

The Incidence and Management of Infusion Reactions to Infliximab: A Large Center Experience

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OBJECTIVE: To assess the incidence and management of infusion reactions to infliximab, a chimeric monoclonal antibody that targets human tumor necrosis factor- α , in patients with Crohn's disease treated at a large infusion center.

METHODS: A total of 165 consecutive patients who received 479 infliximab infusions in the Division of Clinical Immunology Infusion Center at Mount Sinai Medical Center from July, 1998 to January, 2001 were evaluated. Specific treatment protocols for initial and subsequent acute infusion reactions were followed and the outcomes documented.

RESULTS: The overall incidence of infusion reactions to infliximab was 6.1% (29 of 479) of infusions, affecting 9.7% (16 of 165) of patients. Mild, moderate, or severe acute reactions occurred in 3.1% (15 of 479), 1.2% (six of 479), and 1.0% (five of 479) of infliximab infusions, respectively. Use of treatment protocols resulted in rapid resolution of all acute reactions to infliximab. With the prophylaxis protocol, all patients who experienced an initial mild or moderate acute reaction were able to receive additional infusions. Four patients experienced a total of five severe acute reactions. Three patients were retreated: two patients had no further problems, whereas one patient had a second severe acute reaction that rapidly resolved with treatment. Suggesting that acute infusion reactions are not type I hypersensitivity reactions, in 11 patients who experienced 14 acute infusion reactions, serum tryptase levels were normal. Delayed infusion reactions occurred in 0.6% (three of 479) of infusions.

CONCLUSIONS: Infliximab infusions were accompanied by acute reactions in approximately 5% of infusions. These reactions did not seem to be true IgE-mediated type I hypersensitivity events. Using appropriate treatment protocols, these reactions were effectively treated and prevented upon retreatment in nearly all patients. Delayed reactions were rare, occurring in <1% of infusions. (Am J Gastroenterol 2003;98:1315–1324. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

A number of new agents have emerged over the past decade that have broadened treatment options for Crohn's disease (CD). Most notable of these is the biological agent, infliximab. Infliximab is a chimeric (*i.e.*, part murine, part human) monoclonal antibody that binds with high affinity and specificity to tumor necrosis factor- α , a potent proinflammatory cytokine, to neutralize its biological activity. The safety and efficacy of infliximab has been established in a number of controlled clinical trials for the treatment of moderately to severely active and fistulizing CD and rheumatoid arthritis (1–5).

As with any infused protein-derived agent, clinical trials using infliximab have vigilantly assessed the potential of the drug to elicit adverse events, including infusion reactions. Overall, the incidence of infusion reactions to infliximab is low (approximately 5%) (5).

Infusion reactions to infliximab are categorized as either acute or delayed. Any adverse reaction, whether immunologically or nonimmunologically based, which occurs during or within 24 h of an initial or subsequent infliximab infusion, is referred to as an acute infusion reaction. A delayed infusion reaction is defined as any adverse reaction that occurs from 24 h to 14 days after retreatment with infliximab. Both acute and delayed reactions can be further categorized as mild, moderate, or severe, according to the severity of signs and symptoms they produce.

Management of an acute infusion reaction is directed toward alleviating the associated signs and symptoms, which most commonly include fever, chest pain, hypotension/hypertension, or dyspnea. Typically, symptoms improve substantially or resolve completely after infusion rate adjustments and treatment with acetaminophen, antihistamines, steroids, and/or epinephrine.

Delayed infusion reactions, which generally present with symptoms of arthralgia, myalgia, urticarial rash, fever, and malaise, are managed with acetaminophen, antihistamines, and steroids.

In this report, we summarize the incidence and management of infliximab infusion reactions in patients with CD at

the Division of Clinical Immunology Infusion Center, Mount Sinai Medical Center. We also outline a protocol for managing infusion reactions that has proven successful in our practice.

MATERIALS AND METHODS

We conducted a retrospective study of 165 consecutive patients with CD who received a total of 479 infliximab infusions at the Division of Clinical Immunology Infusion Center, Mount Sinai Medical Center during the period of July 1, 1998, through January 23, 2001, to assess the incidence and management of infusion reactions to infliximab. Specific infusion, infusion reaction, and prophylaxis protocols were followed. The infusion reaction and prophylaxis protocols were based on the type (*i.e.*, acute or delayed) and severity (*i.e.*, mild, moderate, or severe) of the reaction. Our infusion reaction protocols for severe acute reactions were developed using previous desensitization protocols for infliximab, 5-fluorouracil, and vancomycin as templates (6, 7). Table 1 lists the commonly reported symptoms associated with mild, moderate, and severe acute infusion reactions. The severity of infusion reactions was assigned by the physician based on the patient's signs and symptoms, which did not always fit neatly into the definition of mild, moderate, or severe reactions. However, classification of the severity of reactions was useful in terms of determining treatment.

The infusion protocol outlined in Figure 1 was followed for all infliximab infusions. The infliximab dose was calculated based on the patient's weight, and the drug was prepared for infusion according to the package insert, using aseptic technique. Intravenous (*i.v.*) access was established, and baseline vital signs were obtained before beginning the infusion. Infliximab was administered at an initial slow rate and was gradually increased to infuse over a period no less than 2 h: beginning at 10 ml/h and increasing to 20 ml/h, 40 ml/h, and 80 ml/h, every 15 min, respectively, as tolerated; followed by 150 ml/h and 250 ml/h every 30 min, respectively, as tolerated. The patient's signs and symptoms were monitored every 30 min throughout the infusion.

