

Tolerability of Shortened Infliximab Infusion in Scheduled Maintenance Therapy for IBD: A Prospective Multi-center European Cohort Study

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ABSTRACT

AIM: Although an infusion time of at least one hour is mandated by the European label for infliximab (IFX) maintenance treatment of patients with IBD, shorter infusion times of 30 min have been reported with low dose treatment in rheumatoid arthritis. The aim of this study was to prospectively evaluate the tolerability of shortened IFX infusions in a multi-center cohort study.

METHODS: Adults with Crohn's disease or ulcerative colitis tolerating at least seven IFX infusions (5 mg/kg) of which at least 3 infusions over one hour, without infusion reactions, were invited to receive the same dose in 30 min for four consecutive infusions and with the same dosing frequency. The primary endpoint was the proportion of patients completing the trial without a severe infusion reaction. Tolerability, infusion times and total procedure times, clinical disease activity and patient preference was assessed at every infusion.

RESULTS: One hundred eleven (25 UC, 84 CD, 2 IBD-unclassified) patients enrolled in the trial. All shortened, 30 minute infusions were completed by 91/111 (83%) patients and no severe infusion reactions were observed. Mild to moderate reactions occurred in 10/111 patients (6 acute) and twenty terminated before week 24; infusion reactions (11), increased dosing of IFX (4), loss of efficacy (4) and 1 patient moved out of the country. Median clinical activity indices and

CRP remained stable throughout the study.

CONCLUSION: In a selected population of patients with IBD, who have tolerated IFX maintenance infusions, infusion times can be shortened from one hour to 30 min. No severe infusion reactions were observed.

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Key words: Inflammatory Bowel Diseases; Crohn's Disease; Ulcerative Colitis; Biologics (IBD)

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INTRODUCTION

Infliximab (IFX), a chimeric monoclonal antibody to human TNF, has proven to be efficacious for the treatment of active luminal and fistulizing Crohn's disease and for active ulcerative colitis. IFX has been traditionally administered as an intravenous infusion over 2 h with a post infusion observation period of 1 h in these indications. The main reason for the 2 hours infusion time is the real risk of infusion reactions. Infusion reactions have been observed in 10-20% of patients and in up to 5% of infusions^[1-3]. These reactions are usually mild, but rare cases of severe anaphylaxis-like reactions have been described. Episodic use of infliximab at disease flare increases the risk of infusion reactions whereas concomitant immunosuppressives are protective^[4]. In clinical practice shorter infusion times of one hour have been used in patients who have demonstrated to tolerate IFX administered on a 2 h basis. In rheumatoid arthritis no increase in infusion reactions was observed in patients receiving accelerated (1-hour) infusions compared with those who had received infusions over a 2-hour period^[5]. This has led to the implementation of 1-hour IFX infusions in the label for treatment of patients with rheumatoid arthritis who have tolerated

three initial 2-hour infusions of IFX. Two recently published cohort studies in a large number of patients have confirmed that one hour infusions with 30 min post infusion observation in patients with IBD tolerating at least 4 infusions over 2 h or more are well tolerated^[6,7]. In addition, recent data suggest that also in IBD 5 mg/kg IFX IV administered over 30 min is well tolerated in selected patients^[8]. To assess the tolerability of short 30 min infliximab infusions in patients with ulcerative colitis or Crohn's disease, we designed a prospective multi-center trial. This strategy should result in greater patient's convenience, financial effects on working availability, and less work load for medical and nursing staff at unit.

