Infusion-Related Reactions to Infliximab in Patients with Rheumatoid Arthritis in a Clinical Practice Setting: Relationship to Dose, Antihistamine Pretreatment, and Infusion Number

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ABSTRACT. ***Objective.*** We describe infusion-related reactions to infliximab (during infusion or within 1 hour postinfusion) in patients with active rheumatoid arthritis (RA) treated in a quaternary care center.

Methods. We followed 113 patients for a mean of 60.6 ± 28.9 weeks, obtaining 10.5 ± 4.9 infusions per patient.

Results. We observed 1183 infusions resulting in 104 infusion reactions (8.8%). All reactions resolved within several hours following cessation of the infusion and none was serious enough to warrant hospitalization. Reactions included allergic reactions (pruritis, urticaria) in 4.2% of infusions, cardiopulmonary (hypotension, hypertension, tachycardia) in 3.0%, and miscellaneous reactions (headache, nausea, vomiting) in 2.0%. Reactions occurred in 8.0% of 3 mg/kg infusions and in 10.3% of 5 mg/kg infusions. Reactions occurred in 13.2% of infusions that involved antihistamine pretreatment compared to only 7.5% of infusions that involved no pretreatment. At both infliximab doses, there was a similar frequency of infusion reactions in patients pretreated due to a previous infusion (12.6%) compared to those pretreated strictly based on infusion number (14.7%). A number of the reactions involving antihistamine pretreatment may be explained by known side effects of diphenhydramine, including headache, dizziness, nausea, and palpitations.

Conclusion. Infusion-related reactions to infliximab were infrequent, rarely severe, and easily manageable. The frequency of reactions was equivalent in patients treated with 3 mg/kg compared to 5 mg/kg. Reactions were significantly more frequent in infusions where patients were pretreated with the antihistamine diphenhydramine, compared to those not involving pretreatment. (J Rheumatol 2004;31:1912–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
TUMOR NECROSIS FACTOR
INFLIXIMAB
ADVERSE EVENTS

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that mediates the production of other inflammatory cytokines and plays a key role in the pathophysiology of rheumatoid arthritis (RA)[1,2]. TNF-α affects the recruitment of inflammatory cells into the joint, activates the cells, causes the release of proteolytic enzymes, and modulates the activity of a number of other proinflammatory cytokines[3-8].

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Infliximab (Remicade®; Centocor Inc., Malvern, PA, USA), a chimeric anti-TNF-α monoclonal antibody, is a potent antiinflammatory agent, which is representative of a new generation of biologics used in the treatment of RA.

Infliximab binds to TNF-α with high affinity, avidity, and specificity[9], and has been shown to lyse TNF-α-producing cells *in vitro* through complement-mediated, antibody-dependent cell-mediated cytotoxicity and apoptosis[10]. Infliximab is administered in combination with methotrexate (MTX) to minimize production of human antichimeric antibodies. Clinical trial data have established that infliximab in combination with MTX results in significantly better response [American College of Rheumatology 20% response (ACR20) and ACR50], as well as a marked reduction in radiological progression and disability, in patients with RA not responding adequately to MTX alone[11].

The most common side effect of infliximab therapy involves infusion reactions that occur during infusion, or

within 1–2 hours postinfusion[11]. Common reactions include fever, chills, headache, pruritis, urticaria, and cardiopulmonary reactions. Results compiled from clinical trials demonstrate that 17% of 771 infliximab-treated patients experienced infusion reactions, compared to 7% in the placebo-treated group. Serious reactions were reported in 0.5% of patients, and only 1.9% of patients discontinued infliximab treatment because of infusion reactions. All patients recovered with treatment and/or discontinuation of infusion[11].

