

A one-hour infusion of infliximab during maintenance therapy is safe and well tolerated: a prospective cohort study

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SUMMARY

Background

Infliximab is a chimeric monoclonal antibody to tumour necrosis factor alpha (TNF α) with efficacy in inducing and maintaining remission of inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis and psoriasis. Infliximab is generally administered over 2 h with a further 1-h postinfusion observation. This time interval has substantial impact on healthcare resources and is costly in terms of patient's time away from work.

Aim

To examine the safety and tolerability of a 1-h, relative to a 2-h maintenance of infusion of infliximab, and to determine the effect of corticosteroid premedication and concurrent immunosuppressor use on infusion reaction rates.

Method

A prospective cohort study with variable follow-up duration of 2165 consecutive infliximab infusions in 415 patients during 2009 was conducted. Diagnosis, infusion episode number, infusion rate, premedication, concurrent immunosuppressor therapy, the nature and the outcome of infusion reactions were examined.

Results

The majority of infusions (74%) were for management of inflammatory bowel disease. Infusion reactions clustered within the first eight infusions with subsequent sporadic reactions. The infusion reaction incidence rate per 1000 person days in 274 1-h infusions from 54 patients and 1356 2-h infusions from 256 patients were 0.08 and 0.28 respectively ($P = 0.07$). Poisson regression model confirmed that the concurrent use of immunosuppressor therapy was associated with a lower infusion reaction rate, whereas corticosteroid premedication was not.

Conclusions

During maintenance therapy, infliximab infusion can be safely administered over 1 h in patients with no past history of significant infliximab infusion reaction. Corticosteroid premedication had no impact on the infusion reaction rates.

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INTRODUCTION

Tumour Necrosis Factor alpha (TNF α) is one of the key inflammatory cytokines that drives inflammatory bowel disease (IBD), psoriasis and rheumatoid arthritis (RA). Infliximab is a chimeric monoclonal antibody that binds to TNF α and thereby exerts its efficacy in inducing and maintaining remission of moderate to severe ulcerative colitis,¹ Crohn's disease,^{2–4} rheumatoid arthritis^{5, 6} and moderate to severe psoriasis.⁷

In 1999, Infliximab was first used in the treatment of Crohn's disease^{3, 8} and subsequently, following completion of the randomised controlled trials, approved for treatment of Crohn's disease in Canada in 2002. An outpatient infliximab infusion standard based upon the protocol used in clinical trials was instituted, whereby the infusion was given to the patient over a 2-h interval, with a further 1 h, on-site, postinfusion observation interval. At the time, no clinical research studies were conducted to determine optimal infusion rates and follow-up. This standard practice (2-h infusion + 1-h observation) has a substantial impact on limited healthcare resources.

Being a chimeric IgG molecule, one of the main concerns of infliximab at the time of infusion is an antibody-induced infusion reaction. Acute infusion reactions, characterised by rash, fever, hypotension, dyspnoea and chest pain, may occur within the first 2 h of infusion, and can be prevented and/or managed by premedication with acetaminophen, antihistamines or corticosteroids. Successful reinfusion of infliximab in the mild and moderate reaction group has been possible. Delayed hypersensitivity reaction was presented 24 h to 14 days after the infusion with symptoms including arthralgia, myalgia, urticarial rash and lethargy. Overall, the incidence of an acute infliximab infusion reaction is approximately 2.5–5.4% of infusions, with mild, moderate or severe reactions occurring in 1.3–3.1%, 1.1–1.2% and 0.1–1% of infusions respectively,^{9, 10} and long-term treatment has a good safety profile.¹¹

Methotrexate and thiopurines have been shown to have similar efficacy in preventing anti-infliximab antibody formation and improving the pharmacokinetics of infliximab.¹² A recent pilot study demonstrated a rise in anti-infliximab antibody level, a rise in CRP and a fall in infliximab concentration when thiopurine was stopped in patients on schedule maintenance infliximab infusion.¹³ In CD patients who are naïve to an immunosuppressor and infliximab, Colombel *et al.* demonstrated clinical superiority of combination therapy over monotherapy.¹⁴ All these studies argued in favour of combination

therapy. However, the use of combination therapy has been questioned due to rare reports of hepato-splenic T cell lymphoma (HSTCL) in young men. Currently, 28 cases of HSTCL have been reported in the literature in Crohn's disease, all of whom received a thiopurine, and 22/28 had concurrent infliximab initially.¹⁵

Multiple studies examined a shortened infliximab infusion protocol in adult IBD patients.^{16–20} In these studies, patients received 0.5–1.5-h infusion with no apparent increase in infusion reactions relative to a 2-h infusion. Moreover, whenever an infusion reaction occurred, this reaction was mild and patients were able to complete the infusion. Similar experience has been reported in patients with rheumatoid arthritis²¹ and paediatric IBD patients.²² The ability to extend these observations in our study by developing a 1-h infusion protocol with no postinfusion observational period has the opportunity to substantially reduce healthcare resource costs and improve quality of life for the patients.