MATERIALS AND METHODS

All patients aged 16 to 80 with Crohn's disease or ulcerative colitis treated with infliximab 5 mg/kg scheduled maintenance therapy at the participating centers were eligible provided they had been tolerating at least three one hour infliximab infusions without infusion reactions and had a sustained clinical response to the antibody. A documented acute or delayed infusion reaction, any prophylactic medical therapy to prevent infusion reactions, need for dose interval decrease below 6 weeks or dose step up to 10 mg/kg, a dosing interval longer than 12 weeks within the 12 months prior to screening, or any condition contraindicating for further infliximab treatment, all sufficed to exclude the patient from participating in the trial. In consented patients with confirmed eligibility all consecutive infliximab infusions during 24 weeks (at least 4 infusions) were administered over 30 min with a post infusion observation period of 15 min. Any adverse events including delayed hypersensitivity reactions, the Harvey-Bradshaw clinical index for patients with CD or the clinical Mayo disease activity index (UC-DAI) for patients with UC^[9], blood analysis including hemoglobin, complete and differential white blood cell count, CRP and concomitant medication use were recorded prior to every IFX infusion. Vital signs (blood pressure, pulse and temperature) were recorded before and immediately after every infusion. The occurrence of acute infusion reactions of any severity or nature was observed and documented during and immediately after the infusion. A delayed infusion reaction was defined as general malaise, fatigue, arthralgias or myalgias occurring after discharge from the infusion and until 10 days after the completion of the infusion. When patients reported an acute or delayed infusion reaction further infusions were administered over one hour or longer and appropriate prophylactic treatment was provided prior to subsequent infusion as per investigator discretion. Patients were asked about the preference of the shortened 30 minute infusion as compared to previous infusions at the end of the 24 weeks period and this was captured on a 5 point Likert scale. The protocol was approved by the ethics committees of all participating centers, Karolinska University for Huddinge and Solna Hospitals, the Leuven University Hospital and Trinity College for Adelaide and Maide Hospitals respectively. All patients provided written informed consent prior to inclusion.

Endpoints and statistical analysis

The primary endpoint was the proportion of patients who tolerated all 30 minutes infusions for 24 weeks (4 infusions) or until discontinuation of infliximab therapy without a severe infusion reaction. Severe acute infusion reactions were defined as any event associated with decreased consciousness, bronchospasm with wheezing, dyspnoea requiring ventilatory support, a drop in systolic blood pressure of 40 mg Hg or a systolic blood pressure below 80 mm Hg with or without any of the above symptoms. Mild infusion reactions were defined as any event leading to new onset facial

erythema, tightness of chest, paraesthesia, dyspnoea, headache or any new symptom occurring during or within 15 minutes after the infusion and judged to be probably or definitely related by the attending physician.

Additional endpoints included: the proportion of patients with mild to moderate infusion reactions, the proportion of patients who returned to longer infusion times, patient preference, the proportion of patients with a loss of response or intolerance to infliximab, the proportion of patients needing a dose or interval adjustment, overall safety, the change in Harvey Bradshaw index or clinical Mayo disease activity index over 24 weeks. All data were analyzed with descriptive statistics. Intention to treat analysis was performed including all patients who were enrolled and received at least one infusion of infliximab in the trial. Last observation carried forward was used for missing continuous values. Potential predictors of infusion reactions and loss of response, including age, sex, disease duration, diagnosis, number of previous infusions, concomitant immunosuppressives and smoking status were tested. Statistical analysis was performed with SPSS software (IBM).

RESULTS

One hundred eleven (25 UC, 84 CD, 2 IBD-unclassified) patients with a median disease duration of 11 years. (1-42) were enrolled in the trial between May 2009 and March 2010. Patients' demographics are summarized in table 1. All four 30 minutes infusions were completed by 91/111 (82%) of patients (primary endpoint, figure 1). No severe infusion reaction was observed but mild to moderate reactions occurred in 11/111 (10%) of patients after a median of 3 infusions. Twenty patients terminated before week 24; 11 because of infusion reactions, 4 because of increased dosing of IFX, 4 because of loss of efficacy and 1 patient emigrated (Figure 1). Infusion reactions were acute in 6/11 and delayed in 5/11 patients. The main symptoms associated with the infusion reactions are presented in table 2. Of the 11 patients with an infusion reaction, 7 returned

Table 1 Patient demographics.