If an infusion reaction developed, the type and severity of the reaction was determined and the patient treated according to the protocols described in Table 1 and Figure 2B. Patients who had experienced previous infusion reactions were also treated according to the prophylaxis protocols in Table 1 and Figure 2B. An emergency kit consisting of epinephrine, saline, oxygen, diphenhydramine, acetaminophen, methylprednisolone, and prednisone, an ambulatory bag and mask, and an emergency crash cart were made readily available (Table 2).

For mild acute reactions, the infusion rate was slowed, *i.v.* diphenhydramine (25–50 mg) and *p.o.* acetaminophen (650 mg) were administered, and vital signs were monitored every 10 min. After waiting for 20 min, the infusion rate was subsequently increased to 20 ml/h, 40 ml/h, and 80 ml/h,

every 15 min, respectively, as tolerated. Vital signs continued to be monitored every 10 min until within normal limits.

For initial moderate acute reactions, the infusion was stopped or slowed, *i.v.* diphenhydramine (25–50 mg) and *p.o.* acetaminophen (650 mg) were administered, and vital signs were monitored every 5 min. After 20 min, the infusion rate was restarted at a slow rate (10 ml/h) and subsequently increased as tolerated.

For initial severe acute reactions, the infusion was stopped and normal saline infused. The airway was maintained and oxygen given, if available. Epinephrine (0.1–0.5 ml, 1:1000) was given subcutaneously (*s.c.*) and could be repeated every 5 min for three doses. Also, *i.v.* hydrocortisone (100 mg) or *i.v.* methylprednisolone (20–40 mg) was then given, followed by *i.v.* diphenhydramine (25–50 mg), and *p.o.* acetaminophen (650 mg). Vital signs were monitored every 2 min. If the patient stabilized, the infusion rate was subsequently restarted at a slow rate and increased as tolerated. It should be noted that epinephrine and diphenhydramine have a rapid onset of action and are given in severe reactions before steroids, which have a slower onset of action.

For prophylaxis in cases of prior mild acute reactions, patients were pretreated with *p.o.* diphenhydramine (25–50 mg) and *p.o.* acetaminophen (650 mg) 1.5 h before infusion. A test dose of infliximab (10 ml/h) was given for 15 min. If tolerated, the rate was increased and the infusion continued over 3 h. Previous moderate acute reactions required pretreatment with *p.o.* diphenhydramine (25–50 mg) and *p.o.* acetaminophen (650 mg) 1.5 h before infusion. A test dose of infliximab (10 ml/h) was given for 15 min. If tolerated, the rate was increased, as tolerated, through completion. For severe acute reactions, patients were pretreated with *p.o.* diphenhydramine (25–50 mg) and *p.o.* acetaminophen (650 mg) 1.5 h before infusion, in addition to *p.o.* prednisone (50 mg) for three doses over 24 hr before infusion. As an alternative to prednisone, *i.v.* hydrocortisone (100 mg) or *i.v.* methylprednisolone (20–40 mg) could be given 20 min before infusion. A test dose of infliximab (10 ml/h) was given for 15 min. If tolerated, the rate was increased, as tolerated, through completion. For these patients, a maximum rate of 100 ml/h was not exceeded.

RESULTS

Incidence and Outcomes of Acute Infusion Reactions

The overall incidence of acute reactions to infliximab was 5.4% (26 of 479) of infusions, affecting 8.4% (14 of 165) of patients. Mild, moderate, or severe reactions occurred in 3.1% (15 of 479), 1.2% (six of 479), and 1.0% (five of 479) of infliximab infusions, respectively. Seven of the 14 patients (50%) who had an initial infusion reaction developed a total of 12 subsequent reactions. Six of the 14 patients (42.9%) were taking azathioprine/6-mercaptopurine or methotrexate. Five patients had a total of 14 mild acute infusion reactions with symptoms that most commonly con-

