

Accelerated infliximab infusions are safe and well tolerated in patients with inflammatory bowel disease

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Introduction Infliximab is used widely for patients with inflammatory bowel disease (IBD). Drug manufacturers advise a 2-h infusion, with subsequent monitoring for a further 2-h period. Accelerated infusions, however, have been used in rheumatological patients with no significant increase in adverse events reported.

Objectives The primary endpoint was to assess the incidence of infusion reactions in IBD patients receiving infliximab via an accelerated infusion protocol. Secondary endpoints were to identify factors that may increase risk of an infusion reaction.

Methods This was a prospective study examining patients with IBD receiving infliximab with the accelerated infusion protocol (first four infusions over 2 h, with 2 h of monitoring, the next five infusions over 1 h, and subsequent infusions over 30 min).

Results Over 40 months, 1146 infusions were administered to 144 patients, 139 patients with Crohn's disease, two with ulcerative colitis, two with pouchitis and one with indeterminate colitis. Fourteen reactions during the 2-h infusion, with four delayed hypersensitivity reactions were observed, 13 during 1-h infusions with one delayed hypersensitivity reaction and 10 during a 30-min

infusion. Thirty-two reactions were mild, allowing completion of the infusion, but five were severe, resulting in cessation of infliximab. Sex, age, disease type (fistulising vs. inflammatory), administration (episodic vs. maintenance infusions), type of immunomodulator or number of infusions were not predictors of an infusion reaction.

Conclusion Rapid infusion of infliximab is safe and well tolerated, with no increase in infusion-related reactions. Where reactions do occur, they are usually mild, allowing completion of therapy. *Eur J Gastroenterol Hepatol* 21:71–75 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Since the publication of the ACCENT I [1] and II trials [2] the anti-TNF α monoclonal antibody, infliximab, has been used widely for patients with Crohn's disease. The ACT I and II trials have also demonstrated benefit for patients with moderate to severe ulcerative colitis, who have had an inadequate response to steroids and immunomodulators [3]. Infliximab is administered as an intravenous infusion, given over 2 h, with a subsequent 2-h monitoring period [4]. The use of infliximab in Crohn's disease has been shown to improve quality of life [5] and reduce number of hospital admissions and surgeries [6,7].

The Immune Mediated Inflammatory Diseases (IMID) centre in Leeds (UK) was established by collaboration between gastroenterologists and rheumatologists in 2004. It provides a facility for infusions where patients are assessed by a specialist nurse, to minimize delay to

initiation of infusion. Patients are, however, still required to attend hospital for a minimum of 4 h to receive the infusion and subsequent monitoring. This represents a significant inconvenience to those individuals who require regular infusions.

One possibility would be to reduce the time taken for infusion, but with reduced infusion times, there is a theoretical potential for an increased risk of adverse reactions. In an earlier study conducted in a large number of patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, an accelerated infusion protocol was followed, with the first four infusions given over 2 h (with a subsequent 2-h period of monitoring), the next five over 1 h (with 1 h of monitoring), and all subsequent infusions at 30 min (with 30 min of monitoring) [8]. No increase in adverse effects was observed in those individuals receiving the accelerated infusions compared with those who had received all their

Table 1 Leeds infusion schedule

Dose number	Infusion time	Midinfusion observations	Postinfusion observations
1–4	2 h	Pulse and BP every 30 min	Pulse and BP every 30 min for 2 h
5–9	1 h	Pulse and BP every 30 min	Pulse and BP every 30 min for 1 h
10+	30 min	Pulse and BP every 30 min	Pulse and BP every 30 min for 30 min

BP, blood pressure.

infliximab infusions over 2 h with a 2-h monitoring period. In 2004 we adapted this protocol (Table 1) for use in our patients with inflammatory bowel disease (IBD) who required infliximab. Although the rapid infusion schedule has been studied in a rheumatology population with no increase in adverse outcomes, there are fundamental differences between the two groups of patients. This is demonstrated by use of different immunomodulator therapies (methotrexate and leflunomide), less concomitant use of steroids and a smaller dose of infliximab (3 mg/kg in patients with rheumatoid arthritis), therefore it is important to reevaluate the safety data with a different patient group.