To date, no group has described in detail the characteristics of infusion reactions to infliximab, post-approval, in a clinical care setting. We describe a prospective, open-label study of 1183 infliximab infusions in 113 patients treated within a special access program of Health Canada, sponsored by Schering-Plough Inc., Canada. Patients were treated in a quaternary care university hospital setting that serves as a referral base for patients with long-standing, intractable RA. In addition to determining the frequency and types of infusion reactions experienced by patients treated with infliximab, we examined the relationship between these reactions and infliximab dose, week of infusion, and the influence of pretreatment with the antihistamine diphenhydramine.

MATERIALS AND METHODS

Subjects. Patients 18–75 years of age with a diagnosis of RA according to the 1987 ACR criteria were eligible for this study. All patients had active disease, despite MTX treatment, and had failed at least 3 disease modifying antirheumatic drugs (DMARD). Patients must have had no previous exposure to biologically-based therapies. Patients were considered to have active disease if they had more than 6 tender and 6 swollen joints in addition to at least 2 of the following: morning stiffness ≥ 45 min, erythrocyte sedimentation rate (ESR) > 28 mm/h, and C-reactive protein (CRP) > 2 mg/dl. Exemptions were allowed for patients with an ESR < 28 mm/h who fulfilled all other criteria. Patients must also have been receiving oral or parenteral MTX treatment for at least 3 months, without discontinuation in treatment of more than 2 weeks during this period. The MTX dose had to be stable at ≥ 12.5 mg/week for at least 4 weeks prior to screening. All other DMARD used in combination with MTX were discontinued at least one month prior to the initiation of infliximab therapy. Concurrent treatment with stable regimens of corticosteroids (≤ 10 mg/day) and/or nonsteroidal antiinflammatory drugs was permitted.

Exclusion criteria included current signs and symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral disease. Patients were also excluded if they had a history of lymphoproliferative disease, including lymphoma, or signs suggestive of such a disease, such as lymphadenopathy. Patients were also required to be free of any known malignant disease and were screened for tuberculosis prior to study initiation. The study was approved by the Mount Sinai Hospital Research Ethics Board. An informed written consent was required prior to study entry.

Dosing. Patients were infused with 3 or 5 mg/kg infliximab over a 2 h period at an average infusion rate of 125 ml/h. Patients were given an initial dose of 3 mg/kg at 0, 2, and 6 weeks. After week 6, all infusions were carried out at 8 week intervals throughout the duration of treatment. At 14 weeks, patients were able to have their dose increased to 5 mg/kg on clinical grounds, without specifically defined criteria.

Monitoring. Patients were monitored by a nurse throughout the duration of treatment and for 60 min postinfusion. Vital signs, including blood pressure, heart rate, and temperature, were monitored every 15 min during first half-hour and every 30 minutes thereafter, during this period.

Infusion reactions. Infusion reactions were defined as adverse events occurring during the treatment or within 1–2 h after infusion. Infusion-related reactions were categorized as (a) allergic, including pruritis, urticaria, and/or facial or generalized swelling, (b) cardiopulmonary, comprising hypotension (decrease in systolic pressure > 20 mm Hg), hypertension (increase in systolic pressure > 20 mm Hg, tachycardia (increase in heart rate > 20 beats/min), and/or shortness of breath, and (c) miscellaneous, including headache, nausea, and/or vomiting.

Pretreatment. When applicable (see below), pretreatment with antihistamine diphenhydramine was carried out 30 min prior to infusion. Diphenhydramine was administered intravenously in doses of 25 or 50 mg. The vast majority of pretreatment doses were 25 mg (> 95%). Only in rare cases of patients > 250 lb were doses of 50 mg used. Previous experience in our center indicated that infusion reactions in patients appeared to occur more frequently at weeks 6 (infusion 3) and 14 (infusion 4) of the treatment protocol (Figure 5). On this account, for some infusions (n = 75, 6.3%), patients (n = 42, 37%) were treated prophylactically with diphenhydramine at weeks 6 and/or 14, in an attempt to reduce the frequency of the infusion-related reactions despite no prior reaction. As well, prior to some infusions (n = 190, 16%), patients (n = 66, 58%) were pretreated with diphenhydramine as a consequence of a previous infusion reaction to infliximab. Isolated reactions, such as headache or nausea, without additional symptoms suggestive of an infusion-related reaction, were deemed to be potentially related to diphenhydramine pretreatment, and as such, were removed from all subsequent analyses where diphenhydramine was used.

