Safety of Infliximab Treatment in Patients with Rheumatoid Arthritis in a Real-world Clinical Setting: Description and Evaluation of Infusion Reactions

JOHN KELSALL, PAMELA ROGERS, GRISELDA GALINDO, and MARY A. De VERA

ABSTRACT. ***Objective.*** To describe acute and delayed infusion reactions in a large cohort of patients with inflammatory arthritis, treated with infliximab (IFX).

Methods. We conducted a retrospective chart review of patients treated with IFX at the Mary Pack Arthritis Centre between 2000 and 2008. The primary outcome was the occurrence of acute infusion reactions during infusions or 1–2 hours after each infusion, and secondary outcome was the occurrence of delayed infusion reactions 1–14 days after an infusion. Descriptive analyses were conducted to summarize study outcomes and identify trends over followup.

Results. Since 2000, 376 patients were referred to the Mary Pack IFX clinic and 200 received 4399 IFX infusions over a mean 140 ± 132 weeks of followup. Of these, 135 were patients with RA who received 2977 IFX infusions over mean followup of 138 ± 132 weeks. In total 258 episodes of acute reactions were observed for an overall acute reaction rate of 5.8%. Acute infusion reactions were mostly mild (42.6%) and moderate (43.8%) and commonly affected sites were head and neck (31.5%) and cutaneous (21.1%). A total of 37 delayed infusion reaction episodes were observed (0.9% rate); reactions were also mostly mild (16.2%) and moderate (64.9%).

Conclusion. These clinical data from 200 patients treated with IFX demonstrate that acute and delayed infusion reactions occur infrequently and are mostly mild to moderate in presentation. (J Rheumatol First Release May 15 2012; doi:10.3899/jrheum.110956)

Key Indexing Terms:
INFLIXIMAB INFUSION REACTIONS RHEUMATOID ARTHRITIS

The development and use of anti-tumor necrosis factor-α (anti-TNF-α) therapy has been recognized as a major advancement in the treatment of patients with inflammatory arthritis including rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) as well as other inflammatory conditions including inflammatory bowel disease (IBD) and psoriasis. Infliximab (IFX) is a chimeric monoclonal antibody that binds with high affinity and specificity to TNF-α, a potent proinflammatory cytokine, and neutralizes its biological activity[1]. The efficacy of IFX in different RA populations has been reported in randomized control trials (RCT) demonstrating that patients receiving IFX in combination with methotrexate had better outcomes as measured by American College of Rheumatology criteria, radiographic scores, and quality of life measures (Health Assessment Questionnaire)[2,3,4,5].

The safety of IFX infusions for RA has been reported in both RCT and observational studies[6,7]. Safety reports based on RCT indicate that 3% of all infusions were associated with infusion reactions, with most events reported as mild or moderate[3,4]. While RCT contribute to current understanding of the safety of IFX, their tightly selected patient populations and relatively short followup periods may limit their applicability to real-world settings. Observational studies based on clinical settings have provided real-world information on the safety of IFX infusions[8,9,10,11]. However, with increasing use of biologics, more information is needed regarding these therapies, with reporting of short- and longterm safety in clinical practice settings. The objective of our study was to describe and evaluate acute and delayed infusion reactions in a large cohort of patients with inflammatory arthritis treated with IFX.

MATERIALS AND METHODS

Subjects. We conducted a retrospective review of all consecutive patients at the Mary Pack Arthritis Centre (MPAC) IFX clinic. The IFX clinic was established in February 2000 when IFX was the first anti-TNF-α widely available to our patients with RA through a special-access program. Initially, patients were eligible for treatment with IFX if they met the following criteria: (1) clinical diagnosis of RA by a rheumatologist, (2) ability to give informed consent, (3) age ≥ 18 years, and (4) prior failure of standard disease-modifying

From the Mary Pack Arthritis Centre, Vancouver; Medicine/Rheumatology, University of British Columbia, Vancouver; St. Paul's Hospital, Vancouver; and the Arthritis Research Centre of Canada, Vancouver, British Columbia, Canada.

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J. Kelsall, MDCM, FRCPC, Mary Pack Arthritis Centre, Clinical Assistant Professor of Medicine, University of British Columbia, St. Paul's Hospital; P. Rogers, MA; M. De Vera, PhD; G. Galindo, MD, Arthritis Research Centre of Canada.

