The safety of infliximab infusions in the community setting

James Ducharme MD1, Cindy Pelletier MSc2, Ramesh Zacharias MD3

BACKGROUND: Tumour necrosis factor-alpha (TNFα) has an important role in the pathogenesis of inflammatory conditions such as rheumatoid arthritis, Crohn’s disease, ulcerative colitis and psoriasis. Infliximab, a chimeric anti-TNFα monoclonal antibody, has been shown to reduce the severity of symptoms or induces remission of active disease. Infusions have generally been limited to the hospital setting due to cost and concerns for patient safety. Studies defining its efficacy and safety have, therefore, originated almost exclusively from hospital settings.

OBJECTIVE: To evaluate the safety of infliximab in a community clinic environment, across all types of patients.

METHODS: A retrospective chart review of 3161 patients who received a combined 20,976 infusions at a network of community clinics over 16.5 months was conducted. Adverse drug reaction (ADR) information was retrieved and coded for time of onset, severity and outcome. Only ADRs that occurred during or within the first 24 h of the infusion were included.

RESULTS: A total of 524 (2.5% of all infusions) acute ADRs in 353 patients (11.2%) were recorded. Most reactions (ie, ADRs) were mild (n=263 [50.2%, 1.3% of all infusions]) or moderate (n=233 [44.5%, 1.1% of all infusions]). Twenty-eight reactions (5.3%, 0.1% of all infusions) were severe. Emergency medical services were called to transport patients to hospital for seven of the severe reactions, of which none required admission. As per pre-established medical directives, adrenaline was administered three times.

CONCLUSIONS: Infliximab infusions are safe in the community setting. Severe ADRs were rare. None required active physician intervention; nurses were able to treat all reactions by following standardized medical directives.

Key Words: Adverse events; Community setting; Infliximab; Safety

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Tumour necrosis factor alpha (TNFα) is a proinflammatory cytokine that has an important role in the pathogenesis of many inflammatory conditions including rheumatoid arthritis, Crohn’s disease, ulcerative colitis and psoriasis (1-6). Infliximab, a chimeric anti-TNFα monoclonal antibody, has been shown to reduce the severity of symptoms or induces remission of active disease. Infusions have generally been limited to the hospital setting due to cost and concerns for patient safety. Studies defining its efficacy and safety have, therefore, originated almost exclusively from hospital settings.

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reaction seemed to be defined by the study patient being unable to continue the active medication, although there appeared to have been no a priori explicit criteria for withdrawal based on acute ADR. In a study by Colombel et al (16), a serious adverse event was defined as an event that led "to or prolonged hospitalization, was fatal or life threatening or that resulted in significant disability". Unfortunately, such implicit criteria are subjective and difficult to reproduce. Furthermore, what may not appear serious in a closely monitored clinical trial or within the confines of a hospital, may be considered serious in a clinic or outpatient setting.

To date, publications describing acute ADRs have been limited to the hospital environment or within the confines of clinical trials. Patients in these publications were preselected and did not represent the full spectrum of patients who might receive infliximab. Such an approach maximizes potential benefit (efficacy) while minimizing risk. Postmarketing studies that include 'all comers' usually demonstrate less benefit (effectiveness), while often identifying greater harm. Therefore, it is important for such community studies to be performed. The goal of the present study was to evaluate the safety of infliximab in a community clinic environment, across all types of patients.

**METHODS**

The current retrospective chart review reports on the infusion reaction rate seen in all patients treated with infliximab in community infusion clinics during the period from December 1, 2006 to April 15, 2008. The multiple infusion clinics located across Ontario followed standardized protocols for the infusion and monitoring of infliximab. Such an approach has been in place for more than six years, with an accumulated total of more than 100,000 infusions.

**TABLE 1**

Infusion protocol outlined by Cheifetz and Mayer (7)