Resolution of reactions. When an infusion-related reaction to infliximab occurred, treatment was immediately halted and the intravenous (IV) flushed with saline. Vital signs were recorded, and the reaction either resolved spontaneously, or patients were treated with diphenhydramine (25 or 50 mg as described above), and/or IV corticosteroids (methylprednisolone sodium succinate, 40 mg) and, rarely, oxygen. Diphenhydramine dosing was consistent for a single patient in terms of pretreatment versus treatment of an infusion reaction (i.e., if a patient was given 25 mg as a pretreatment, the same dose was used to treat an infusion-related reaction). In most cases, infusions were restarted slowly following resolution of reactions. All reactions resolved within several hours following the infusion and none was serious enough to warrant hospitalization.

Statistical analysis. Demographic data are presented as means ± standard deviations. Differences between groups were analyzed by means of a chi-square test. $P < 0.05$ was taken as statistically significant.

RESULTS

Demographics. One hundred thirteen patients with RA, according to ACR criteria, received a total of 1183 infusions of IV infliximab in doses of 3 or 5 mg/kg. Patients received a mean of 10.5 ± 4.9 infusions over a period of 60.6 ± 28.9 weeks. Demographic characteristics of the patient population were as follows: mean age of 45.7 ± 12.6 years, 87% female, disease duration of 13.6 ± 9.9 years, and 4.4 ± 2.3 DMARD failures. All patients were receiving MTX (mean dose 16.2 ± 8.7 mg/week), while 59% of patients were receiving prednisone (mean dose 6.7 ± 4.1 mg/day). At baseline, patients had an average of 21.3 ± 13.0 tender joints and 10.8 ± 4.8 swollen joints.

Frequency of infusion-related reactions to infliximab. We observed 104 infusion-related reactions out of 1183 infusions performed (8.8%). Allergic reactions occurred in 3.8%

(n = 45) of all infusions, and cardiopulmonary reactions occurred in 3.0% (n = 35) of infusions, while miscellaneous reactions occurred in 2.0% (n = 24) of all infusions. The most common infusion reaction was urticaria (13% of reactions), followed by headache (9%), hypotension (9%), pruritis (7%), and hypertension (6%). While an infusion-related reaction to infliximab occurred during only 8.8% of infusions, 60 of 113 patients (53%) experienced at least one reaction during the course of their treatment. Twenty-three percent (n = 26) of patients experienced 2 or more reactions, 8% (n = 9) experienced 3 or more reactions, and 4% (n = 58) 4 or more reactions, respectively (Figure 1). Only 2.7% of patients (n = 3) discontinued therapy because of infusion reactions. If an infusion-related reaction is defined as described by Maini, *et al*[11], i.e., only those involving allergic and/or cardiopulmonary symptoms, 47% (n = 53) of patients experienced at least one infusion reaction. As described, those adverse events reported to be related to diphenhydramine treatment (1.1%, n = 13) were eliminated from the analyses when they presented in isolation, in the absence of other events known to be potentially associated with infliximab treatment. There was no relationship between infusion reaction type, severity, or number and MTX or prednisone dose.

Frequency of infusion reactions and time course of treatment. We next examined the relationship between infusion-related reactions to infliximab and the course of an individual's treatment (Figure 2). In agreement with previous data[11], our results showed that infusion reactions were most common during infusion 3 at week 6 (23%, n = 24) and during infusion 4 at week 14 (19%, n = 20), accounting for 42% of all infusion reactions. Of note, allergic and cardiopulmonary reactions were the 2 most frequent categories of infusion-related reactions (77% of all infusion reactions).