Address correspondence to Dr. J. Kelsall, Rheumatology/Internal Medicine, University of British Columbia, 202–1160 Burrard Street, Vancouver, British Columbia V6Z 2E8, Canada.
E-mail: JKelsall@providencehealth.bc.ca

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antirheumatic drug (DMARD) therapy. Later, patients with other indications and conditions were treated at the MPAC IFX clinic, including PsA, AS, arthritis related to IBD, and ocular inflammatory disease. Contraindications for IFX included pregnancy, recurrent or active infection, New York Heart Association class 3 or 4 congestive heart failure, or history in the patient or first-degree relative of multiple sclerosis or lymphoma. Prior to the first IFX infusion, patients were screened for tuberculosis by history, skin test, and chest radiograph. The University of British Columbia Research Clinical Ethics Board granted ethical approval for this study.

Dosing and monitoring. A standardized dosing and monitoring protocol was implemented at the MPAC IFX clinic. The drug was administered per manufacturer's instructions during the period of the special-access program; as of June 2001 it was administered per the approved product monograph of IFX. Accordingly, RA patients were infused with 3 mg/kg IFX, typically rounding-up the required dose to the nearest 100 mg increment; all other patients were infused 5 mg/kg IFX. The infusion schedule included induction infusions at Weeks 0, 2, and 6 and then maintenance infusions every 8 weeks thereafter. Patients' signs and symptoms were reviewed by a rheumatologist every 2 to 3 infusions. If there appeared to be an inadequate or loss of effect of IFX, a number of interventions were undertaken, including evaluation and management of precipitants for disease flare. Other interventions may have included lifestyle modification, titration of medications including nonsteroidal antiinflammatory drugs, corticosteroids, analgesics, and traditional DMARD therapies. If necessary, IFX dosage was increased. The general approach consisted of increasing the frequency of infusions, typically in 1-week increments, to every 7 or 6 weeks. Alternatively, but as a second choice, IFX dosage may be increased in 100 mg increments.

All infusions were administered in an outpatient clinic by a registered nurse (RN). IFX was diluted in 200 cc of normal saline and infused over a period of 2 h in a sequential manner: initially infused at 20 ml/h, increasing at 15 min intervals to 40 ml/h, 80 ml/h, and then to 150 ml/h for 45 min, and finally to 200 ml/h until finished. The infusion rate titration occurred provided there were no acute infusion reactions. Most recently, some patients have been treated with a shortened infusion protocol (1 h) if they have a record of no infusion reactions. Monitoring was conducted by the RN before, during, and after each infusion. Before each infusion, patients were assessed for features of infection, current antibiotic use, and previous infusion reactions. According to the MPAC IFX protocol, patients with no previous infusion reactions were not initially given premedication. Vital signs including temperature, pulse, and blood pressures were recorded prior to infusion, every 30 min thereafter, and 30 min post-infusion. The MPAC IFX clinic followed a strict protocol and clinical orders for handling infusion reactions. Briefly, for mild acute reactions, steps may include slowing the infusion, providing medications, and monitoring of vital signs every 15 min. For moderate acute reactions, steps may include stopping the infusion, positioning the patient either upright or supine according to symptoms, providing medications, administering O_2 if saturation is < 94%, and monitoring vital signs every 5 min, with resumption of infusion upon symptom resolution. For severe acute reactions, steps may include stopping the infusion, placing the patient in reclined position, providing medications, giving epinephrine if anaphylaxis is suspected, maintaining airway, administering O_2, and monitoring vital signs every 2 to 5 min. According to the protocol, patients who experience a reaction during their IFX course are subsequently prescribed premedications to prevent future reactions. For those who experienced acute reactions, premedications may include diphenhydramine, acetaminophen, hydrocortisone, dimenhydrinate, or desloratadine. Patients who experienced delayed reactions were instructed to take desloratidine/loratidine once a day for 3 days, then 3 days before the next infusion, or acetaminophen.

Data collection. Detailed clinical data were extracted from medical records of eligible patients seen at the MPAC IFX clinic from February 2000 to November 2008. A trained rheumatologist performed all chart review data extraction. Data were abstracted into standardized forms and included demographic information (sex, age); disease characteristics (diagnosis, disease duration, duration of morning stiffness, rheumatoid factor, 28 swollen and tender joint count, visual analog scales for global health, pain and physician global assessment of disease activity, Health Assessment Questionnaire Disability Index, erythrocyte sedimentation rate, C-reactive protein); and comorbid medical conditions. Medication histories and previous and concurrent medication were recorded, including prednisone, DMARD, (antimalarials, cyclophosphamide, cyclosporine A, D-penicillamine, gold, leflunomide, methotrexate, sulfasalazine, tetracyclines), and previous biologics used. A detailed history of infusions was recorded, including infusion date, patient weight, infusion dose, and duration of infusion.