Table 1. Infiximab Acute Infusion Reactions: Treatment and Prophylaxis Protocols

Type of Reactions	Treatment Protocol	Prophylaxis for Subsequent Infiximab Infusion
Mild		
Hyperemia	Slow infusion rate to 10 ml/h (four drops/min)	Pretreat with diphenhydramine (25–50 mg <i>p.o.</i>) and acetaminophen (650 mg <i>p.o.</i>) 1.5 h before infusion
Palpitations	Diphenhydramine (25–50 mg IVPB)	Test dose infiximab at 10 ml/h (four drops/min) for 15 min
Diaphoresis	Acetaminophen (650 mg <i>p.o.</i>)	If tolerated, increase rate to infuse over 3 h
Headache	Monitor VS every 10 min until WNL	
Dizziness	Wait 20 min, then increase infusion rate to 20 ml/h (seven drops/min), 40 ml/h (14 drops/min), and 80 ml/h (27 drops/min) every 15 min, respectively, as tolerated	
Nausea	Monitor VS every 10 min until WNL	
Moderate		
Hypo/hypertension (≥ 20 points SBP)	Stop or slow infusion rate to administer diphenhydramine (25–50 mg IVPB)	Pretreat with diphenhydramine (25–50 mg <i>p.o.</i>) and acetaminophen (650 mg <i>p.o.</i>) 1.5 h before infusion
Hyperemia	Acetaminophen (650 mg <i>p.o.</i>)	Test dose infiximab at 10 ml/h (four drops/min) for 15 min
Chest discomfort (<i>e.g.</i> , tightening, pressure)	Monitor VS every 5 min until WNL	If tolerated, increase infusion rate to 20 ml/h (seven drops/min), 40 ml/h (14 drops/min), 80 ml/h (27 drops/min), 100 ml/h (34 drops/min), and 125 ml/h (41 drops/min) every 15 min, respectively, as tolerated through completion
Shortness of breath	Wait 20 min, then restart infusion rate at 10 ml/h (four drops/min) for 15 min	
Elevated temperature	Increase infusion rate to 20 ml/h (seven drops/min), 40 ml/h (14 drops/min), and 80 ml/h (27 drops/min) every 15 min, respectively, as tolerated	
Palpitations	Monitor VS every 5 min until WNL	
Urticaria		
Severe		
Significant (≥ 40 points SBP) hypo/hypertension	Stop infusion	Pretreat with diphenhydramine (25–50 mg <i>p.o.</i>) and acetaminophen (650 mg <i>p.o.</i>) 1.5 h before infusion
Elevated temperature with rigors	Infuse normal saline (500–1000 ml/h)	Prednisone (50 mg <i>p.o.</i>) for three doses over 24 h before infusion; or hydrocortisone (100 mg <i>i.v.</i>); and methylprednisolone (20–40 mg <i>i.v.</i>) 20 min before infusion
Hyperemia	Maintain airway; give oxygen if available	Test dose infiximab at 10 ml/h (four drops/min) for 15 min
Chest discomfort (<i>e.g.</i> , tightening, pressure)	Epinephrine ([1:1000] 0.1–0.5 <i>s.c.</i>); may repeat every 5 min for three doses	If tolerated, increase infusion rate to 20 ml/h (seven drops/min), 40 ml/h (14 drops/min), 80 ml/h (27 drops/min), and 100 ml/h (34 drops/min) every 15 min, respectively, as tolerated through completion
Significant shortness of breath	Hydrocortisone (100 mg <i>i.v.</i>) or methylprednisolone (20–40 mg <i>i.v.</i>)	
Stridor (if potential to lose airway, call EMS for transport to ER)	Diphenhydramine (25–50 mg IVPB)	
	Acetaminophen (650 mg <i>p.o.</i>)	
	Monitor VS every 2 min until WNL	
	If patient stabilizes, increase infusion rate to 20 ml/h (seven drops/min), 40 ml/h (14 drops/min), and 80 ml/h (27 drops/min) every 15 min, respectively, as tolerated	
	If patient requires a second dose of epinephrine, call EMS to transfer patient to ER for monitoring	

EMS = emergency medical services; ER = emergency room; IVPB = intravenous “piggyback”; VS = vital signs; SBP = systolic blood pressure; WNL = within normal limits.

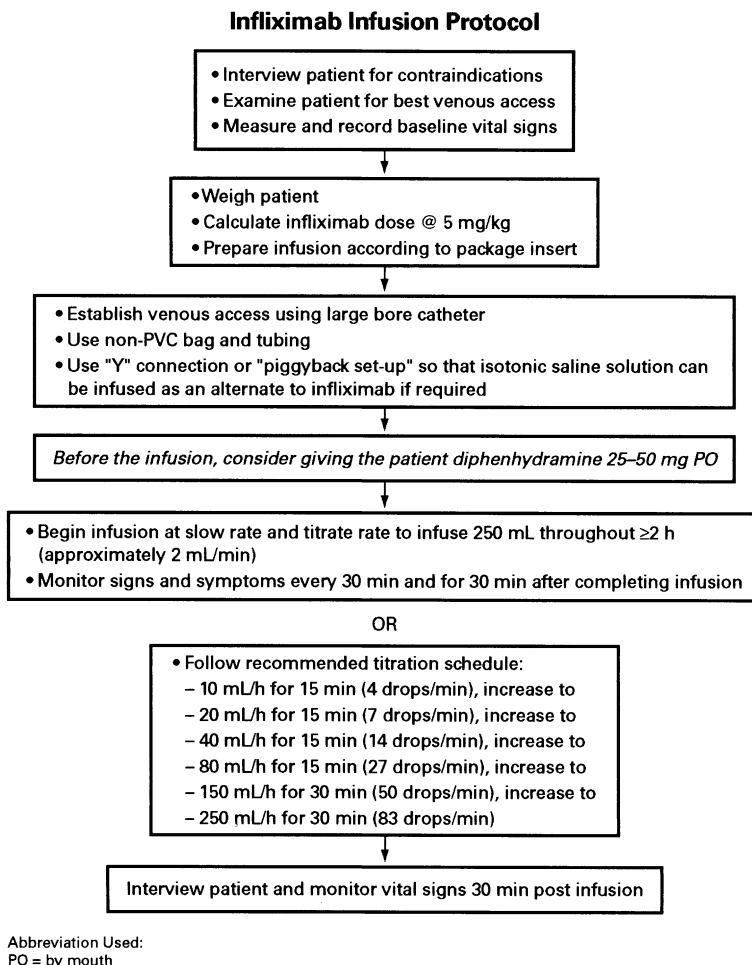


Figure 1. Infliximab infusion protocol. PVC = polyvinyl chloride.

sisted of flushing, lightheadedness, and chest tightness. Three patients who had no previous infusion reactions to infliximab developed moderate acute reactions that consisted of chest tightness, dyspnea, and flushing or palpitations. One patient had two moderate reactions to separate infliximab infusions (one consisted solely of chest heaviness, dyspnea, flushing, and dizziness, whereas the other also included fever, joint pains, and rigors). One patient had a moderate reaction consisting of urticaria. All mild and moderate infusion reactions rapidly resolved after administration of acetaminophen, antihistamines, steroids, and/or epinephrine. In all but one case, the infusion was successfully restarted at a slower rate after treatment.