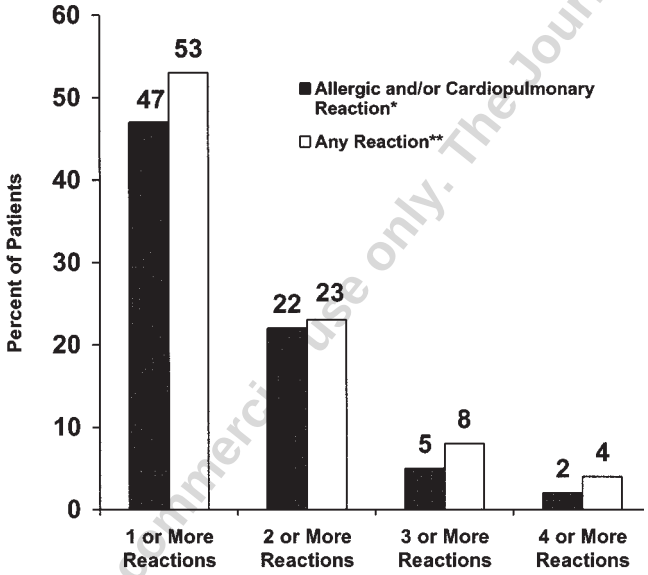

Figure 1. Percentage of patients experiencing infusion-related reactions to infliximab. *Previous definitions of infusion-related reactions included only those of an allergic or cardiopulmonary nature[12]. **Any reaction includes allergic reactions, cardiopulmonary reactions, and those of a miscellaneous (nonspecific) nature, including headache, nausea, and vomiting.

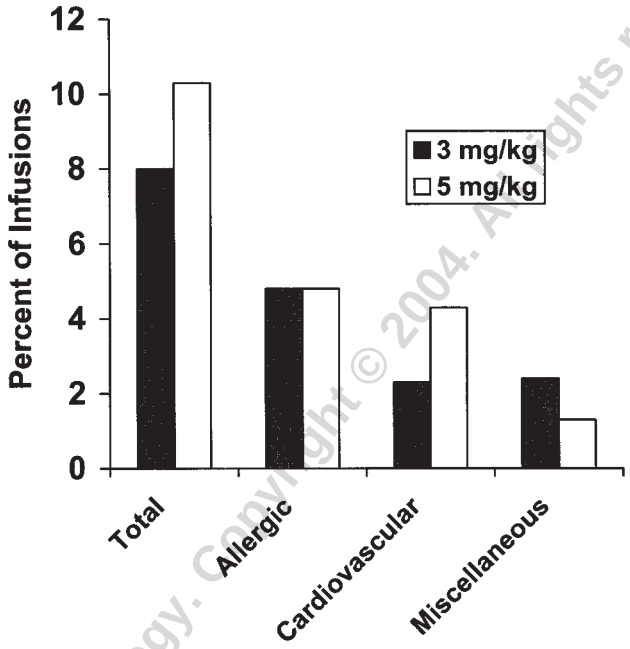

Figure 2. Relationship between infliximab dose and frequency of reactions expressed as percentage of infusions. The difference between frequency of reactions in patients treated with 3 mg/kg versus 5 mg/kg infliximab, p > 0.05.

Relationship between infliximab dose and frequency of infusion reactions. We also compared the frequency of infusion-related reactions with the 3 and 5 mg/kg dose of infliximab (Figure 3). Of the 1183 infusions studied, 3 mg/kg was given in 66% of infusions (n = 786), while 5 mg/kg was given in 34% of infusions (n = 397). There was no significant difference in the frequency of infusion reactions to infliximab between the 3 mg/kg dose (n = 63, 8.0% of infusions) and the 5 mg/kg dose (n = 41, 10.3% of infusions; p > 0.05). Also, there were no statistically significant differences between the types of infusion reactions experienced by patients receiving the 2 different infliximab doses (p > 0.05). However, the 5 mg/kg dose was given later in the treatment course, when fewer reactions are expected; thus based on this data, we can only conclude that no increase in infusion-related reactions was seen when doses were increased from 3 mg/kg to 5 mg/kg.