Outcomes. The primary study outcome was the occurrence of acute infusion reactions, defined as any adverse event occurring during infusions or 1 h after each infusion and deemed by study rheumatologist as related to, probably related to, or possibly related to the IFX infusion. Reactions that were related to IFX were characterized by symptoms that were suggestive of the infusion, manifested upon onset of infusion, could not be attributed to other factors, and disappeared after the infusion was stopped. Reactions that were probably related to IFX were also suggestive of the infusion but did not have immediate onset with infusion, and/or could be attributed to other factors. Finally, reactions that were possibly related to IFX may or may not have been suggestive of the infusion but could also be attributed to other factors. Secondary study outcomes were the occurrence of delayed infusion reactions, defined as adverse events occurring 1 to 14 days after an IFX infusion. For the purpose of this analysis, infections were excluded and not classified as infusion reactions. Acute and delayed infusion reactions were described according to (1) patient counts (i.e., number of patients that experienced at least 1 reaction episode over study followup); (2) episode counts (number of episodes of infusion reactions that a given patient had over followup, as some patients had multiple reactions); and (3) manifestation counts (number of events — different symptoms or signs that a patient experienced during a given infusion reaction — that comprise a reaction episode). For all infusion reactions, we recorded information on the type and site of reaction, severity of the episode, and when during the course of IFX treatment the infusion reaction occurred. Similar to a previous report on infusion reactions during IFX treatment, mild acute reactions were brief in duration, self-limiting, and resolved spontaneously after temporary cessation of the infusion or reduction of infusion rate. Moderate acute reactions had a longer duration and required closer attention and extended observation period. Severe acute reactions involved respiratory symptoms or a symptomatic blood pressure drop and need for close monitoring, often for a whole day[12]. According to the MPAC IFX protocol, mild delayed reactions were easily tolerated symptoms or minor irritants causing no loss of time from normal activities. Moderate delayed reactions were persistent or manifested with discomfort severe enough to interfere with usual activities and may require treatment. Finally, severe delayed reactions were incapacitating, precluded patients from doing usual activities, and warranted intervention.

Analysis. Descriptive statistics were used to characterize demographics, clinical histories, and acute and delayed infusion reactions. Rates of acute and delayed infusion reactions were calculated as the number of reaction episodes divided by the number of IFX infusions over time. Analyses were performed using SAS statistical package (SAS Institute, Cary, NC, USA).

RESULTS

Patients. Since 2000, 376 patients were referred to the MPAC IFX clinic. Of these, 201 patients were eligible for IFX treatment; data for 1 subject were excluded from the analyses due to insufficient baseline information. Of the 200 patients, 135 (67%) had RA, 23 (12%) PsA, 22 (11%) AS, 6 (3%) ocular inflammatory disease, and 14 (7%) other inflammatory arthritis. Baseline data, recorded on the first IFX infusion, are shown in Table 1. Mean age (SD) for all patients was 50.9 ± 14.6 years and 69% were women. Mean disease duration at first infusion was 15.8 ± 10.9 years. When we limited descrip-

Table 1. Baseline characteristics of patients.

Characteristic*	All Patients, N = 200
Type of arthritis	
Rheumatoid arthritis	135 (67)
Ankylosing spondylitis	22 (11)
Psoriatic arthritis	23 (12)
Ocular (inflammation)	6 (3)
Other arthritis	14 (7)
Age, yrs, mean (SD)	50.9 ± 14.6
Gender	
Male	61 (31)
Female	139 (69)
Disease duration, yrs, mean (SD)	15.8 ± 10.9
Duration of morning stiffness, min, mean (SD)	185.9 ± 333.6
Erythrocyte sedimentation rate, units	36.9 ± 25.5
C-reactive protein, mean (SD) mg/l	27.5 ± 37.4
No. tender joints, mean (SD) 28 count	17.3 ± 14.4
No. swollen joints, mean (SD) 28 count	12.6 ± 12.1
Patient global assessment, mean (SD)	6.6 ± 7.9
Patient pain assessment, mean (SD) VAS	5.9 ± 2.3
Physician global assessment, mean (SD)	7.1 ± 8.9
Presence of comorbid conditions at baseline	
Yes	66 (33)
No	134 (67)
No. previous DMARD	
0	9 (4.5)
1	11 (5.5)
2	16 (8.0)
3	29 (14.5)
4	38 (19.0)
5	45 (22.5)
6	26 (13.0)
7	14 (7.0)
8	7 (3.5)
9	3 (1.5)
10	2 (1.0)
Previous biologics	
No	161 (80.5)
Yes	39 (19.5)

* Values are number of patients (%), unless otherwise specified. DMARD: disease-modifying antirheumatic drugs; VAS: visual analog scale.

tion only to patients with RA, mean baseline age was 54.9 ± 14.0 years and mean disease duration at first infusion was 16.7 ± 11.2 years.

