other-treatments-only groups. An increased risk of serious infection with infliximab was observed, although CD severity and use of prednisone or narcotic analgesics carried higher risks. Risk factors associated with both mortality and serious infections were age, disease location (ileum, mortality; colon, serious infection), and prednisone and narcotic analgesic use; these have been reported previously.[1, 2, 5–11] Infliximab use, moderate/severe disease, and disease duration were associated with serious infections.[1, 2] An increased risk of serious infection in elderly patients with inflammatory bowel disease (IBD) has been reported previously.[12–14] Additionally, our retrospective analysis showed that age group was not a risk factor for time to first serious infection, when both infliximab and other-treatments-only patients were considered together. However, an increased risk of serious infection was observed with age (>52 years vs ≤30 years) among patients receiving infliximab.

Among other SAEs, the occurrence of thromboembolic events among infliximab-treated (34, 0.16/100 patient-years) and other-treatments-only (15, 0.10/100 patient-years) patients warrants comment. Mechanistically, the hypercoagulable state in patients with IBD involves factors related to impaired platelet and platelet-endothelial interactions,[15, 16] hypercoagulation,[16–19] and hypofibrinolysis.[20, 21] Disease activity and extent of disease are positively associated with an increased risk of clotting.[22–24] In this registry, patients treated with infliximab had more severe CD relative to patients who received other treatments; thus these results are consistent with the positive relationship between disease severity and thromboembolic event risk.

The higher percentage of patients reporting a history of smoking in the infliximab-treated group (23.3%) than in the other-treatments-only group (17.2%) may have contributed to the higher rate of serious respiratory AEs among those patients. An increased risk of malignancy with smoking in this registry was previously reported.[3]

In TREAT, melanoma occurred in 9 infliximab-treated patients (0.04/100 patient-years) and 4 other-treatments-only patients (0.03/100 patient-years), rates consistent with those reported previously.[3] A recent meta-analysis indicated that patients with IBD may have an increased melanoma risk compared with the general population,[25, 26] independent of biologic

use. Among patients with IBD, TNF-antagonist use, but not thiopurine use, was associated with an increased risk of melanoma. Ongoing and past exposure to thiopurines has been observed to significantly increase the risk of nonmelanoma skin cancer (NMSC) in patients with IBD.[27] Currently, recommendations are that patients with IBD should practice sun avoidance, sun protection, and receive routine skin screening examinations.[26, 27] Nonmelanoma skin cancers occurred at rates consistent with those reported previously.[3] Among patients in this registry with NMSC, no significant difference was observed between patients with and without exposure to immunosuppressants (eg, AZA, 6-MP, and/or MTX) before event onset.[3] Contrary to reports of an association between immunosuppressant use and NMSC,[28] our finding of no association is likely related to the small number of events and imprecision in documentation of immunosuppressant dosage and timing with respect to NMSC diagnosis.

Compared with the other-treatments-only group, infliximab was not associated with an increased risk of developing congestive heart failure. In TREAT, MS events were uncommon and occurred more frequently in the other-treatments-only group. Other demyelinating events and neurologic reactions were uncommon and occurred more frequently in the infliximab-treated group; it is unclear if these events may be MS related (eg, MS exacerbations or initial events). Hypersensitivity and autoimmunity events (Lupus-like syndrome, specifically) also occurred more frequently among infliximab-treated patients, and they are consistent with the product labeling of infliximab and other TNFα antagonists.

Patients with IBD may experience an increase in dermatologic manifestations, reportedly related to disease, nutritional deficiency, or disease therapies.[29] Skin manifestations were most commonly reported as rash. All skin manifestations occurred at higher rates in the infliximab-treated group. The rate of new-onset psoriasis reported in this registry seems lower than the 7% to 11%[29] reported among inflammatory bowel disease patients treated with TNFα antagonists. It is plausible that both the design of the TREAT Registry with an every-6-month data collection cycle and the recognition of this paradoxical relationship with biologic treatment during the latter stages of registry conduct resulted in the lower reported rate of psoriasis.

Due to the intrinsic gradual registry attrition over time, TREAT could accrue data for patients who were no longer representative of the overall population, and thus could lead to misinterpretation of data from a population with retention bias. Over the last few active years of the registry, no new safety signals were detected, and the likelihood of detecting new safety signals during the next years would be further compromised by registry attrition. Despite inherent biases (ie, selection, channeling, treatment, reporter/recall, retention), incomplete/missing data, voluntary participation, retrospective data collection, and the observational nature of this study, no clinically meaningful differences were observed with respect to the rate of key safety events, including benign or malignant neoplasms and serious infections among patients exposed to infliximab or other treatments only. Similarly, no meaningful changes were observed in additional predictor analyses for serious infections and mortality. Collectively, these facts led to the decision to discontinue the TREAT Registry.

In conclusion, results from the final TREAT Registry as described here are representative of real-world experience among infliximab-treated patients with CD and are consistent with the known risks of disease activity and TNFα antagonist therapy. No new safety signals were identified, suggesting a favorable profile of infliximab for the treatment of patients with CD. Infliximab use was associated with serious infections, as described in the prescribing information, but not mortality.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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