| Reaction type, symptoms | Treatment protocol | Prophylaxis |
|-------------------------|-------------------|-------------|
| MILD                    | Slow infusion rate to 10 mL/h | Pretreat with diphenhydramine 25 mg to 50 mg and acetaminophen 650 mg PO 1.5 h before infusion |
| Flushing                | Infuse normal saline (500 mL/h to 1000 mL/h) | (Five days of a second-generation antihistamine can be substituted to decrease sedation) |
| Dizziness              | Diphenhydramine 25 mg to 50 mg IVPB | Test dose at 10 mL/h before for 15 min. Increase infusion rate to 20 mL/h, 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min, as tolerated |
| Headache               | Acetaminophen 650 mg |  |
| Diaphoresis            | Monitor vital signs every 10 min, until within normal limits |  |
| Nausea                 | Wait 20 min, then increase infusion rate to 20 mL/h for 15 min, then 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min, as tolerated |  |
| Palpitations           | Slow infusion rate to 10 mL/h or stop infusion | Pretreat with diphenhydramine 25 mg to 50 mg and acetaminophen 650 mg PO 1.5 h before infusion |
| Moderate               | Acetaminophen 650 mg | (Five days of a second-generation antihistamine can be substituted to decrease sedation) |
| Chest discomfort       | Monitor vital signs every 5 min until within normal limits | Test dose at 10 mL/h before for 15 min. Increase infusion rate to 20 mL/h every 15 min, as tolerated |
| Shortness of breath    | Wait 20 min, then restart infusion at 10 mL/h for 15 min |  |
| Hypo/hypertension (>20 points SBP) | Increase infusion rate to 20 mL/h × 15 min, then 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min, as tolerated |  |
| Increased temperature  |  |  |
| Palpitations           |  |  |
| Urticaria              |  |  |
| Severe                 | Stop infusion | Prednisone 50 mg PO every 12 h BID × 3 doses before infusion or Hydrocortisone 100 mg IV or methylprednisolone 20 mg to 40 mg IV before infusion |
| Hypo/hypertension (>40 points SBP) | Infuse normal saline (500 mL/h to 1000 mL/h) | Pretreat with diphenhydramine 25 mg to 50 mg and acetaminophen 650 mg PO 1.5 h before infusion |
| Increased temperature with rigors | Maintain airway; oxygen if available | (Five days of a second-generation antihistamine can be substituted to decrease sedation) |
| Chest discomfort       | Adrenaline (1:1000) 0.1 mL to 0.5 mL subcutaneous (may repeat every 5 min × 3) | Test dose at 10 mL/h before × 15 min. Increase infusion rate to 20 mL/h, 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min, as tolerated |
| Shortness of breath with wheezing | Diphenhydramine 25 mg to 50 mg IVPB |  |
| Stridor (if potential to lose airway, call emergency medical services for transport to emergency room) | Hydrocortisone 100 mg IV or methylprednisolone 20 mg to 40 mg IV |  |
| Flushing               | Monitor vital signs every 2 min until within normal limits |  |
|                       | If patient stabilizes, wait 20 min, then restart infusion at 10 mL/h for 15 min |  |
|                       | Increase infusion rate to 20 mL/h × 15 min, then 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min, as tolerated |  |
|                       | If patient requires second dose of adrenaline, call emergency medical services and transfer patient to emergency room for monitoring |  |
| DELAYED                | Acetaminophen 650 mg to 1000 mg PO QID | Pretreat with diphenhydramine 25 mg to 50 mg and acetaminophen 650 mg PO 1.5 h before infusion |
| Rash/urticaria         | Second-generation antihistamine or diphenhydramine | (Five days of a second-generation antihistamine can be substituted to decrease sedation) |
|                       | 50 mg QD to BID | Test dose at 10 mL/h before for 15 min. Increase infusion rate to 20 mL/h, 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min, as tolerated |
| Myalgias               | Methylprednisolone dose pack if joint pain is severe |  |
| Flu-like symptoms      | Acetaminophen 650 mg to 1000 mg PO QID | Pretreat with diphenhydramine 25 mg to 50 mg and acetaminophen 650 mg PO 1.5 h before infusion |
| Joint stiffness and pain |  | (Five days of a second-generation antihistamine can be substituted to decrease sedation) |
| Headache               | Second-generation antihistamine for 7 days postinfusion | Test dose at 10 mL/h before × 15 min. Increase infusion rate to 20 mL/h, 40 mL/h, 80 mL/h, 100 mL/h, 125 mL/h every 15 min, as tolerated |
|                       | Prednisone 50 mg PO every 12 h BID × 3 doses before infusion or Hydrocortisone 100 mg IV or methylprednisolone 20 mg to 40 mg IV before infusion |  |
|                       | Methylprednisolone dose pack if joint pain is severe |  |