The primary aim of this study was to determine the frequency of reactions with the accelerated infusion protocol in our IBD patients. Secondary end points were to assess whether infusion reactions were related to the speed of infusion, to assess any relationship to concomitant immunomodulator therapy, to report the incidence of adverse events during the infusion or postinfusion monitoring period, and to assess if these reactions had any relationship to the time between infusions (administered regularly or on an episodic basis).

Materials and methods

This was a study of all IBD patients attending the IMID centre in Leeds for infliximab infusions between April 2004 and October 2007. Data were collected prospectively on patient demographics, use of concomitant steroids and immunomodulators, the dose of infliximab required, the total number of earlier infusions, and the number of infusions received previously over 2 h, 1 h and 30 min.

The infusion regimen is shown in Table 1. Neither hydrocortisone nor chlorpheniramine were administered routinely in our patients. Intravenous hydrocortisone of 200 mg was, however, given as standard therapy to any patients who were not on an immunomodulator, and who were taking less than 30 mg of prednisolone per day. In addition, if a patient experienced an adverse reaction during the infusion, hydrocortisone 100 mg and chlorpheniramine 10 mg were intravenously administered immediately and before all subsequent infusions in the future.

For every patient, the pulse and blood pressure were monitored every 30 min (Table 1). In addition, patients were asked if they were experiencing any adverse reactions (rash, breathlessness, wheeze, headache, dizziness, nausea or nonspecific symptoms of feeling unwell). Any adverse reactions were recorded, and these were classified as acute (during the infusion) or delayed (after completion of the infusion and during the postinfusion observation). A severe reaction involved a drop in systolic blood pressure to less than or equal to 80 mmHg, bronchospasm, or rash resulting in cessation of the infusion. A minor reaction was defined as a drop in systolic blood pressure below baseline, but remaining above 80 mmHg with or without nonspecific symptoms (e.g. headache or nausea), which required temporary cessation of the infusion.

The influence of numerous demographic data on the likelihood of an infusion reaction were explored in all patients using univariate analysis. Patients were dichotomized on the basis of whether or not they had ever experienced any infusion reaction, with both accelerated and conventional infusion schedules. Factors assessed included age, sex, disease subtype, concomitant use of immunomodulators, time interval between infusions (maintenance vs. episodic), infusion schedule (2 h, 1 h or 30 min), and number of earlier infusions. Independent risk factors were determined by performing multivariate logistic regression to control for all these variables. All statistical analyses were performed using SPSS for Windows version 14.0 (SPSS Inc., Chicago, Illinois, USA). Results are expressed as an odds ratio with 95% confidence interval.

Results

Patient characteristics are summarized in Table 2. Between April 2004 and October 2007, a total of 1146 infusions were administered (range 1–31 infusions per person) to a total of 144 patients (age range 14–91 years; 89 females, 55 males). The majority of patients had Crohn's disease (139, 95.8%). The reasons for requiring infliximab therapy were Crohn's disease nonresponsive to immunomodulatory therapy in 82 (56.9%), fistulising disease in 52 (36.1%), arthropathy associated with Crohn's in three (2.1%) and pyoderma gangrenosum with Crohn's disease in one (0.7%). In addition, two patients (1.4%) had pouchitis, two (1.4%) ulcerative colitis and one (0.7%) indeterminate colitis.

One hundred and seven patients (74.3%) were taking an immunomodulator at the time of their infliximab infusions, of whom 82 were on azathioprine (2–2.5 mg/kg/day) (56.9%), 20 on methotrexate (25 mg intramuscularly on a weekly basis for the first 4 weeks, then 15 mg weekly) (13.9%), four were receiving 6-mercaptopurine (1–1.5 mg/kg/day) (2.8%) and one mycophenolate mofetil