This prospective cohort study, with follow-up duration of up to 1 year, examined the safety of a 1-h infliximab infusion without postinfusion monitoring when compared with the standard 2-h infusion in patients using infliximab for IBD and non-IBD indications. As a secondary objective, we examined the impact of concurrent immunosuppressor use and corticosteroid premedication on the rate of infusion reactions.

MATERIALS AND METHODS

Infliximab infusion protocols

In January 2009, a 1-h infliximab infusion protocol with no postinfusion observational period was introduced, and patients were prospectively recruited and individually assessed for eligibility to enter and then remain in the 1-h infliximab infusion protocol. All patients who received infliximab were naïve to infliximab at the time of their first induction dose. An infliximab infusion reaction was defined as an adverse event requiring either infusion rate adjustment or treatment with acetaminophen and/or diphenhydramine and/or corticosteroids. IBD patients received 5 mg/kg infliximab infusions, whereas non-IBD patients received 3 mg/kg infliximab infusions.

The criteria for entrance into the 1-h infliximab infusion protocol were: (i) no infliximab infusion-related adverse reaction (within 24 h postinfusion) during previous three 2-h infusions and, (ii) the last three 2-h infusions were at a constant dose (≤ 6 mg/kg) and frequency.

The criteria for remaining in the 1-h infliximab infusion protocol were: (i) if the infliximab infusion dose or frequency increased, the patient was required to have one uneventful 2-h infusion before reverting back to the 1-h infusion and, (ii) the last 1-h infusion must have been without any significant adverse event.

Patient selection

Twenty eight percent of eligible patients entered the 1-h infusion protocol, as the 1-h infusion required the above criteria to be met and patient consent. Eligible patients could enter the 1-h infusion protocol at various points during the 1-year study. Reasons for not entering the 1-h infusion protocol were equally allocated, and represented either failure to meet the above criteria or absence of patient consent.

All out-patient infliximab infusions at the Zeidler Ledcor Gastroenterology Health and Disease Center, Hys Centre and 124th Street Infusion Centre, Edmonton, Alberta, Canada from 2nd January 2009 to 31st December 2009 were reviewed. Data collected include baseline demographical, diagnosis, premedication (hydrocortisone 100–200 mg and/or diphenhydramine 50 mg intravenously immediately prior to the infliximab infusion), sequence number of the infliximab infusion, concurrent immunosuppressor therapy (azathioprine 2.5 mg/kg/day or mercaptopurine 1.25 mg/kg/day or methotrexate 15–25 mg weekly) and nature of infusion reaction.

Figure 1 outlines the infliximab infusion groups. Induction group; received 2 h infusions at infliximab induction dose number 1,2 and 3, corresponding to 0, 2 and 6 weeks, respectively, and maintenance dose number 4, 5 and 6, corresponding to q8 week infusions. Maintenance Group: consisting of Cohort A; received 2-h maintenance infliximab infusions from dose number 7 onwards; Cohort B; received 1-h maintenance infliximab infusions from dose number 7 onwards. Patients with infusion reactions were excluded from further analysis.

Infusion reactions were monitored and recorded by Registered Nurses trained in infliximab infusions and adverse reactions. Infusion reactions were defined as acute infusion reaction that occurred during or within 24 h of the infusion. Infliximab infusion reactions were treated with a protocol that included sequential slowing and/or stopping the infusion, followed by a cascading treatment algorithm with intravenous diphenhydramine (50 mg), followed by intravenous hydrocortisone (200 mg) and, if necessary, intravenous epinephrine.

The University of Alberta Health Research Ethics Board approved the study.