*BID Twice daily; IV Intravenous; IVPB IV piggyback; PO Orally; QD Once a day, QID Four times a day; SBP Systolic blood pressure*
TABLE 2
Patients according to primary diagnosis

| Primary diagnosis               | n (%)      |
|--------------------------------|------------|
| Crohn’s disease                | 1401 (44.3) |
| Rheumatoid arthritis           | 663 (21.0)  |
| Ulcerative colitis             | 352 (11.1)  |
| Fistulizing Crohn’s disease    | 283 (9.0)   |
| Ankylosing spondylitis         | 219 (6.9)   |
| Psoriatic arthritis            | 91 (2.9)    |
| Psoriasis                      | 43 (1.4)    |
| Other                          | 109 (3.4)   |
| Total                          | 3161 (100.0)|

TABLE 3
Patients according to premedications

| Premedication(s)                          | n (%)      |
|------------------------------------------|------------|
| None                                     | 1100 (34.8) |
| Antihistamines                            | 230 (7.3)   |
| Acetaminophen                             | 102 (3.2)   |
| Steroids                                  | 597 (18.9)  |
| Antihistamines and acetaminophen          | 227 (7.2)   |
| Antihistamines and steroids               | 323 (10.2)  |
| Acetaminophen and steroids                | 82 (2.6)    |
| Antihistamines, acetaminophen and steroids| 500 (15.8)  |
| Total                                     | 3161 (100.0)|

All patients had been referred to one of the pre-established infusion clinics by their primary care physician or specialist for infusions of infliximab at a dose established by that physician. Referred patients were diagnosed with one of the following: inflammatory bowel disease – including ulcerative colitis and Crohn’s disease, rheumatoid arthritis, psoriasis or uveitis. The decision to use premedications (eg, antihistamines, steroids and/or acetaminophen) was also made by the referring physician. Patients would initially receive three loading doses at zero, two and six weeks, followed by maintenance infusions at intervals determined by their referring physician (typically every six or eight weeks). On arrival to the clinic, patients were first assessed for abnormalities in vital signs, active infections, recent vaccinations and recent surgery. If all was normal, they received any prescribed premedication and then received infliximab over a 2 h period. In case of abnormality, the onsite physician was contacted for further instructions. During the infusion, vital signs were monitored and recorded every 30 min; a nurse was expected to be with no more than three patients for any one infusion period. Postinfusion, patients were observed for 1 h for side effects and, on discharge, were advised to seek medical attention should any side effect occur. All nurses received standardized training regarding the mixing and infusion of infliximab, as well as the recognition and management of any related acute ADRs. A physician was on site for the duration of each infusion session but was not restricted to that sole task, routinely seeing his regular patients in another area. All physicians received a 1 h education session about infliximab, including the recognition and management of potential acute adverse drug events related to its infusion.

Any ADRs occurring during the 3 h stay were addressed as per the protocol detailed in Table 1 and noted by the nurse on a standardized adverse event form. Patients were asked to advise the nurse of any novel symptoms they were feeling. Patients were asked to call the 24 h hotline to advise the clinic coordinator and/or referring physician of any symptoms that arose after departure from the clinic. If such a call was received, an adverse event form was completed. In an effort to capture all ADRs, the patients were asked at their next appointment about any possible acute ADR they had failed to report. After every documented adverse event, both the referring physician and Schering-Plough Canada were notified by fax.

The data required for the present retrospective chart review were partly available in an existing electronic database, while the rest were available in the paper hardcopy of the patient records. Every new patient had an electronic record containing general patient profile and appointment data that was mostly used to schedule appointments. The hardcopy of a patient’s record is a standardized datasheet that was completed at each visit, and included weight, presence and level of severity of new symptoms, history of infection(s) or hospitalization(s) since the previous infusion, recent surgery or planned surgery, blood tests, or other investigations (eg, colonoscopy) and any change in medications. Details on any previous or new ADRs were included in the hardcopy of the patient’s record.

The required electronic data elements were extracted from the database and supplemented with data extracted from paper records. The data elements obtained from the electronic database were the following: age, diagnosis, weight, infusion intervals, infliximab dosage, number of infusions received during the study period and medications to be taken before infliximab infusion. The data extracted from the paper records were the following: steroid premedication dosage, azathioprine use, severity of adverse event according to Cheifetz and Mayer’s (7) stratification and onset of adverse event (during infusion, within 24 h postinfusion or delayed).