Diagnosi (n=111)	
CD	84
UC	25
IBD-U	2
Sex (Female/Male)	39/72
Age (median, range)	36 (18-71)
Disease duration (median, range)	11 (1-42)
Previous nr of IFX infusions (median range)	20 (7-57)
Concomitant immunosuppressives	
AZA/6-MP	19
MTX	2
IFX monotherapy	90
Smoking status	
Current	21
Ex	22
No	68

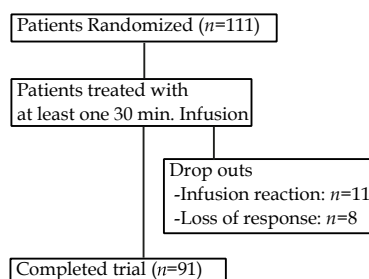


Figure 1 Patient distribution.

to one hour infusions with no further reactions, and one patient was discontinued from further infusions due to a delayed reaction. None of the above mentioned potential predictors (age, sex, disease duration, diagnosis, number of previous infusions, concomitant immunosuppressive and smoking) were associated with infusion reactions or with loss of response in univariate analysis (all $p > 0.1$) and therefore were not tested in multivariate analysis.

Table 2 Infusion reactions.

Infusion reactions	
Acute (6/111, 5.4% of patients)	Headache 2/6 Tightness, nausea, erythema 2/6 Fatigue: 2/6
Delayed (5/111, 4.5% of patients)	Headache 2/5 Fatigue 1/5 Palpitations 1/5 Pruritus and skin erythema 1/5

Median clinical Mayo index (UC-DAI) was 0 (range 0-10) at baseline and at week 24 (range 0-4). The median Harvey-Bradshaw index (CD-HBI) index at baseline was 3 (0-16) and 2 (0-16) at week 24. Median scores of the indices remained stable throughout the trial. The median CRP values also remained stable throughout the trial and baseline values did not differ from values at week 24 (Figure 2).

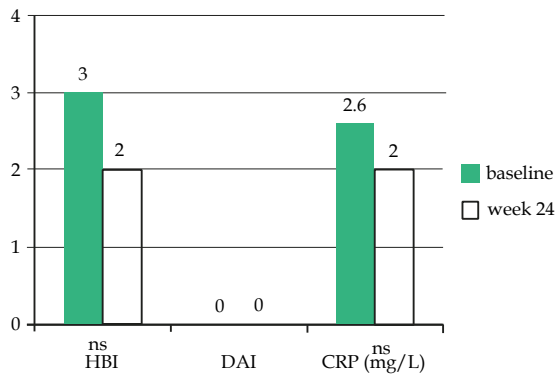


Figure 2 Clinical disease activity (HBI for CD and UC-DAI) and C-reactive protein (CRP) at baseline and at the end of study. Values represented are medians. ns (not significant).

Median infusion time was 30 minutes (range 25-90, mean 31) and median time on the unit was 65 minutes (range 37-290, mean 68). In 31 cases (infusions) the total time on the unit was 50% longer than the median of 65 minutes, with the reasons being the work load of the nursing staff (7/31) or of the attending physician (11/31), concomitant iron sucrose infusion (4/31) or infusion pump dysfunction (9/31).

Ninety-one/111 (82%) patients returned the preference questionnaire at the end of the trial. Of those 65% expressed a strong preference towards 30 minute infusions and 23% reported some preference (Figure 3).

Adverse events other than infusion reactions and considered to be at least possibly related to infliximab, occurred in 39/111 (35%) of patients for a total of 45 adverse events (Table 3). One patient had a pulmonary embolism that required hospitalization and resolved with treatment.

DISCUSSION

Maintenance anti TNF therapy, when successful, restores quality of life and removes disease related symptoms, which allows patients

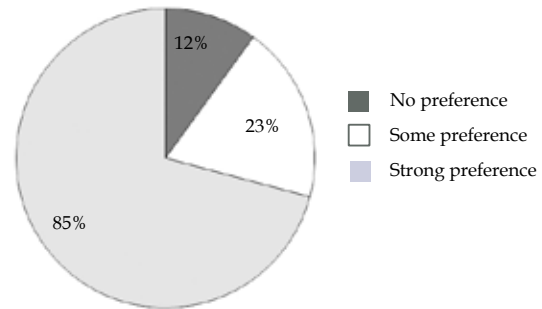


Figure 3 Patients completing the trial reported their preference for the short infusions on a 5 point Likert scale ranging from a strong preference for the shortened infusions to a strong preference for the longer infusions.