IFX infusions. Overall, 4399 IFX infusions were administered for all patients in the cohort between 2000 and 2008, with 2977 infusions among the patients with RA. Figure 1 provides a summary of all infusions for all patients and patients with RA over the followup. On average, all patients received 22 ± 19 IFX infusions and were followed for 140 ± 132 weeks and the number of infusions per patient ranged from 1 to 74. Patients with RA received an average of 22 ± 19 IFX infusions (range 1–66) and mean followup was 138 ± 132 weeks.

Acute infusion reactions. Patient counts. Of the 200 patients in the IFX clinic, 90 (45%) did not experience any acute infusion reactions and 110 (55%) experienced at least 1 acute infusion reaction episode. Of these 110 patients, 31 experienced an acute episode that resulted in an infusion not being completed. When we evaluated the acute reaction episode that caused incomplete infusion, most were moderate (61.3%) or severe (25.8%) in presentation. The number of episodes of acute reactions observed over the followup ranged from 1 to 7. Most patients (43.6%) experienced only 1 acute reaction episode over the followup. We observed a declining trend in the proportion of patients experiencing 2 or more episodes. Specifically, 21 (19.1%) experienced 2 episodes, 16 (14.5%) experienced 3 episodes, 13 (11.8%) experienced 4 episodes, 6 (5.5%) experienced 5 episodes, 4 (3.6%) experienced 6 episodes, and 2 (3.6%) experienced 7 episodes.

Episode counts. Description of acute infusion reactions in terms of numbers of patients, episodes, and manifestation counts is summarized in Table 2. Of 4399 infusions in all patients, we recorded 258 infusions that resulted in an acute reaction for an overall rate of 5.9%. While most of the acute infusion reaction episodes were deemed by the study rheumatologist as causally related to the concurrent IFX infusion (59.7%), episodes were mild (42.6%) or moderate (43.8%) in severity. We also counted the number of manifestations and found a mean of 2.0 ± 1.4 per acute infusion reaction episode. When we examined the relationship between acute infusion reaction episodes and the course of IFX therapy, we found that infusion reactions were most common during earlier infusions for all patients (Figure 2). Specifically, the percentages of total numbers of acute infusion reactions that occurred during the first, second, and third infusions were 22.5%, 18.5%, and 15.0%, respectively, for all patients. This dropped to 9.2% for the fourth infusion and remained low for the remaining infusions.

Manifestation counts. Many episodes of acute infusion reactions had more than 1 sign or symptom (i.e., reaction manifestation). The mean number of manifestations per acute infusion reaction episode was 2.0 ± 1.4. In total, we recorded 508 specific manifestations of acute infusion reactions in all patients. Table 2 describes manifestations according to affected sites for all patients. The most commonly affected site was the head and neck (31.5%), followed by the skin (21.1%). In terms of specific manifestations, the most commonly observed were pruritis of the trunk/extremities (11.2%), headache (9.6%), facial flushing (7.3%), and chest tightness (7.1%; a detailed summary of the number and proportion of each specific manifestation of acute and delayed reactions is given in the Appendix).

Delayed infusion reactions. A description of delayed infusion reactions with numbers of patients, episodes, and manifestation counts is summarized in Table 3. Overall, 30 patients experienced at least 1 delayed infusion reaction. In terms of episode counts, there were 37 episodes of delayed infusion reactions out of 4399 infusions (overall delayed infusion reaction rate, 0.84%). Delayed infusion reaction episodes were