RESULTS

In total, 3161 patients received a combined 20,976 infusions during the study period. All infusions performed during the study period were included in the analyses. While most patients were already receiving infliximab at the start of data collection, 778 new patients were started during the study period. Patients ranged in age from 10 to 92 years, with a mean and median age of 44 years. Females represented 54.1% (n=1711) of the population. Patients received a mean of 6.64 (median seven) infusions during the study period. The mean weight of patients was 75.26 kg (median 73 kg). The mean infliximab dose was 5.16 mg/kg of body weight (median 5 mg/kg). The average time between infusions was 7.37 weeks (median eight weeks, range four to 20 weeks), with the great majority of infusions (91.5%, n=16,478) occurring within six to eight weeks. The most common diagnoses were Crohn’s disease and rheumatoid arthritis. The range of primary diagnoses are summarized in Table 2. The majority of patients (75.2%, n=2061) were prescribed premedications. The most frequently used premedications were steroids (47.5%, n=1502 [hydrocortisone in 97.4% of cases]). Further details on the types and combinations of premedications prescribed are outlined in Table 3.

Adverse events were categorized according to their onset and severity. In total, 884 (4.2% of all infusions) adverse events in 597 patients (18.9%) were recorded. Of these, 353 (39.9%) were delayed (ie, more than 24 h after infusion). The reactions after discharge were heterogeneous and included possible
symptoms from infliximab infusion as well events most likely unrelated to the medication such as hospitalization for elective surgery. Given the voluntary nature of these reports and the inclusion of arguably unrelated events, subsequent analysis and discussion will focus on acute adverse events occurring within 24 h of the infusion.

There were 524 acute ADRs, of which 405 (1.9% of all infusions) occurred during the infusion and 119 ADRs (0.6% of all infusions) occurred within 24 h, for an overall acute ADR rate of 2.5%. The ADRs occurred in 353 patients (11.2%), of which 37 (10.5% or 1.2% of all patients) were receiving infliximab for the first time. Patients with certain primary diagnoses (\( \chi^2=40.812, \) degrees of freedom [df] = 7; \( n=20,976, P<0.01 \)) and younger patients (\( \chi^2=23.438, \) df = 6; \( n=20,966, P<0.01 \)) were more likely than others to experience an ADR (see Table 4 for further details on the occurrence of moderate and severe ADR by primary diagnosis, and Table 5 for the ADR rate and count for each age group). Women (\( \chi^2=23.722, \) df = 1; \( n=20,976, P<0.01 \)) were more likely to experience an ADR (2.9% ADR rate per infusion versus 1.9% for men). Finally, patients receiving their first infusion had an acute ADR rate of 4.8% (\( n=37 \) of 778 patients) — a rate statistically higher than the overall rate of 2.5% (\( \chi^2=16.794, \) df = 1; \( n=20,931, P<0.01 \)).

Overall, most reactions were mild (\( n=263, 50.2\% \) of 524 ADRs [1.3% of all infusions]) or moderate (\( n=233, 44.5\% \), 1.1% of all infusions), with 28 being severe (5.3%, 0.1%). As required by protocol, emergency medical services were called to transport patients to hospital for seven of the severe reactions. Adrenaline was administered only three times. No patient required hospital admission.

Complete resolution of ADRs occurred in 75.6% of patients before discharge from the clinic, with improvement noted in 28 (0.13%) were reported as improved by the time the patient left the clinic. Of those 39 patients, 10 patients maintained their scheduled infliximab treatment plan and returned for their following scheduled infusion, while 27 patients did not return for further infusions. The return status of two patients was unknown because their ADR occurred near the end of the study and their next scheduled infusion was beyond the study period.

## DISCUSSION

In almost all clinical studies, infliximab has been infused in a controlled setting, either in hospital clinics or to admitted patients on a ward. Studies are more easily controlled in such an environment. In addition, concerns for patient safety – due to ADRs during infliximab infusion – have continued to restrict these infusions to hospital settings. Such a restriction is often inconvenient for many patients due to travel requirements. It may also provide inefficient care, asking patients to stay for many hours longer than the infusion itself requires. Such concern over patient safety may not be justified. While 3% of patients in ACCENT I had their treatment suspended due to adverse events (15), only two of 2211 infusions in a study by Colombel et al (16) ‘required’ the use of adrenaline. In a study by Takeuchi et al (17), the rate of serious adverse events was also low, occurring in 0.5%. Most reactions considered serious can be controlled by temporary cessation of the infusion, followed by a slower infusion rate when restarted. They do not necessarily require treatment, as is often suggested.