Table 2 Patient characteristics

Patient characteristics	Frequency	Number of patients (% of total)
Males : females	55 : 89	
Mean age (range in years)	39 (14–90)	
Crohn's alone	83 (57.6%)	
Crohn's and fistulae	52 (36.1%)	
Crohn's and arthropathy	3 (2.1%)	
Pouchitis	2 (1.4%)	
Ulcerative colitis	2 (1.4%)	
Crohn's and pyoderma gangrenosum	1 (0.7%)	
Indeterminate colitis	1 (0.7%)	
Immunomodulator:		
Azathioprine		82 (56.9)
Methotrexate		20 (13.9)
6-Mercaptopurine		4 (2.8)
Mycophenolate		1 (0.7)
Oral prednisolone >30 mg daily at some point		18 (12.5)
Intravenous hydrocortisone prior to infusion at some point		64 (44.4)
Currently on infliximab infusions		96 (66.7)
Reason for stopping in 48 patients		
Infusion reactions		10 (6.9)
Primary nonresponse		9 (6.3)
Secondary nonresponse		4 (0.8)
In remission and patient request		4 (2.8)
Bridge to immunomodulator		2 (1.4)
Pregnancy		2 (1.4)
Moved to different hospital trust		2 (1.4)
Abnormal liver function		1 (0.7)
Intraabdominal sepsis		1 (0.7)
Cancer in fistula		1 (0.7)
Heart failure		1 (0.7)
Unclear		11 (7.6)
Regular : intermittent infusions in 96 patients continuing infliximab	94 : 2	

(1 g twice a day) (0.7%). Prednisolone use varied during the course of infliximab infusions. In total 64 patients (44.4%) were given intravenous hydrocortisone before infliximab, either because they were not taking an immunomodulator, were taking less than 30 mg of prednisolone, or had experienced an earlier infusion reaction (the latter patients were given concomitant chlorpheniramine). The majority of patients were administered infliximab at a dose of 5 mg/kg, with the exception of three patients who were thought to have developed antibodies to infliximab, and therefore had between one and three doses of 10 mg/kg with no adverse effects.

The incidence of infusion reactions is summarized in Table 3. Eighteen reactions occurred in 15 patients during or after the infusion at 2 h (5.2% of 2-h infusions), 14 reactions in nine patients during or after the infusion at 1 h (3.7% of 1-h infusions) and 10 reactions in six patients during or after the infusion at 30 min (2.3% of 30-min infusions).

Of the 119 patients who received 344 infliximab infusions over 2 h, 11 experienced minor acute reactions (3.2% of 2-h infusions), with symptoms of nausea, lightheadedness, wheeze or an erythematous rash. All of these settled with

Table 3 Summary of infusion reactions

	Infusion duration			
	2 h	1 h	0.5 h	Total
Number of patients having infusions of different duration (% of total number)	119 (82.7%)	102 (70.8%)	70 (48.6%)	NA
Total number of infusions	344	376	426	1146
Total number of mild infusion reactions : treatment continued (% of total number infusions at each duration)	11 (3.2%)	13 (3.5%)	8 (1.9%)	32 (2.8%)
Total number of severe infusions reactions : treatment stopped (% of total number of infusions at each duration)	3 (0.9%)	0	2 (0.5%)	5 (0.4%)
Total number delayed hypersensitivity reactions (% of total number infusions)	4 (1.2%)	1 (0.3%)	0	5 (0.4%)
Total number of infusion reactions (% of infusions at each duration)	18 (5.2%)	14 (3.7%)	10 (2.3%)	42 (3.7%)
Total number patients who had no further infusions because of reaction (% total patient number)	3 (2.1%)	1 (0.7%)	2 (1.4%)	6 (4.2%)

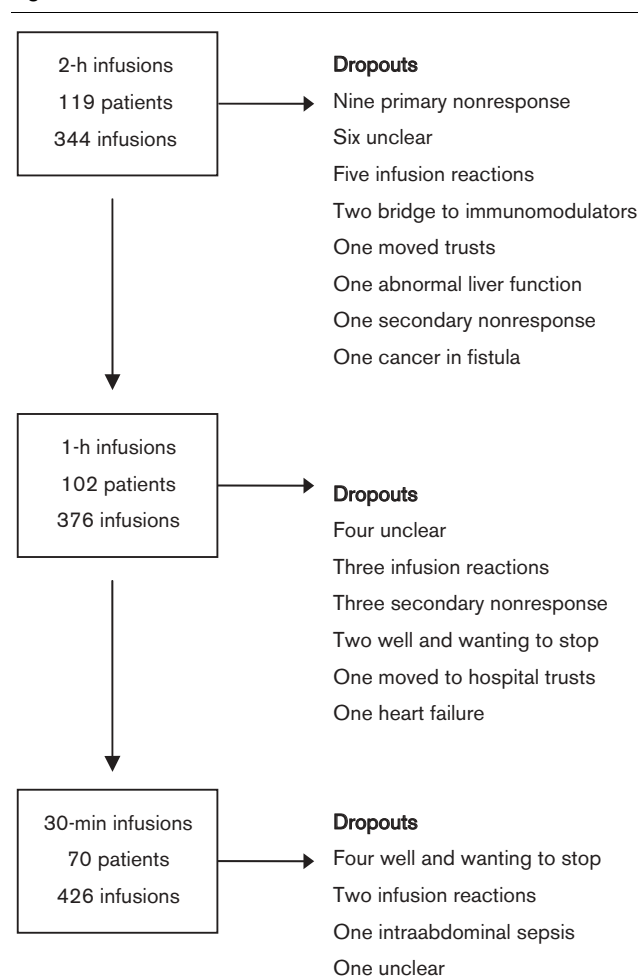
In addition, two patients developed infections (iliopsoas abscess and finger pulp infection) one a perforated colon requiring a right hemicolectomy and one carcinoma in a perianal fistula.
NA, not applicable.