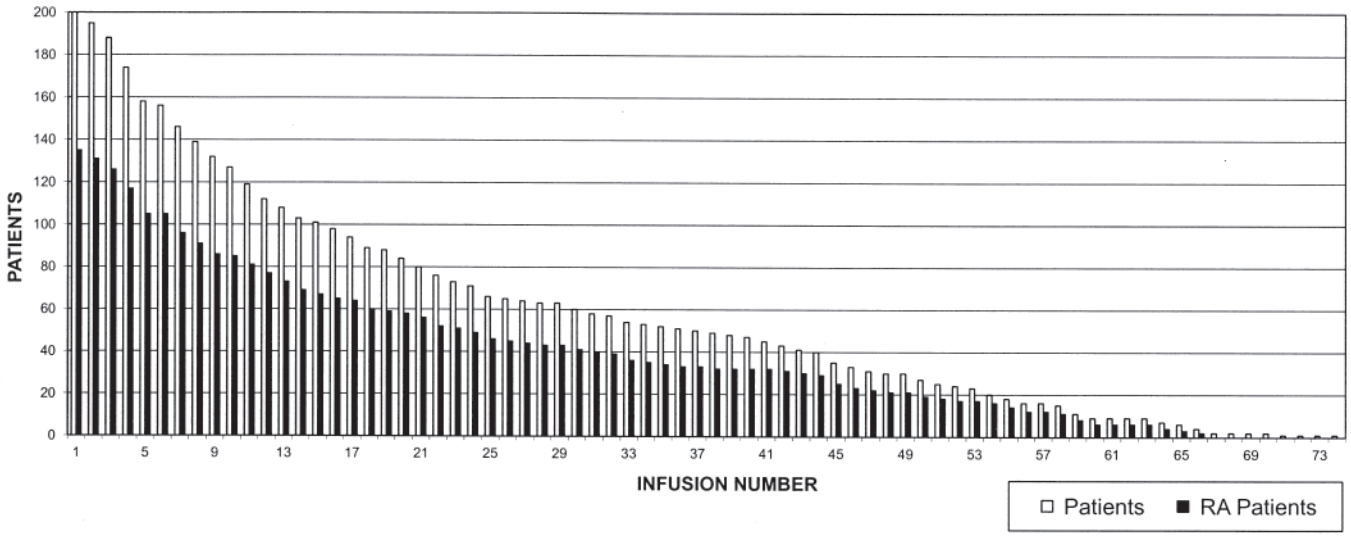

Figure 1. Summary of infusions, infliximab clinic 2000-2008. RA: rheumatoid arthritis.

Table 2. Acute infusion reactions in terms of patient, episode, and manifestation counts. Data are n (%) unless otherwise specified.

	All Patients
Patient counts	
No. patients with acute reactions	110
Episode counts	
No. episodes	258
Severity	
Mild	110 (42.6)
Moderate	113 (43.8)
Severe	25 (9.7)
Missing data	
Relation to infliximab (causality)	
Possibly related	18 (6.9)
Probably related	78 (30.2)
Related	154 (59.7)
Missing data	8 (3.17)
Manifestations per episode, mean ± SD	2.0 ± 1.4
Manifestation counts	
No. manifestations (symptoms or signs)	508
Sites	
Head and neck	160 (31.5)
Cutaneous	107 (21.1)
General	78 (15.4)
Chest/respiratory	70 (13.8)
Cardiovascular	49 (9.7)
Gsatrointestinal	44 (8.7)

mostly moderate in severity for all patients (64.9%) and patients with RA (66.7%). There was a mean of 1.8 ± 1.5 specific manifestations for each delayed infusion reaction episode. We also calculated the number of days between a delayed infusion reaction episode and the prior associated IFX infusion and found a mean duration of 7.2 days.

In terms of manifestation counts, we observed 41 specific symptoms or signs in all patients. The most common affected sites for all patients were chest/respiratory system (34.2%), general (26.8%), and skin (24.4%). Figure 3 shows that, similarly to acute infusion reaction episodes, delayed infusion reaction episodes occurred in earlier infusions.

DISCUSSION

Our study provides a detailed description of acute and delayed infusion reactions in a large cohort of patients treated for rheumatologic conditions in a real-world setting. We observed an acute reaction rate of 5.9% overall, and 5.2% specifically for patients with RA. Delayed infusion reaction rates of 0.84% overall and 0.81% specifically for patients with RA were observed. Both acute and delayed infusion reactions tended to occur with the first few infusions, with the majority occurring in the first 10 infusions. Most patients who experienced a reaction had a small number of episodes. The largest proportion of patients experienced only 1 infusion reaction (43%) judged acute and 51% delayed. We found that 77% of patients who experience acute infusion reactions had 3 or fewer episodes, and 85% of patients who experienced a delayed infusion reaction had 3 or fewer episodes. Signs and symptoms varied but the majority were deemed mild to moderate in severity.