Cheifetz and Mayer (7) have demonstrated that ADRs are not related to the presence of antibodies. They stated that “the reactions are largely not anaphylactic (IgE mediated), making it possible to re-treat patients using specific protocols”. Such information further supports the concept that use of adrenaline – as is recommended for anaphylaxis – may be of no value for infliximab-related acute adverse events.

Our study evaluated the safety of infliximab infusions administered in a community setting using a standardized protocol, and is the largest report of acute adverse event rates to date. The results demonstrate convincingly that infliximab can be infused in a community clinic without untoward patient risk. Furthermore, it would appear that the onsite presence of a physician – as required in Canada – may not be warranted, provided appropriate medical directives are in place.

While our study’s per-infusion reaction rate was low, the per-patient rate was higher than that previously reported. It has been suggested that the greater the number of infusions a patient receives, the more likely it is that that patient will experience at least one ADR. As stated above, Cheifetz and

### TABLE 4

| Primary diagnosis                  | Moderate | Severe |
|-----------------------------------|----------|--------|
| Psoriatic arthritis               | 7 (1.1)  | 2 (0.3) |
| Rheumatoid arthritis              | 47 (1.0) | 11 (0.2) |
| Ulcerative colitis                | 42 (2.2) | 4 (0.2) |
| Fistulizing Crohn’s disease       | 18 (1.1) | 2 (0.1) |
| Crohn’s disease                   | 84 (0.9) | 8 (0.1) |
| Ankylosing spondylitis            | 24 (1.6) | 1 (0.1) |
| Psoriasis                         | 1 (0.5)  | 0 (0.0) |
| Other                             | 10 (1.3) | 0 (0.0) |
| Total                             | 233 (1.1)| 28 (0.1)|
Mayer (7) have demonstrated that the reactions are not related to antibody formation. If infusion reactions were related to antibody formation, one would expect that there could be no such reactions with a first infusion. Our study found the exact opposite: the acute ADR rate was almost twice as high in first-time infusions than was seen overall. Any therapy that has the potential to place a patient at risk of a serious adverse event should be performed in a monitored setting. Identifying the true risk to patients from acute infusion reactions requires a large cohort. To date, most studies have focused on delayed or longer-term risk, which fails to establish the safety of the infusion itself. The severity of acute infusion reactions has been difficult to characterize because adverse events are often grouped together in randomized trials studying therapeutic effects, and are only reported in a single paragraph. Justifiably, there has been a focus on risk of infection after the infusion and on risk of malignancy at some point thereafter. While of high importance, such studies do not enable the patient or the physician to know if monitoring is required or whether treatment should take place in a hospital setting. Our results establish that the practice of infusing infliximab in a community setting is extremely safe. An overall ADR rate of 2.5% per infusion is well below previous clinical studies. Hanauer et al (15) reported 106 reactions in 2026 infusions (5.2%). Of all acute ADRs reported to arise from the 20,976 infusions, none were so severe as to require an intervention of greater than what was provided by existing medical directives. No monitoring other than vital signs and oxygen saturation was required, and no specific physician intervention was required. All cases in which the initiation of an emergency medical service response was mandated by protocol were improved or resolved before arrival of the paramedics.

The present study examined the largest cohort of infusions reported to date and demonstrated that infliximab can be safely infused in the community setting, provided standardized protocols are used. Severe adverse events were extremely rare, none of which required active physician intervention; nurses were able to treat all reactions by following established medical directives. It may be possible to provide such infusions without immediate physician response or on-site presence, and rely on emergency medical service response for truly exceptional events.

The retrospective nature of the study limits the quality and depth of the information available because the data were originally collected for patient care and administrative purposes rather than for research. Therefore, updated information regarding comorbidities and concomitant medications was not available, nor was valuable information regarding the follow-up of severe reactions unless the patient subsequently returned to the clinic for another infusion. A greater level of communication between clinics and referring physicians would address this issue and improve future infusions because lessons learned could also be shared between referring physicians via the clinics. There was a risk of incorporation bias: patients who had experienced severe ADRs before this data collection period would probably have been taken off infliximab. This should have been offset by the ongoing recruitment of new patients. There is the possibility that patients who were more ill would have had their initial infusions during a hospital admission, rather than in a community clinic; however, significantly more than 95% of our patients have their three loading doses administered in our clinics. Our patients, therefore, appear to highly represent the complete spectrum of disease seen in adolescents and adults.

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