administration of intravenous hydrocortisone and chlorpheniramine. The infliximab infusion was stopped temporarily for a short time, but was later completed. Three patients (0.9% of 2-h infusions) had severe acute reactions, and despite similar management, the infusion was not able to be completed. None of these three patients received any further infusions of infliximab.

Delayed hypersensitivity reactions occurred in four patients, two of whom had already experienced a mild reaction. These individuals experienced myalgia, polyarthropathy or rash. Finally, one other patient had to discontinue infliximab infusions because of development of a fistula-associated malignancy (only one infusion had been given, therefore this association is unlikely to be causative), and another patient developed an iliopsoas abscess, which required computed tomography-guided drainage, but was able to recommence infliximab infusions at a later date.

For the 102 patients receiving 376 infliximab infusions over 1 h, there were 13 mild reactions in nine patients (3.5% of 1-h infusions), but no severe infusion reactions. In addition to this, one patient developed a finger pulp space infection, which was treated successfully with oral antibiotics. This occurred after the fifth infusion at 1 h and the patient has since received six further infusions, without incident. Another patient developed severe

Fig. 1



Flow chart of patients who stopped infliximab infusions.

abdominal pain several hours postinfusion, and was found to have perforated a segment of Crohn's-involved small bowel, which required a right hemicolectomy. The patient subsequently had a flare of his Crohn's disease with severe IBD-associated arthropathy, and has since recommenced infliximab without incident.

Seventy patients received 426 infliximab infusions over 30 min. Eight mild reactions in four patients (1.9% of 30-min infusions) and two severe infusion reactions (1.9% of 30-min infusions) on the 10th and 15th infusions were observed, respectively. Both patients with severe reactions had no further infliximab infusions.

From the original group of 144 patients, 78 had an induction regimen of infusions at 0, 2 and 6 weeks after regular maintenance infusions; 37 had episodic infusions initially and were then converted to maintenance infusions; 18 had induction with no subsequent infusions (either because of primary nonresponse or a reaction) and

Table 4 Summary of univariate and multivariate analysis

	Univariate	Multivariate
Sex: male versus female	1.03; $P=0.95$ (0.45–2.33)	1.35; $P=0.55$ (0.51–3.54)
Age	0.99/year; $P=0.40$ (0.96–1.02)	0.98/year; $P=0.31$ (0.94–1.02)
Disease type	1.23 $P=0.62$ (0.54–2.81)	0.97; $P=0.96$ (0.35–2.73)
Fistulising versus no fistulae		
Administration		
Episodic then regular versus 0, 2 and 6-week induction then regular	2.64; $P=0.04$ (1.05–6.6)	2.53; $P=0.07$ (0.92–6.95)
Infusion intervals:		
6 weekly versus 8 weekly	2.62; $P=0.21$ (0.58–11.93)	1.76; $P=0.49$ (0.35–9.93)
12 weekly versus 8 weekly	2.91; $P=0.26$ (0.46–18.66)	3.58; $P=0.22$ (0.47–27.37)
Use of immunomodulators:		
MTX/prednisolone versus AZA/6-MP	1.21; $P=0.68$ (0.49–3.03)	–
No immunomodulator versus AZA/6-MP	0.89; $P=0.85$ (0.27–2.97)	–
No immunomodulator versus any	0.84; $P=0.77$ (0.26–2070)	0.71; $P=0.69$ (0.13–3.90)
Number of infusions		–
OR of reaction with increasing number of infusions	0.98/infusion; $P=0.47$ (0.93–1.04)	
Less than 10 infusions versus more than 10	0.85; $P=0.69$ (0.38–1.89)	1.02; $P=0.98$ (0.32–3.19)