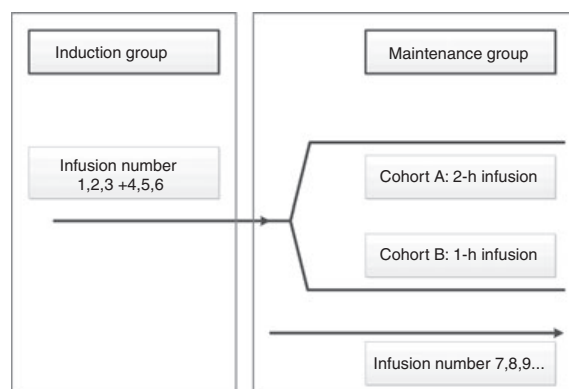


Figure 1 | Infliximab infusion groups. Induction group: received 2-h infusions at infliximab induction dose number 1, 2 and 3 and 2-h infusions at infliximab maintenance dose number 4, 5 and 6. Maintenance group: consisting of Cohort A; received 2-h maintenance infliximab infusions from dose number 7 onwards and Cohort B; received 1-h maintenance infliximab infusions from dose number 7 onwards.

Statistical analysis

The results were presented descriptively, expressed as the number of infusion reactions per 1000 person days followed up. The infusion reaction rate between Cohort A (2-h infusion) and Cohort B (1-h infusion) was examined using Poisson distribution. Poisson regression and Fischer's exact test were used to determine the effect of immunosuppressor, steroid premedication and diagnosis on infusion reaction rate.

RESULTS

A total of 2165 infusions were administered to 415 patients. The indication for infliximab infusion at the Zeidler Ledcor Gastroenterology Health and Disease Center was nearly exclusively IBD; whereas Hys Centre and 124th Street infusion centre were predominately rheumatological indications.

Table 1 summarises the number of infusions and patient characteristics per group. Overall, IBD and Crohn's disease (CD) represented the majority of infusions. Patients undergoing a 2-h maintenance infliximab infusion (Cohort A) had similar infusion reaction rate as a 1-h maintenance infliximab infusion (Cohort B) (0.28 vs. 0.08 infliximab infusion reactions per 1000 person days, $P = 0.07$ respectively) (Table 1). Moreover, differences in the infusion reaction rates were not statistically significant between a 2-h and a 1-h infusion protocol when stratified by IBD ($P = 0.22$) vs. non-IBD ($P = 0.58$). It is important to note that infliximab infusion reactions

Table 1 | Infliximab infusion group characteristics and infusion reaction rate

Infliximab infusion characteristics	Induction group	Maintenance group	
	2-h infusion	2-h infusion Cohort A	1-h infusion Cohort B
Number of infusions (<i>n</i>)	535	1356	274
Number of patients (<i>n</i>)	105	256	54
Proportion with reactions	22/535 (4.1%)	17/1356 (1.25%)	1/274 (0.36%)
Number of infusions (<i>n</i>)			
IBD (CD) (<i>n</i>)	447 (310)	971 (819)	197 (195)
Rheumatoid arthritis (<i>n</i>)	55	204	64
Ankylosing spondylitis (<i>n</i>)	27	157	15
Psoriasis (<i>n</i>)	6	31	0
Reaction rate per 1000 days	0.14	0.282	0.082*

* $P = 0.07$, 1-h infusion vs. 2-h infusion.

clustered around the first eight infusions and thereafter became sporadic (Figure 2).

Concomitant immunosuppressor (azathioprine 2.5 mg/kg/day or mercaptopurine 1.25 mg/kg/day or methotrexate 25 mg weekly) was used in 52.7% of IBD patients and 47.1% of non-IBD patients. This was associated with significantly lower infliximab infusion reaction rates in patients with IBD ($P = 0.002$), but not in non-IBD patients ($P = 0.42$) (Table 2). In contrast, the use of corticosteroid premedication was not associated with a difference in infliximab infusion reaction rates in patients with IBD ($P = 0.27$) (Table 3). Regardless of premedica-

tion, reaction rates were similar for the 1-h and 2-h infusions (Tables 2 and 3).

All of the acute infliximab infusion reactions were of mild to moderate severity, and they were successfully managed with diphenhydramine, and/or hydrocortisone and/or acetaminophen. The nature of infusion reactions that occurred in the maintenance group, Cohort A and B, 2-h and 1-h infusions, respectively, is summarised in Table 4.

The total direct cost for a single patient to remain in the infliximab infusion clinic for 1 h (including infrastructure and personnel but excluding drug) is \$CDN