Our findings of low rates of acute reactions are comparable with previous reports from clinical settings. Similar to our study, Ducharme, *et al* carried out a retrospective chart review of patients in a community clinical setting in Canada[8]. Their cohort included 3161 patients, mainly patients with Crohn's disease (44.3%) but also patients with arthritis, specifically RA, PsA, and AS (31%). Over 16.5 weeks of followup in 20,976 IFX infusions, the investigators reported 524 adverse drug reactions occurring during or within the first 24 hours after an infusion, for an overall rate of 2.5%. While a lower rate compared to our current study (2.5% vs 5.9%), this may be due to the dissimilar patient compositions. Similar to our

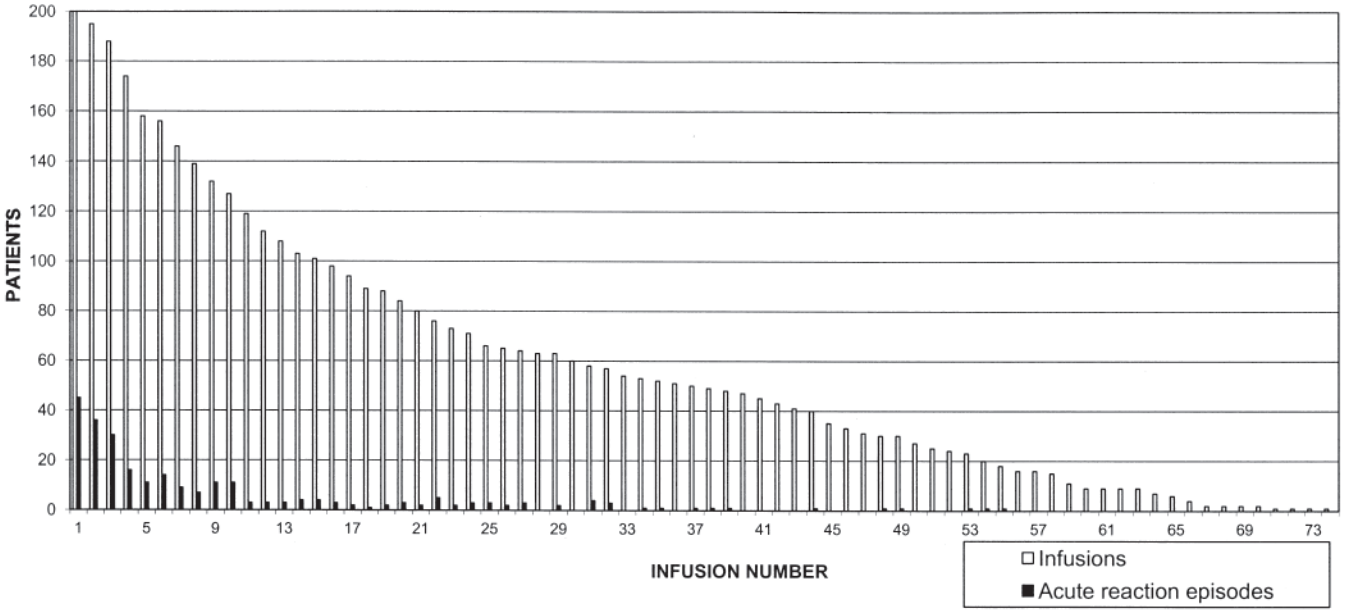

Figure 2. Timing of acute infusion reaction episodes.

Table 3. Delayed infusion reactions in terms of patient, episode, and manifestation counts. Data are n (%) unless otherwise specified.

	All Patients
Patient counts	
No. patients with delayed reactions	30
Episode counts	
No. episodes	37
Severity	
Mild	6 (16.2)
Moderate	24 (64.9)
Severe	7 (18.9)
Missing data	
Relation to infliximab (causality)	
Possibly related	8 (21.6)
Probably related	17 (45.9)
Related	12 (32.4)
Missing data	
Manifestations per episode, mean ± SD	1.8 ± 1.5
No. days from prior infliximab infusion, mean ± SD	7.2 ± 4.8
Manifestation counts	
No. manifestations (symptoms or signs)	41
Sites	
Chest/respiratory system	14 (34.2)
General	11 (26.8)
Cutaneous	10 (24.4)
Gastrointestinal	3 (7.3)
Head and neck	2 (4.9)
Arthritis	1 (2.4)

observations, most of the acute events in that study were mild to moderate in severity. Another Canadian report of acute reactions to IFX included 113 patients with RA treated with IFX in a quaternary care center[9]. Out of 1183 infusions over a mean 60.6 weeks of followup, authors reported 104 infusion reactions for an overall rate of 8.8%.