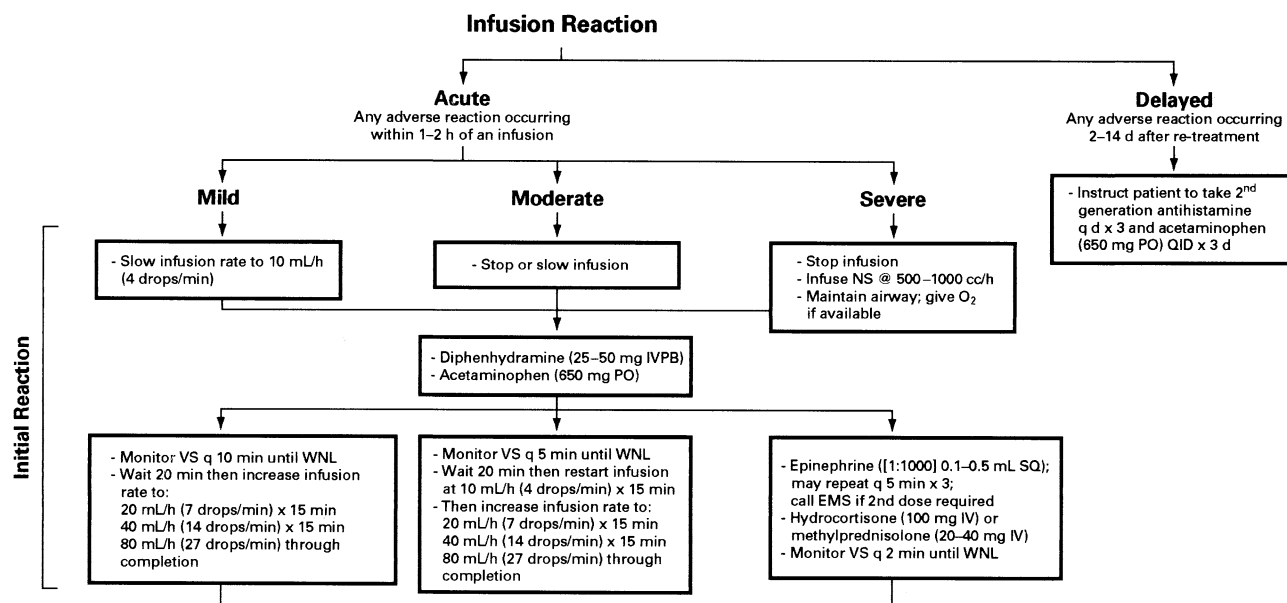
Fifteen of 29 (51.7%) infusion reactions occurred after one of the first three infusions. Two of 29 (6.9%) reactions took place during the initial infusion, and eight of 29 (27.6%) reactions occurred with the second infusion (Fig. 3).

All of the patients who experienced mild or moderate acute infusion reactions that required retreatment with infliximab were able to complete reinfusions after receiving the appropriate premedication. The willingness of the phy-

sician to reinfuse infliximab after an infusion reaction increased as the physician's experience increased. One patient who developed a moderate acute infusion reaction early in the study period was not reinfused because of the physician's limited experience with treating infusion reactions at that time.

Four patients initially treated at the infusion center had a total of five reactions that were classified as severe (dyspnea, hypotension, or cardiopulmonary symptoms combined with urticaria). Three of the patients were retreated: two patients had no further problems, whereas one patient had a second severe acute reaction during retreatment. In this case, no further infusions were attempted. One patient, initially referred to the center for a severe infusion reaction and successfully treated, subsequently developed a second severe acute reaction after seven infusions without complications. However, this infusion was completed after therapy at a slower rate. Thus, only one of 165 patients treated and one of 16 patients with a previous acute reaction were unable to tolerate infliximab reinfusion secondary to infusion-related reactions. Because of our center's experience with infliximab infusion reactions, four patients who had