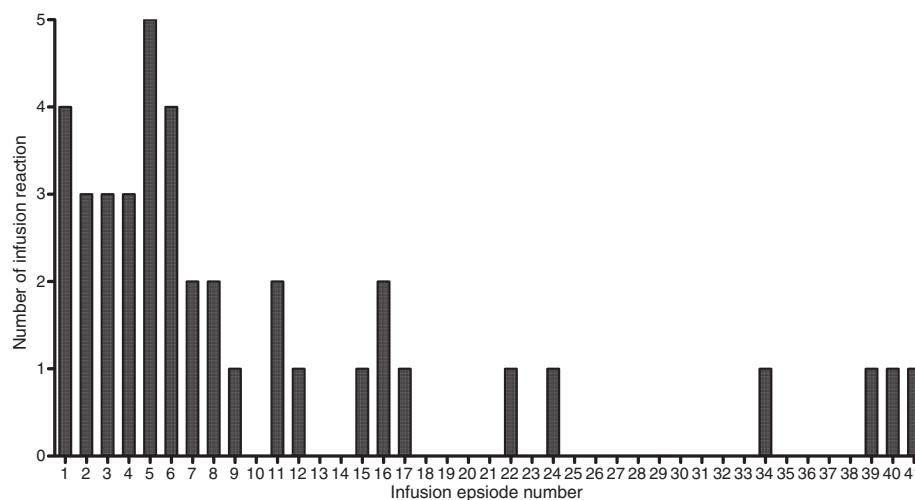


Figure 2 | Infliximab infusion reaction frequency over time. The infusion episode number reflects the number of infusions ever received by the patient. Infliximab infusion reactions clustered around the first eight infusions and thereafter became sporadic.

Table 2 | Infliximab infusion reaction rate relative to concomitant immunosuppressor therapy

Immunosuppressor use§	Yes				No‡			
Disease	IBD		Non-IBD		IBD		Non-IBD	
Infusion rate	2-h	1-h	2-h	1-h	2-h	1-h	2-h	1-h
Reaction rate per 1000 days	0.10	0.14*	0.30	0†	0.4	0†	0.38	0†
Proportion with reactions	2/86 (2.3%)	1/30 (3.3%)	2/28 (7.1%)	0	9/97 (9.3%)	0	4/41 (9.8%)	0

* $P = 0.56$, 1-h vs. 2-h infusion for IBD on immunomodulator therapy.

† $P = 1.00$, 1-h vs. 2-h infusion for non-IBD on immunomodulator therapy and both IBD and non-IBD not on immunomodulator therapy.

‡ $P = 0.01$ and 1.0 , reaction rate per 1000 days for patients not using immunomodulator therapy vs. using immunomodulator therapy for IBD, 2-h and 1-h infusion rate respectively.

§ Immunosuppressor therapy: azathioprine 2.5 mg/kg/day or mercaptopurine 1.25 mg/kg/day or methotrexate 15 to 25 mg weekly.

Table 3 | Infliximab infusion reaction rate relative to corticosteroid premedication

Corticosteroid premedication	Yes				No‡			
Disease	IBD		Non-IBD		IBD		Non-IBD	
Infusion rate	2-h	1-h	2-h	1-h	2-h	1-h	2-h	1-h
Reaction rate per 1000 days	0.31	0.12*	2.95	0†	0.16	0†	0.18	0†
Proportion with reactions	9/135 (6.7%)	1/36 (2.8%)	3/6 (50%)	0	2/47 (4.3%)	0	3/63 (4.8%)	0

* $P = 0.17$, 1-h vs. 2-h infusion for IBD on corticosteroid therapy.

† $P = 1.00$, 1-h vs. 2-h infusion for non-IBD on corticosteroid therapy and both IBD and non-IBD not on corticosteroid therapy.

‡ $P = 0.19$ and 1.0 , reaction rate per 1000 days for patients not using corticosteroid therapy vs. using corticosteroid therapy for IBD, 2-h and 1-h infusion rate respectively.

95.00, (\$US 92, € 69). Using this \$CDN 95.00 value, a 1-h infusion with no observation period would cost \$CDN 95.00, (\$US 92, € 69), in contrast, a 2-h infusion and 30 min observation period would cost \$CDN 237.50 (\$USD 230, € 172.50).

DISCUSSION

Infliximab infusion reactions are more common during the first few infusions and this may be due to hypersensitivity reaction to the chimeric protein and/or mediated by the development of anti-infliximab antibodies in the subsequent infusions. A strong relationship between antibody to infliximab formation and infusion reactions had been described,² and the concurrent use of an immunosuppressor is associated with a lower antibody to infliximab formation²³ as well as better efficacy in Crohn's Disease.¹² The protective effect of concurrent immunosuppressor use from an infliximab infusion reaction is not demonstrated in our study, and this may be due to the

small number of infusion reaction encountered, with only one reaction noted in the 1-h infusion cohort. Nevertheless, based on the literatures, it is our clinical practice to continue concomitant immunosuppressor use for long term to optimise the maintenance of clinical remission.