All results are expressed as the odds ratio with P value (95% confidence interval). AZA, azathioprine; 6-MP, 6-mercaptopurine; MTX, methotrexate; OR, odds ratio.

the remainder had episodic infusions throughout. At the point of data collection, 96 patients (44.4%) were still having infliximab infusions, with 94 on regular maintenance (eight patients (8.5%) every 6 weeks, 81 patients (86.2%) every 8 weeks and five patients (5.3%) every 12 weeks).

For the 48 patients no longer having infliximab, the most common reasons for discontinuation were infusion reactions in 10 patients (6.9%) primary nonresponse with no response after three dose inductions in nine patients (6.3%), secondary nonresponse with loss of efficacy at a later stage in four patients (0.8%) and at patient request (as in remission) in four (0.8%). Details for all patients are shown in Table 2 and Fig. 1.

The results of univariate and multivariate analysis are shown in Table 4. Univariate analysis suggested that infusion reactions were more likely in those patients receiving episodic, rather than planned maintenance, infliximab infusions. No obvious association with sex, age, fistulising or nonfistulising Crohn's disease, infusion interval, use of immunomodulatory therapy, or total number of earlier infusions was present. The association between likelihood of infusion reaction and episodic infusion schedule approached statistical significance following logistic regression to control for all demographic data.

Discussion

Infliximab is now used routinely in the management of patients with Crohn's disease, and more recently ulcerative colitis. NICE guidelines allow its use in Crohn's patients with severe disease, those who have either failed or are intolerant to immunomodulators and where surgery is deemed inappropriate [9].

Infliximab is generally well tolerated, although ACCENT I reported a rate of infusion reaction between 9 and 23% [1]. Importantly, there was no significant difference in adverse effects between patients receiving one or several infusions. Cheifetz *et al.* [10] also reported rates of adverse reactions in 165 patients receiving 479 infusions, where 3.1% were mild, 1.2% moderate, 1% severe and 0.6% delayed.

ACCENT I demonstrated the efficacy of 8 weekly maintenance infusions, with 39% of patients on 5 mg/kg in remission at week 30, compared with 21% of patients receiving placebo, following an initial infusion [1]. Maintenance infusions reduce the burden of surgery and inpatient stays [6,7], however, this requires patients to attend hospital every 8 weeks for both the infusion and subsequent monitoring period.

Following publication of rapid infusion safety data in rheumatology patients from our unit [8], our practice changed to mirror the reduced time for infusion. The current data demonstrate low rates of both mild and severe reactions. Rates of severe reactions for reduced infusion times in our patients are similar to the data reported by Buch *et al.* [8], although mild reactions occurred in a higher proportion of our patients (2.8% of all infusions in IBD patients compared with 0.6% in the mixed group of rheumatology patients). The reason for this is unclear; however, patients with a mild reaction were able to complete the infusion. It seemed from univariate analysis that infusion reactions were more likely in those receiving episodic infusions rather than regular maintenance infusions, though this association was not as strong following logistic regression. As these data were collected in a nontrial setting, antibodies to

infliximab were not measured. It was also notable that frequency of reactions seemed to diminish, as the rate of infusion increased. This may be explained by a dropout of patients who had already experienced an infusion reaction during the 2 h infusions (five patients) and 1 h infusions (three patients) (Fig. 1).

In summary, rapid infusion of infliximab seems to be safe and well tolerated and reduces the time patients spend in hospital. This is an important improvement in care that has been welcomed by patients attending the IMID centre. We did not observe any increase in infusion-related reactions in our patients, and when reactions did occur, these were usually treated successfully by the administration of intravenous hydrocortisone and chlorpheniramine, allowing recommencement and completion of the infusion. Although an assessment of patient satisfaction is still ongoing, we believe that this is likely to enhance patient care, by minimizing the length of time in hospital for patients with IBD.

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