To address the issue of dose effect on infusion reactions, we examined infusion-related reactions in patients treated with 3 mg/kg versus 5 mg/kg infusions post-week 14 (infusion 4), since the majority of reactions occurred in the first 4 infusions (n = 54, 52%) with the 3 mg/kg dose, while the majority of 5 mg/kg infusions (n = 375, 95%) were administered after 14 weeks. At infusions 5 and thereafter, there

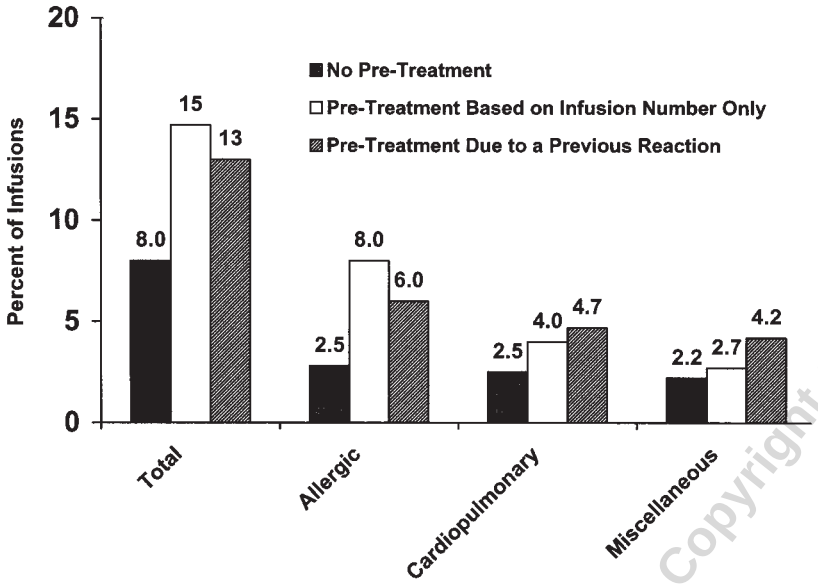

Figure 3. Effect of diphenhydramine prophylaxis on frequency and type of infusion-related reactions to infliximab (expressed as percentage of infusions). Difference between no pretreatment and pretreatment with diphenhydramine, *chi-square $p < 0.05$.

were 338 infusions administered with 3 mg/kg, resulting in 21 infusion-related reactions (6.2%), and 375 infusions administered with 5 mg/kg, resulting in 29 infusion-related reactions (7.7%). On the basis of these findings, we were able to conclude there was no significant difference between the probability of infusion reactions based on the dose administered ($p > 0.05$), after 14 weeks.

Influence of prophylactic antihistamine pretreatment on frequency of infusion reactions. Twenty-two percent (n = 265) of infusions in this study involved pretreatment with diphenhydramine. In 16% of infusions (n = 190), pretreatment was given because of the patient's previous infusion reaction. In 6.3% of infusions (n = 75) pretreatment was given prophylactically at infusions number 3 and 4, based only on the increased likelihood of reactions during these infusions. Our results showed that infusion reactions occurred in 13.2% of infusions (n = 35) in patients prophylactically pretreated with diphenhydramine, regardless of the basis for the pretreatment, compared to 7.5% of infusions (n = 69) in patients who were not pretreated ($p < 0.05$; Figure 4). There was a similar frequency of infusion-related reactions in patients pretreated due to a previous reaction (12.6%, n = 24) compared to those pretreated strictly based on infusion number (14.7%, n = 11). There was no significant difference in the rates of reactions in these groups of patients treated with 3 mg/kg infliximab compared to those receiving 5 mg/kg (Table 1).