Infliximab Infusion Reaction Protocol

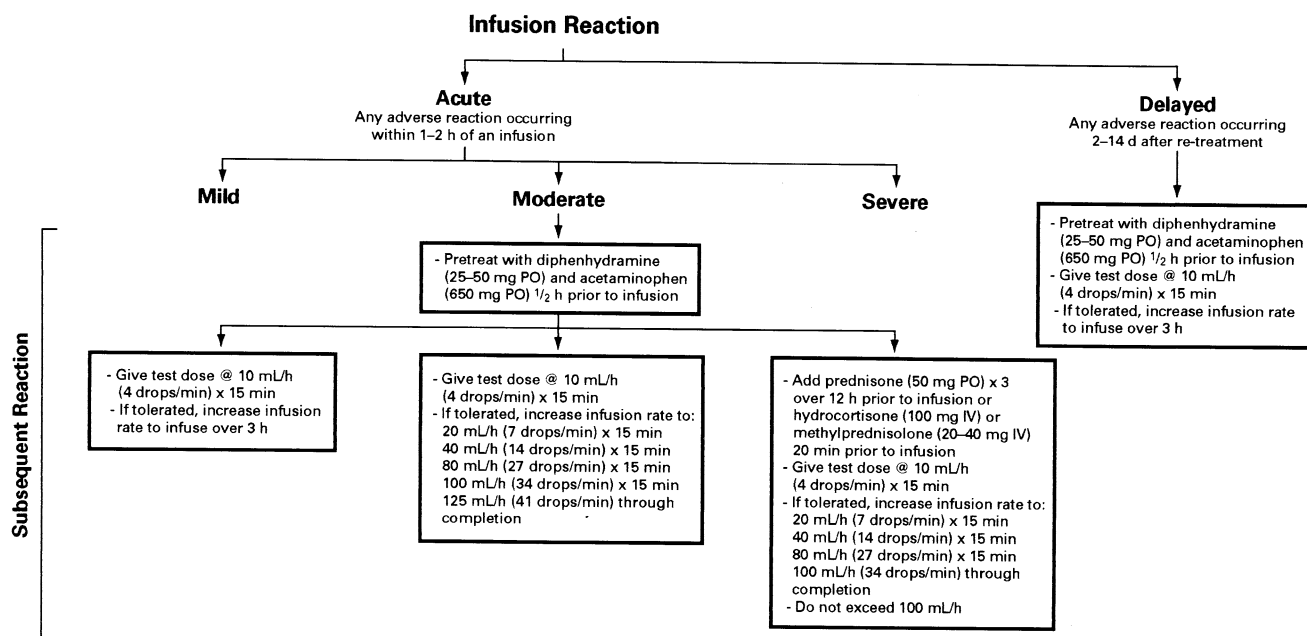


Abbreviations used:

EMS = Emergency Medical Services; IV = intravenous(ly); IVPB = intravenous "piggyback"; NS = normal saline; PO = by mouth; q = every; q d = every day; QID = 4 times daily; SQ = subcutaneous(ly); VS = vital signs; WNL = within normal limits

A

Infliximab Infusion Reaction Protocol



Abbreviations used:

EMS = Emergency Medical Services; IV = intravenous(ly); IVPB = intravenous "piggyback"; NS = normal saline; PO = by mouth; q = every; q d = every day; QID = 4 times daily; SQ = subcutaneous(ly); VS = vital signs; WNL = within normal limits

B

Figure 2. Infliximab infusion reaction protocol.

severe reactions at outside practices were referred for re-treatment. All four patients received the appropriate prophylactic measures and underwent successful reinfusion.

Of the 165 patients included in this analysis, 50 were primarily treated for enterocutaneous fistulas: 44 received

infliximab induction at weeks 0, 2, and 6; and six patients received infusions at weeks 0 and 2. After this induction, the approach at our center was to retreat upon the development of minimal symptoms of fistula drainage. These 50 patients had a total of 205 infusions over the study period. The mean

Table 2. Infliximab Acute Infusion Reaction: Emergency Kit Contents

Epinephrine 1:1000 for s.c. administration
i.v. saline (0.9%) with large catheter
Oxygen with nasal cannula
Diphenhydramine (parenteral and p.o.)
Acetaminophen
Methylprednisolone and prednisone
Ambulatory bag and mask
Emergency crash cart if no emergency center is within convenient distance

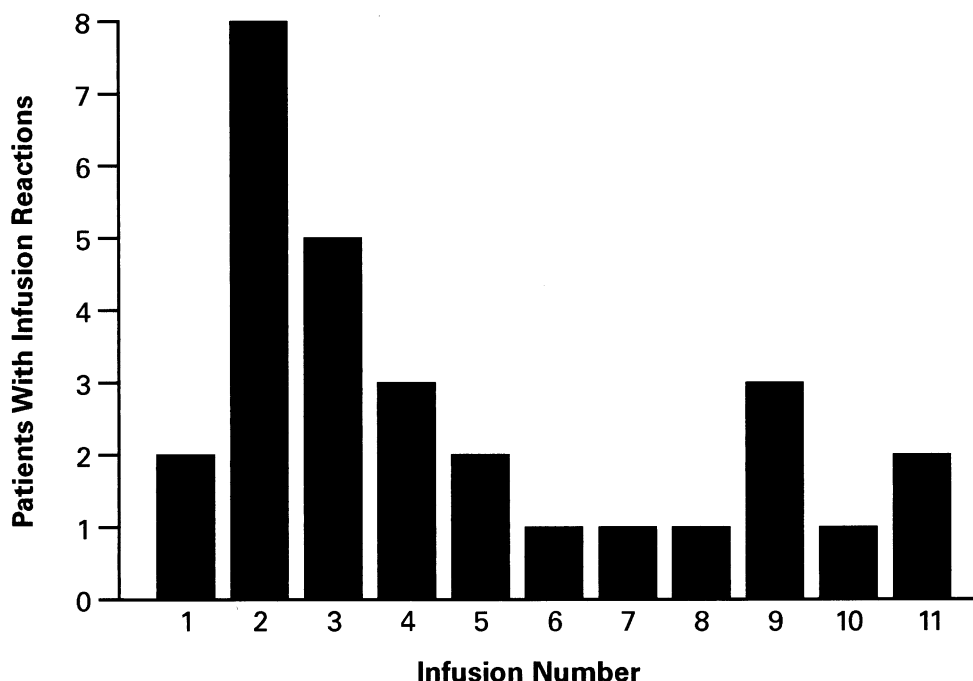
interval ($\pm$ SD) between infusions was 7.9 ± 11.0 wk. Three patients in this group developed acute infusion reactions. The mean interval between infusions in patients who did and did not develop acute infusion reactions was similar (5.1 ± 2.7 vs 8.4 ± 11.7 wk, respectively).

A total of 115 patients were treated for the indication of active inflammatory CD without fistulas. Patients were treated with a single infusion at week 0, then retreated episodically when they developed minimal symptoms of disease activity. In this group, 55 patients were infused only once during the study period. Two of these patients developed an acute infusion reaction. Sixty patients received multiple infusions during the study period (219 total infusions). The mean interval ($\pm$ SD) between infusions was 13.1 ± 13.7 wk. Eleven patients developed acute infusion reactions. Once again, mean interval between infusions in patients who did and did not develop acute infusion reactions was similar (11.4 ± 9.3 vs 13.7 ± 14.7 wk, respectively).