Table 3 Adverse events not classified as infusion reactions and occurring in at least 5% of patients.

All adverse events (at least possibly related)	45 (in 39/111 patients)
Adverse events occurring in at least 5% of patients	
Arthralgias	6
Eczema	9
Infections (total)	17
Urinary	1
Upper Respiratory	9
Gastroenteritis	3
Skin	3
Other	1

with IBD to return to their job, school and family life. However, monoclonal antibody therapy requires intravenous or subcutaneous administration, and the need for the 2 hour infliximab infusion and 1 hour post infusion observation mandated in the original label has interfered with quality of life and acceptance of the therapy. In this prospective open label trial, we demonstrate that in selected patients with good tolerance to an induction treatment with infliximab and to several one hour infusions, infliximab administration can be accelerated to 30 min with 15 min post infusion observation with very good safety. No severe infusion reactions were observed and only 10% of patients experienced a mild reaction. Most of these patients returned to one hour infusions without further reactions. It is unclear at this time why some patients don't tolerate 30 minutes infliximab administration. The incidence of infusion reactions observed in our trial was in line with what has been reported in randomized clinical trials^[1,2]. However, in the recently published cohort studies a lower incidence of infusion reactions was reported with 1 hour infusions^[5,6]. The present study was an open label trial and patients were aware of the accelerated infusion time, which may have triggered some of the mild reactions. Interestingly, all patients returned to one hour infusions without further problems. We were not able to identify predictors of infusion reactions in patients who all tolerated 1 hour infusions. Even if concomitant immunosuppression was not associated with a decreased risk of infusion reactions in the entire population, most reactions occurred in one center (U of Leuven Hospitals) treating a greater proportion of patients with infliximab monotherapy.

This study was performed in three different infusion units using the same infusion protocol. No clear differences between the sites were observed, although the percentage of patients who did not tolerate 30 min infusions and returned to one hour infusions was numerically higher in one site.

In general, no new signals were detected in the adverse events other than infusion reactions. Also, clinical activity scores and CRP were not influenced by the 30 minutes infusion, indicating that the accelerated infusions didn't interfere with a durable response. When questioned at the end of the trial, 88% of patients expressed at least

some preference for the accelerated infusions and for most (65%) this preference was outspoken. However, only patients completing all 4 short, 30 minutes infusions, provided input on their preference and this may introduced some bias towards a more favourable opinion on the shortened infusions.

In this trial we also registered the actual infusion times and times on unit. As expected, the median infusion time was 30 minutes with some deviations due to infusion pump dysfunction. Some variability was also observed in the total time on unit. Longer procedure times were caused by predictable events such as work load and additional IV therapies. Therefore, the impact of accelerated infusions over 30 minutes on the convenience of intravenous treatment procedures is highly dependent on the organisation of the unit and on the availability of medical and nursing staff. If for example, local procedures require infliximab to be ordered and to be prepared in the hospital pharmacy, the shortened infusion time will not have a major impact on the total time in hospital or on the unit.

Our study has several limitations. Patients and care givers were not blinded to the infusion time and this may have provoked some of the mild reactions. Second, we carefully selected patients for durable response and tolerability of previous infusions. Therefore, we would advise to use the accelerated infusion strategy only in patients with clear tolerability to all previous infusions including several infusions over one hour.

In conclusion, this prospective multicenter study demonstrated that 30 min infliximab infusions at a dose 5 mg/kg are safe and well tolerated in selected patients. This confirms the findings from a previously reported single center observational study^[8]. Shorter hospital stays for IV treatment offer perspectives of a decreased impact on social and professional activities in a young patient population.

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