To determine whether prophylactic pretreatment with diphenhydramine reduced infusion reactions at infusions 3 and 4 in patients without previous reactions, we compared the outcomes of patients who were or were not pretreated with diphenhydramine specifically at infusions 3 and 4. The results (Table 2) revealed that reactions to infliximab occurred in 14.3% (15/105) of infusions in patients who were not pretreated at these 2 infusions, compared to 14.7% (11/75) of those patients pretreated strictly on the basis of infusion number. In contrast, in patients pretreated at these weeks because of a previous reaction, infusion reactions occurred in 22.5% (9/40) of infusions. Patients who experienced an infusion reaction were then given prophylaxis at all subsequent infusions.

DISCUSSION

Our study represents the first report detailing the frequency and characteristics of infusion-related reactions to infliximab in a prospective, open-label study of infliximab in a clinical care setting. Patients in this study had severe, longstanding, intractable RA evidenced by their high baseline disease activity, long disease duration, and substantial number of prior DMARD.

Our findings suggest that infusion reactions to infliximab are frequent, but rarely severe, and are easily manageable. Adverse events during infliximab infusion or within 1–2 h after infusion occurred in 8.8% of all infusions. All infusion reactions resolved spontaneously, usually within 30 min after discontinuation of treatment, with or without additional treatment with diphenhydramine, methylprednisolone sodium succinate (20–40 mg), and/or, rarely, oxygen. The rare reaction involving chest tightness, shortness of breath, and flushing resolved in minutes after initiation of IV diphenhydramine and/or methylprednisolone sodium succinate. All reactions resolved within several hours after cessa-

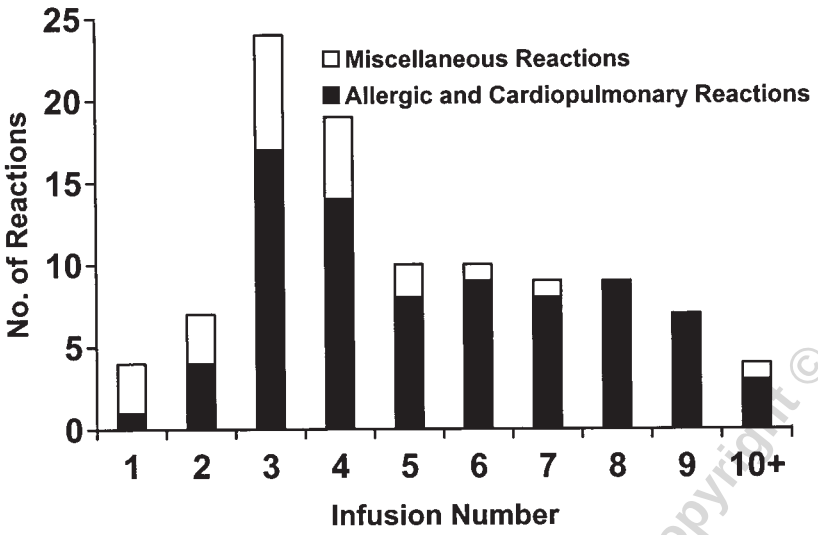

Figure 4. Relationship between infusion number and frequency of infusion reactions.

tion of infusion and none was serious enough to warrant hospitalization. While the overall percentage of infusions involving a reaction was relatively low, a significant proportion of patients (53%) experienced at least one reaction. This is considerably higher than the 16–20% of patients reported by Maini, *et al*[11]. This discrepancy is likely related to the broader definition of infusion reaction used in our study. It is worth noting that the proportion of patients who experienced at least one adverse reaction in our study is in accord with that seen in most clinical therapeutic studies. As noted, the overwhelming majority of adverse events experienced by patients in this study were relatively mild (itching,

Table 1. Effect of diphenhydramine pretreatment and infliximab dose on the frequency of infusion reactions (percentage of infusions).