There were 35 patients who had an interval of 20 wk or more between infusions. Of these patients, five developed infusion reactions (four acute, one delayed) after the extended interval. All five patients who developed reactions were treated episodically for inflammatory CD.

Most Acute Infusion Reactions Are Not IgE-Mediated Acute Hypersensitivity Reactions

Several clinical features of the acute infusion reactions encountered in our analysis suggest that the reactions may not be IgE-mediated acute hypersensitivity events. First, after management of an initial infusion reaction, patients were successfully retreated with reductions in the rate of infusion. Second, despite significant respiratory compromise and dyspnea in some cases, no objective evidence was found of wheezing on pulmonary auscultation, a hallmark of an allergic hypersensitivity response. Therefore, to begin to investigate the pathogenesis of these reactions, we studied a cohort of 11 patients who had a total of 14 acute infusion reactions between January, 2000 and January, 2002. The reactions were mild, moderate, or severe in five, five, and four cases, respectively. Twenty minutes after each reaction, serum was obtained and evaluated for the presence of the mast cell enzyme tryptase, which is elevated after IgE-mediated acute hypersensitivity reactions. Serum tryptase was within the normal range in every case (mean $\pm$ SD, 4.4 ± 1.5 μ g/ml; range 2.9–9.0 μ g/ml; $n = 14$) (normal serum tryptase 1.9–13.5 μ g/ml). Additionally, to look for a generalized predisposition to atopy/allergy in patients who experienced acute infusion reactions, serum IgE was evaluated in six patients who experienced seven reactions at the same

**Figure 3.** Incidence of infusion reactions correlated to infusion number.

time. Once again, total IgE levels were within the normal range in every instance (mean $\pm$ SD, 22.5 ± 21.3 IU/ml; range 8.4–60.9 IU/ml; $n = 7$) (normal total serum IgE 1–365 IU/ml). Therefore, in our experience, acute infusion reactions did not seem to be true IgE-mediated acute hypersensitivity events. This likely explains why the majority of these reactions can be managed and prevented by reductions in the rate of infusion.

Incidence and Outcomes of Delayed Infusion Reactions

Over the 2.5-yr study period, three delayed infusion reactions were observed. We had defined delayed infusion reactions to include any infliximab-related event that occurred greater than 24 h after infusion. Although somewhat arbitrary, this time frame would be consistent with a different immunopathogenesis than for the reactions that occur within the first 24 h. The three patients who developed delayed infusion reactions were all treated for the indication of active inflammatory CD without fistulas and therefore received only a single induction infusion.

One of the patients who developed a delayed infusion reaction was originally sent to the infusion center from an outside institution for retreatment with infliximab after a severe acute reaction. The patient's delayed infusion reaction resolved without treatment. Of the other two patients who developed delayed infusion reactions, one patient developed a delayed reaction after the initial infliximab infusion, whereas the other patient developed a delayed reaction after the fourth infliximab infusion, which was administered 8 wk after the third infusion. Both patients' symptoms included jaw tightness, arthralgias, myalgias, and fever, and both patients had complete resolution of their symptoms without treatment. The patient who developed symptoms after the initial infusion was retreated with infliximab without problems. Another patient who experienced a delayed reaction was referred from an outside practice and successfully retreated with a concomitant 1-wk course of *p.o.* diphenhydramine and acetaminophen.

DISCUSSION

Our experience in a large academic infusion center indicates that acute and delayed infusion reactions to infliximab have a low incidence of occurrence. Acute infusion reactions usually resolve with rate adjustments, diphenhydramine, acetaminophen, and steroids. The routine use of prophylaxis protocols in situations where they are warranted allows patients to be safely retreated with infliximab in an outpatient setting.

All patients with mild and moderate reactions were safely retreated using the described prophylaxis protocols. However, prophylaxis does not always prevent subsequent infusion reactions. Therefore, although we describe successes, we do not advocate routine retreatment in patients who experience severe reactions to infliximab. In the case of severe infusion reactions, the risks and benefits of medical

and surgical treatment options need to be carefully considered. Some patients may elect not to be retreated. Patients who are candidates can be retreated successfully in an office setting and do not require hospitalization. Our success in treating severe infusion reactions in an office setting suggests an alternative to an earlier report by Puchner *et al.* in which patients were hospitalized in the intensive care unit for retreatment (7).

The description of infliximab-associated infusion reactions has created a confusing nomenclature that does not necessarily reflect the pathogenesis of these events. The erroneous terms "acute" and "delayed hypersensitivity reactions" have been applied to most infliximab-related infusion reactions. Hypersensitivity reactions define specific immune-mediated phenomena. Also referred to as drug reactions or drug allergies, hypersensitivity reactions to therapeutic agents are generally categorized by one of four immunological mechanisms based on the Gell-Coombs classification. These include type I acute hypersensitivity reactions mediated by IgE antibodies, the chief example of which is anaphylaxis, type II cytotoxic hypersensitivity reactions induced by complement-mediated cytotoxic IgM or IgG antibodies, type III immune complex hypersensitivity reactions mediated by immune complexes formed in slight antigen excess, and type IV cell-mediated or delayed hypersensitivity reactions induced by sensitized T lymphocytes. True hypersensitivity reactions are observed with the pharmacological use of many protein- and nonprotein-derived therapeutic agents. The antigenicity of a drug depends upon a host of drug-specific and patient-specific factors, including the dose, duration, number of exposures, route of administration, and chemical properties of a drug as well as the age, gender, atopy, and specific genetic polymorphisms of a patient. Although antigens are usually proteins, antigenic polymers such as polysaccharides, nucleic acids, and other macromolecules have been described. For example, penicillin, a penicillic acid variant, is one of the most common pharmacological culprits mediating hypersensitivity reactions (8).