To our knowledge, this is the first clinical study to describe delayed infusion reactions to IFX within well-defined time periods among patients with inflammatory arthritis. In their study of patients with RA and spondyloarthritis, Lequerré, *et al* defined delayed infusion reactions as a "systemic reaction [that occurred] within days after IFX infusion"[10]. They reported 5 out of 203 patients experienced such a reaction. Ducharme, *et al*[8] reported on delayed infusion reactions occurring more than 24 hours after an infusion; similarly to Lequerré, *et al*[10], they did not further specify a time frame. Nonetheless, Ducharme, *et al* reported 353 delayed infusion reactions in 20,976 infusions[8]. In contrast to these studies, our definition for a delayed infusion reaction incorporated both a fixed period of 14 days after an IFX infusion and an evaluation of causality. While delayed infusion reactions from IFX treatment have not been well documented in patients with inflammatory arthritis, they have been well described in a cohort of patients with Crohn's disease[11]. Using a more specific definition for a delayed infusion reaction, that is, any adverse reaction that occurs from 24 hours to 14 days after retreatment with IFX, Cheifetz, *et al* reported 3 reactions out of 479 reactions for a delayed infusion reaction rate of 0.6%[11]. Indeed, this low delayed infusion reaction rate is comparable to the low rate we observed.

Strengths and limitations of our study deserve comment. A comprehensive evaluation of reactions to IFX is important to advance knowledge on safety of this drug; in our study, definitions used to describe acute and delayed infusion reactions were specific and incorporated both temporal and causal components. We further described frequency of reactions, multiple reactions, symptoms, and signs. However, observational studies using retrospective chart reviews are vulnerable to limita-

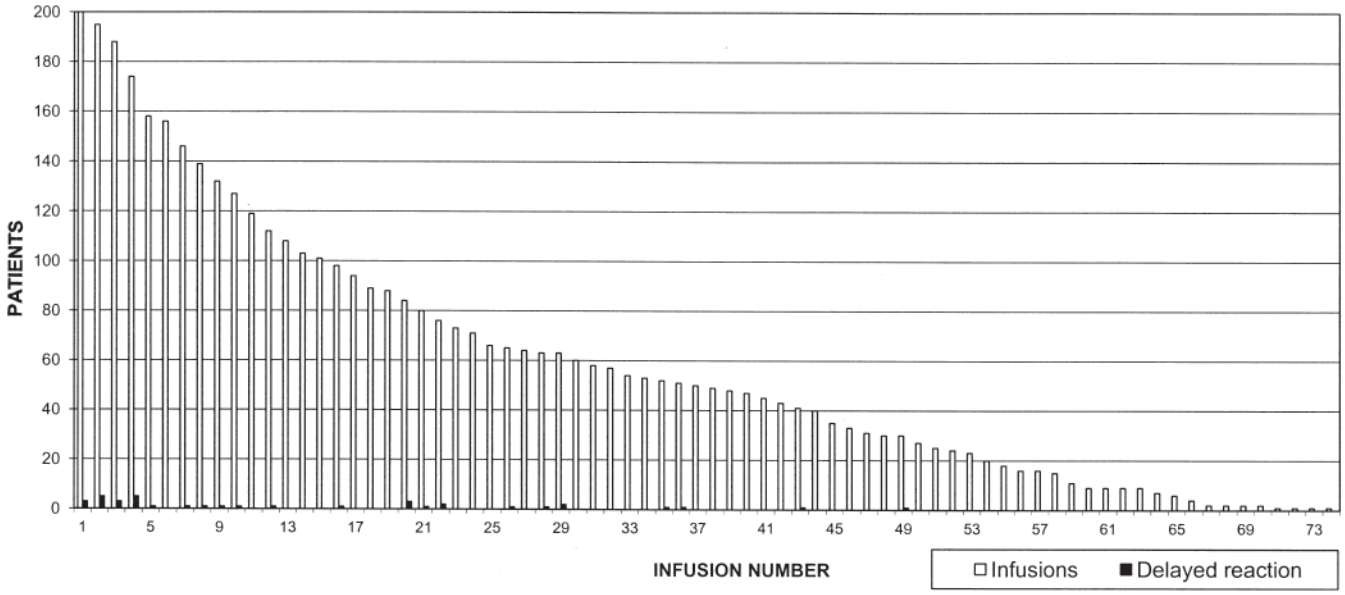

Figure 3. Timing of delayed infusion reaction episodes.