	3 mg/kg		5 mg/kg	
	No Pretreatment, n = 644	Pretreatment, n = 142	No Pretreatment, n = 274	Pretreatment, n = 123
No. of reactions (%)	44 (6.8)	19 (14.4)	25 (9.1)	16 (13.0)
Allergic	18 (2.8)	8 (5.6)	8 (2.9)	11 (8.9)
Cardiopulmonary	10 (1.6)	8 (5.6)	13 (4.8)	4 (3.3)
Miscellaneous	16 (2.5)	3 (2.1)	4 (1.5)	1 (0.8)
No reaction	600 (93.2)	123 (86.6)	249 (90.9)	104 (84.6)
Total	63/786 (8.0)		41/397 (10.3)	

Table 2. Effect of diphenhydramine on the frequency and characteristics of infusion reactions at infusions 3 and 4.

	No Pretreatment	Prophylactic Treatment	
		Due to Previous Reaction	Based on Infusion Number
No. of infusions	105	40	75
No. of reactions (%)	15 (14.3)	9 (22.5)	11 (14.7)
Allergic	6 (5.7)	6 (15)	6 (8.0)
Cardiopulmonary	4 (3.8)	2 (5.0)	3 (4.0)
Miscellaneous	5 (4.8)	1 (2.5)	2 (2.7)
No reaction	90 (85.7)	25 (62.5)	57 (76)

pruritis, headache, etc.), and only 2.7% of patients discontinued therapy due to infusion-related reactions. We did not assess any potential correlation between the frequency of infusion reactions and clinical response.

The incidence of infusion reactions to infliximab was similar at the 3 mg/kg dose compared to 5 mg/kg dose. This suggests that escalating the dose of infliximab from 3 mg/kg to 5 mg/kg does not increase the frequency of infusion reactions. This is noteworthy, as a significant proportion of patients with severe RA do not respond adequately to 3 mg/kg infliximab and require dose escalation.

Previous data (Centocor Inc., personal communication; 2002) as well as our own preliminary findings established that infusion reactions to infliximab appear to be most common at weeks 6 (infusion 3) and 14 (infusion 4) of the treatment regimen. Our study confirmed these findings by demonstrating that 43% of all reactions occurred at these infusions. On this account, we attempted to reduce infusion-related reactions at these 2 timepoints. However, our results indicated that pretreatment with diphenhydramine failed to reduce the frequency of infusion reactions in patients without prior reactions at infusions 3 and 4. Whether prophylaxis in patients with prior reactions reduced the frequency of subsequent infusion-related reactions remains unclear, since all patients were given prophylaxis after an initial reaction. Of importance, a significant number of the reactions in those patients pretreated with diphenhydramine included pruritis, flushing, hypotension, and headache, which may be explained by the known side effects of the antihistamine. These data suggest that other forms of prophylaxis, such as steroids or long-acting antihistamines, may be more beneficial than diphenhydramine. Our data do not support the prophylactic use of diphenhydramine at infusions 3 and 4 unless a prior reaction has occurred.

In contrast to data reported by Maini, *et al*[11], we did not find that the frequency of infusion reactions was highest at the initial infusion. We did note that the type of infusion reaction was related to the treatment course, with allergic and cardiopulmonary reactions occurring later in the treatment regimen than miscellaneous reactions.

In summary, infusion-related reactions to infliximab treatment were frequent, but almost always mild, with few patients discontinuing treatment on the basis of the reactions. Escalated infliximab dosing did not increase the frequency of infusion reactions, while antihistamine prophylaxis with diphenhydramine failed to reduce the increased frequency of infusion reactions at the 3rd and 4th infusion. Indeed, prophylactic treatment appeared to increase the frequency of adverse events. These data suggest that prophylactic therapy with the antihistamine diphenhydramine may be indicated only for patients experiencing a prior infusion-related reaction, while other modes of pretreatment such as long-acting antihistamines should be evaluated. Taken together, our data suggest that infliximab is well tolerated in patients with severe, long-standing, DMARD-resistant RA.

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