True hypersensitivity reactions to therapeutic agents should not be confused with other adverse drug reactions that result from dose-dependent drug toxicity, secondary effects of a drug, or drug-drug interactions. Because non-immunologically based adverse reactions are also often described as "acute" or "delayed," this may add to the confusion. In this study, we designate all reactions occurring within 24 h as acute infusion reactions, and those that occur past 48 h as delayed infusion reactions. This definition of acute and delayed infusion reactions was designed to conservatively include all types of possible adverse reactions to infliximab. To better reflect the mechanistic spectrum of these reactions, we have eliminated the term "hypersensitivity." For future analyses, we propose the following nomenclature be adopted for uniformity (Fig. 4). Acute infusion reactions can be further subdivided into immune- and nonimmune-mediated reactions. Acute immune-mediated

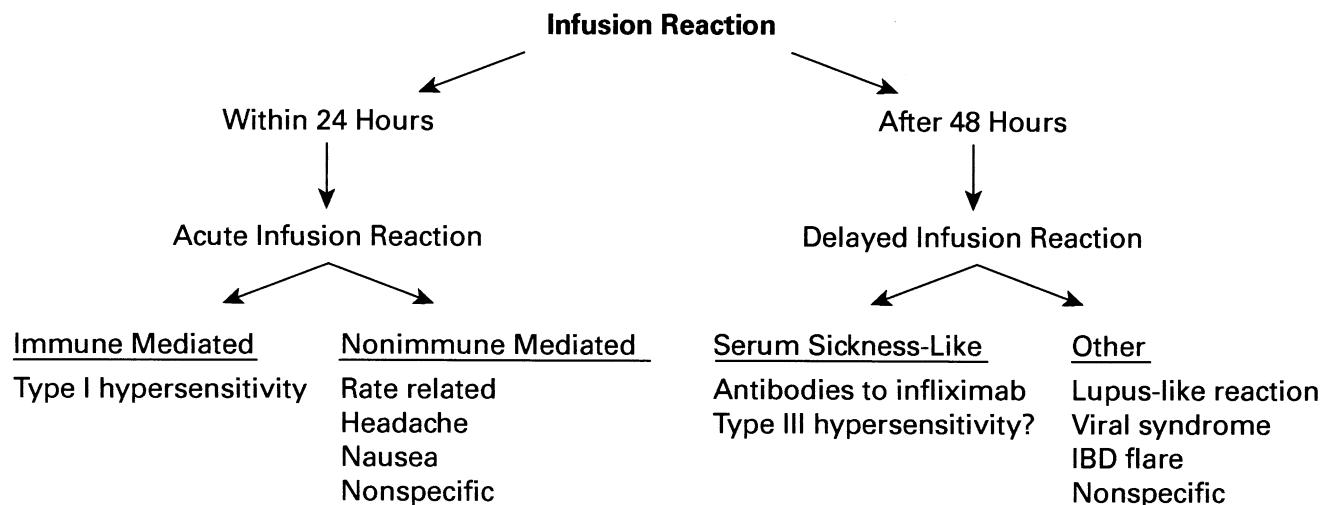


Figure 4. Suggested nomenclature for infusion reactions (IBD = inflammatory bowel disease).

events by definition are type I hypersensitivity reactions. Among the acute nonimmune-mediated infusion reactions are the common rate-related phenomena, as well as a constellation of mild, nonspecific symptoms such as headache and nausea.

Few acute infliximab infusion reactions are likely to be true type I hypersensitivity reactions. Although no rigorous attempts have been made to subdivide immunological from nonimmunological reactions in this and other studies, there are a few criteria that may serve as a point of departure for more detailed analyses. The occurrence of urticaria likely represents a type I hypersensitivity reaction. Of the 16 patients in this study who experienced infusion reactions, two developed urticaria. One of the two patients was classified as having a severe reaction and the other a moderate infusion reaction. Both were successfully retreated, suggesting that the presence of a true immunological reaction does not preclude future therapy with appropriate prophylactic measures.

Our results suggest that the majority of acute reactions are not immunologically mediated type I hypersensitivity events. In 11 patients who developed 14 acute infusion reactions, serum tryptase levels were evaluated 20 min after onset of the reaction. In all patients, tryptase levels were within the normal range. Tryptase is a mast cell enzyme that is released upon degranulation during a type I reaction and is detected in the serum shortly after a reaction. Although dyspnea was a clinical feature associated with severe infusion reactions, frank wheezing on examination was not noted. Again, the absence of bronchospasm suggests that these phenomena are not IgE mediated.

Acute infusion reactions that occur during the first infliximab infusion are, by definition, not immunologically mediated, as type I hypersensitivity reactions require prior antigen exposure. In this series, two of 16 patients reacted during or after the first infusion. One patient had a mild reaction, completed the infusion, and has been successfully

retreated. The second patient developed arthralgias 1 wk after the infusion and therefore was classified as having a delayed reaction. This patient was successfully retreated without prophylactic measures, suggesting that the initial event may have been unrelated to infliximab.

Therefore, the incidence of true hypersensitivity reactions is most likely far less than the published incidence when considering the broadness of the definition for infusion reactions. In addition, the incidence of immune- and non-immune-mediated reactions to infliximab is low when compared with that of other therapeutic agents. For example, 10% of hospitalized patients report hypersensitivity reactions to penicillin (the prevalence of penicillin hypersensitivity in the general population is unknown). Lupus-like features, including hypersensitivity vasculitis, have been reported in 15–30% of patients taking procainamide. Vancomycin has been reported to cause drug fever, skin rash, or “red man’s syndrome” in 50–90% of patients (8).