tions associated with this methodology. One of these limitations is availability and accuracy of information that may arise from missing forms or if the information was not recorded in the first place. Another challenge with chart reviews is interpretation of information found in the documents — for example, use of jargon or acronyms. However, having all data abstraction completed by a rheumatologist mitigated any potential errors due to interpretation of information. Further, use of standardized data abstraction tools also ensured systematic recording of chart information. Despite limitations associated with retrospective chart reviews, they remain a useful method for collecting data for health research studies. Finally, evaluations of predictors of infusion reactions, including dose, concomitant DMARD use, and baseline comorbidities, were beyond the scope of this study and remain subjects for future research.

Overall, our study provides a detailed description of acute and delayed reactions among patients with inflammatory arthritis treated with IFX in a clinical setting and demonstrates that infusion reactions occur infrequently, and when they do occur, they are generally mild to moderate in expression. Future research evaluating predictors of infusion reactions including IFX dose and concomitant DMARD use in similar clinical settings would be valuable.

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APPENDIX. Distribution of manifestations of acute and delayed infusion reactions in the infliximab (IFX) clinic.

Acute Infusion Reactions		Delayed Infusion Reactions	
Manifestation	N (%)	Manifestation	N (%)
Pruritis, trunk/extremities	57 (11.2)	Cough	9 (21.9)
Headache	49 (9.6)	Rash	7 (17.1)
Facial flushing	37 (7.3)	Chest pain	4 (9.8)
Chest tightness	36 (7.1)	Malaise/flu	4 (9.8)
Flushing	31 (6.1)	Pruritis	3 (7.3)
Nausea	25 (4.9)	Diarrhea	2 (4.9)
Shortness of breath	21 (4.1)	Fatigue	2 (4.9)
Rash, trunk/extremities	18 (3.5)	Headache	2 (4.9)
Chills/rigors	17 (3.3)	Myalgia	2 (4.9)
Urticaria	15 (3.0)	Decreased libido	1 (2.4)
Dizzy/lightheaded	14 (2.8)	Elevated liver enzymes	1 (2.4)
Sweats	13 (2.6)	Fever	1 (2.4)
Hypotension	12 (2.4)	Peripheral arthritis/IFX-induced lupus	1 (2.4)
Hypertension	10 (2.0)	Pleuritic pain	1 (2.4)
Palpitations	10 (2.0)	Weight gain > 10 kg	1 (2.4)
Cough	9 (1.8)	Eyes, bloodshot	2 (0.4)
Tachycardia	9 (1.8)	Fever	2 (0.4)
Vomiting	9 (1.8)	Myalgia	2 (0.4)
Diarrhea	8 (1.6)	Numbness, finger	2 (0.4)
Swollen trunk/extremities	7 (1.4)	Paresthesia, unspecified	2 (0.4)
Fatigue	6 (1.2)	Pruritis face	2 (0.4)
Malaise	6 (1.2)	Rash, facial	2 (0.4)
Anxiety	5 (1.0)	Rhinitis	2 (0.4)
Erythema/flushing, face	5 (1.0)	Scratchy throat	2 (0.4)
Eyes, blurry/double vision	4 (0.8)	“Blue foot”	1 (0.2)
Paresthesia, mouth	4 (0.8)	Atrial fibrillation	1 (0.2)
Swollen eyes	4 (0.8)	Bruising at injection site	1 (0.2)
Throat, irritation/tightness	4 (0.8)	Dry mouth	1 (0.2)
Vasovagal response	4 (0.8)	Hyperventilating	1 (0.2)
Back pain	3 (0.6)	Numbness, unspecified	1 (0.2)
Brachycardia	3 (0.6)	Pale	1 (0.2)
Chest pain	3 (0.6)	Pruritis eyes	1 (0.2)
Erythema/flushing, unspecified	3 (0.6)	Pruritis neck	1 (0.2)
Paresthesia, extremities	3 (0.6)	Pruritis throat	1 (0.2)
Paresthesia, face	3 (0.6)	Shakiness	1 (0.2)
Subjective warmth	3 (0.6)	Swollen tongue	1 (0.2)
Swollen lips	3 (0.6)	Throat, lump	1 (0.2)
Abdominal pain	2 (0.4)		
Body ache	2 (0.4)		