The role of intravenous hydrocortisone premedication in the prevention of antibody to infliximab formation and infusion reaction remains unclear. Farrell *et al.* demonstrated a lower infusion reaction rate when hydrocortisone was used, however, it did not prevent the formation of antibodies of infliximab.²³ Our study did not demonstrate a lower infusion reaction rate in hydrocortisone premedication cohort.

The observation that in infliximab, naïve patients and after six 2-h infusions switch to a 1-h infliximab maintenance infusion had a similar infusion reaction rate as a 2-h infliximab maintenance infusion is consistent with the current literatures.^{18, 19} One limitation with our study

Infusion number	Diagnosis	Corticosteroid premedication	Immunomodulator	Reaction
7	UC	Yes	0	Sore throat
	CD	Yes	0	Dermatological
8	UC	Yes	0	Cardiological
	RA	No	0	Cardiological
9	UC	Yes	0	Derm/cardiological
11	AS	No	0	GI/Dermatological
	AS	No	0	GI/Dermatological
12	CD	Yes	AZA	Dermatological
15	CD	Yes	0	Dermatological
16	CD	Yes	AZA	Cardiological
	CD	Yes	0	Oedema
17	CD	Yes	0	Cardiological
22	UC	Yes	0	Dermatological
24	AS	No	0	Dermatological
34	CD	Yes	0	Dermatological
39	RA	No	MTX	Cardiological
40	RA	No	MTX	GI
41	CD	Yes	MTX	Dermatological

Dermatological = localised and/or generalised skin rash; Cardiological = palpitations and/or chest tightness; GI, gastrointestinal (nausea and/or abdominal discomfort); Neurological = headache; Edema = localised and/or swelling; AZA, azathioprine; MTX, methotrexate.

An infliximab infusion reaction was defined as an adverse event requiring either infusion rate adjustment or treatment with acetaminophen and/or diphenhydramine and/or corticosteroids. All of the above infusion reactions were of mild to moderate severity.

Table 4 | Nature of infliximab infusion reactions that occurred after infusion number six

is the risk of selection bias, because not all eligible patients entered the 1-h infusion protocol. This is because, in this prospective study, to enter the 1-h infusion protocol, patients had to meet the criteria outlined in the methods as well as have consent of the patient, therefore 28% of the eligible patients received 1-h infusions.

In our environment, changing a patient from a 2-h infusion with a 30 min postinfusion observation period to a 1-h infusion with no postinfusion observation required would effect a cost saving of \$142.50 per patient or an annual cost saving of \$85 500 per 100 patients. As more eligible patients are switched to 1-h protocol, greater healthcare saving is possible, and it would allow for less intrusion into patients' life and work.

The strength of this prospective cohort study includes having experienced infusion nurses from three major Edmonton infliximab infusion centres collecting the data prospectively. These 2165 infusions represented over 90%

of all infliximab infusions that took place in Northern Alberta in 2009, making the result generalisable and reflective of real life clinical practice. Although the number of 1-h maintenance infliximab infusions was smaller than a 2-h maintenance infliximab infusion, there was no signal to suggest that a 1-h infusion was associated with a higher infusion reaction compared with a 2-h infusion.

In addition, corticosteroid premedication use was not associated with a lower infliximab infusion reaction rates, but concomitant immunosuppressor use was. This implies that corticosteroid premedication prior to infliximab infusion could be removed from standard protocols. Our study indicated that concurrent immunosuppressor use was associated with lower infusion reaction, which is consistent with current evidence, and we would suggest continuing concomitant immunosuppressor therapy for its long-term efficacy benefit. Finally, similar infusion reaction rates were noted when it was stratified by diagnoses – IBD (5 mg/kg) vs. non-IBD (3 mg/kg) in

both 2-h and 1-h infusion cohorts – implying the generalisability of the 1-h safety data.

This is the first prospective multicentre study of its size to examine the impact of 1-h infliximab infusions with no postinfusion monitoring in a cohort of patients receiving infliximab for either IBD or non-IBD indications. These results demonstrate that a 1-h infliximab infusion protocol during maintenance therapy is safe and well tolerated. Previous studies have included much smaller numbers of patients and fewer numbers of infusions.^{16–22} Indeed the current study has over double the number of total infusions relative to the next largest study. It is also the first study to systematically examine the safety of a 1-h infliximab infusion with no postobservational period.

In conclusion, this prospective cohort study shows that an infliximab infusion can be safely administered over

1 h in patients without postinfusion monitoring who have had no past history of significant infliximab infusion reactions. The use of concurrent immunosuppressor therapy was associated with lower infliximab infusion reaction rates, whereas corticosteroid premedication was not.

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