The nomenclature associated with delayed infusion reactions to infliximab also has caused confusion. These have been called “delayed hypersensitivity reactions,” which by standard immunological criteria (type IV reactions), they are not. Delayed reactions have been more appropriately referred to as “serum sickness-like” reactions to reflect their time course and the occurrence of a clinical syndrome in the absence of standard biochemical evidence of serum sickness (type III reactions). However, these reactions, if properly identified, likely represent true immunological phenomena. In the original description, their occurrence in every case was associated with the presence of antibodies to infliximab. It is possible that delayed infusion reactions are mild forms of true type III hypersensitivity events and that decreased serum complement and circulating immune complexes are not detected by standard assays. A problem in classification, as illustrated in this study, is that symptoms can often have other causes. Therefore, we propose the use of the term “delayed immune-mediated infusion reaction” if the clinical

syndrome fits the established definition of the described “serum sickness-like” reactions (Fig. 4).

The presence of antibodies to infliximab may be useful in a research setting to classify this type of reaction, but the clinical significance of antibody development is unknown. There are other syndromes to consider under this clinical definition, including lupus-like reactions associated with antidouble strand DNA antibodies, viral infections, and extraintestinal manifestations of CD (Fig. 4). It is important to emphasize that the term “delayed hypersensitivity reaction” is inappropriate to describe reactions to infliximab, as delayed hypersensitivity denotes a well-defined immunological process (type IV reaction).

In the infliximab clinical trials database containing safety data on both open-label and randomized controlled clinical trials in patients with CD and RA, 771 patients received a total of 4797 infliximab infusions, and 192 patients received a total of 2121 placebo infusions. Acute infusion reactions developed in 5.3% of infliximab infusions, affecting 17% of patients, as compared with 2.1% of placebo infusions, affecting 7% of patients (5). Approximately 4% of acute infliximab infusion reactions were accompanied by nonspecific signs and symptoms such as headache, nausea, fevers, or chills; approximately 1% were accompanied by pruritus or urticaria; approximately 1% were accompanied by cardiopulmonary reactions consisting primarily of chest pain, hypotension, hypertension, or dyspnea; and approximately 0.1% were accompanied by combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Reactions considered serious occurred in about 0.5% of acute infusion reactions. In the majority of these acute infusion reactions, rapid resolution of signs and symptoms occurred after infusion rate adjustments and treatment with acetaminophen, antihistamines, steroids, and/or epinephrine. Less than 2% of infliximab-treated patients had infliximab therapy discontinued because of infusion reactions (5).

In a separate clinical trial of infliximab, delayed infusion reactions were reported in 10 of 40 (25%) patients who were readministered infliximab after a 2- to 4-yr interval without infliximab treatment. Symptoms, generally consisting of myalgia and/or arthralgia with fever and/or rash, developed 3–12 days after reinfusion. However, nine of the 10 (90%) patients received an experimental liquid formulation of infliximab that is no longer used. All 10 patients improved with medical management. A recent study reported the occurrence of delayed infusion reactions in eight of 86 adult and pediatric patients undergoing episodic retreatment with infliximab. The notable risk factor for the development of these reactions was a second infusion 20 wk or more from the first infusion (9). We report a lower incidence of delayed infusion reactions. Of the three patients who developed delayed reactions, only one had an extended interval of 2 yr between previous infusions. Similar to their findings, in patients who developed a reaction after a hiatus of 20 wk or more between infusions (five of 39 patients), none had received an induction regimen of infliximab—all were

treated episodically. Therefore, an induction regimen of infliximab upon initiation of therapy may be protective against the development of infusion reactions with subsequent infusions.

The ACCENT I trial demonstrated benefit of maintenance infliximab therapy in patients with active CD (10). In the safety analysis of 573 patients, acute infusion reactions occurred in 23% of patients (6% of 993 infusions) who received 5 mg/kg of infliximab every 8 wk (group II), 19% of patients (4% of 1033 infusions) who received 10 mg/kg of infliximab every 8 wk (after three induction doses of 5 mg/kg at weeks 0, 2, 6) (group III), and 9% of patients (3% of 837 infusions) who received a single 5 mg/kg dose and then were randomized to receive placebo (group I). Twelve patients discontinued the study agent because of an infusion reaction, all in groups II and III. Delayed infusion reactions were reported in 2% of patients in group I, 3% of patients in group II, and 3% of patients in group 3. Therefore, the overall occurrence of acute and delayed infusion reactions is similar in ACCENT I to that reported in our cohort of patients.

Consistent with previous studies, in this analysis, 51.7% (15 of 29) of reactions occurred with the first three infusions. Eight of these reactions occurred with the second infusion alone. We did not routinely medicate any patients with diphenhydramine and/or acetaminophen before an infusion unless they had a history of a reaction. It is possible that the incidence of reactions may be further reduced by routine premedication. However, as the incidence of reactions is low, and they are easily managed, premedication is not necessary in the majority of patients. Furthermore, there may be reasons not to give diphenhydramine, particularly if a patient wishes to drive after the infusion.

The current data from clinical trials, commercial sales of infliximab in the United States, and the Division of Clinical Immunology Infusion Center at Mount Sinai Medical Center experience consistently demonstrate that the incidence of acute and delayed infusion reactions to infliximab is low and can be successfully managed in an office setting.

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