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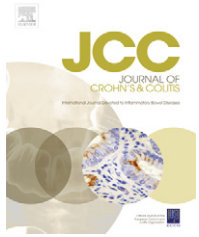

Infliximab administered with shortened infusion times in a specialized IBD infusion unit: A prospective cohort study

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Abstract

Background and aims: Biological therapy with anti TNF agents requires parenteral administration and in the case of infliximab this involves in hospital treatment. We aimed to prospectively assess the safety and tolerance of infliximab infusion in patients with IBD in a specialized unit adhering to strict standard operation procedures including switch to accelerated 1 h infusions.
Methods: A prospective audit of a referral center IBD infusion unit was performed. We recorded infusion times and all adverse events including hypersensitivity reactions. Patients were also polled about the impact of the treatment on quality of life (QOL).
Results: On 20 consecutive days 177 patients were treated with infliximab and all participated. Of those infliximab 117 received 1 h infusions and 4 (2.2%) had an immediate infusion reaction. Median time on unit was optimal for those with 1 h infusions [1:35 h (IQR: 1:25–1:50)] without an increased risk of infusion reactions. Prophylactic therapy significantly increased the time on unit [3:20 h (IQR: 2:50–3:45), $p<0.001$]. Patients reported a high global satisfaction and a good tolerability of the infusions with a considerable or strong impact on studies, work or QOL in one third.
Conclusions: A dedicated IBD infusion unit can achieve high quality of care and shortened 1 h infliximab infusions are well tolerated in patients with scheduled maintenance therapy.

1. Introduction

Anti TNF therapy has been introduced more than a decade ago in the medical management of patients with IBD and has opened the perspective of renewed disease control in patients with refractory disease. 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. Because it is a large and complex protein, IFX is administered intravenously.[1–5] Infusion reactions have been observed in 10–20% of patients and in up to 5% of infusions with infliximab administration.[1–5] These reactions

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are usually mild but anaphylactic reactions, although rare, have been described. In a recent cohort study from a tertiary referral center, acute infusion reactions were observed in 17% of patients and infusion reactions were associated with episodic therapy.[6] The risk of infusion reactions has led to the requirement for in hospital or office based administration in the infliximab label.[7] To downscale the risk of infusion reactions the infliximab label also demands IFX to be administered as a 2 h infusion. However, in clinical practice shorter infusion times of 1 h have been used in patients who have demonstrated to tolerance to infliximab administered on a 2 h basis, and this has now been implemented in the label for treatment of patients with rheumatoid arthritis (RA). The IFX dose administered to patients with RA, is lower (3 mg/kg vs. 5 mg/kg in IBD) and therefore the tolerability of 1 h infusions in RA cannot be directly extrapolated to patients with IBD. These shorter infusion times are always reserved for patients with scheduled maintenance and not for those with episodic use of IFX.

The main objective of this trial was to prospectively assess the safety and tolerance of infliximab infusion in patients with IBD in a specialized unit adhering to strict standard operation procedures including switch to accelerated 1 h infusions. As a secondary objective we performed an audit of the infusion unit with prospective registration criteria reflecting quality of care and patient satisfaction during a predefined time interval.

2. Methods

All patients admitted for 20 consecutive operating days (April–May 2008) to our infusion unit were invited to participate. The unit services exclusively to IBD patients at the Leuven University Hospital and uses strict standard operating procedures for infusions of biologicals and of iron sucrose. The unit nursing staff registered the patient flow including time on unit and time in hospital, infusion specific details (need for prophylactic pre-medication, type of infusion and number of previous infusions, pre-specified infusion time, pump infusion rate, actual infusion time), number of venopunctures needed to establish an IV line and reasons for delay. Capturing the interval between entry into the hospital, admittance to the unit and discharge was facilitated by the hospital electronic charts, which automatically register these events. The medical and nursing staff recorded any adverse event during and immediately after an infusion. Delayed infusion reactions were captured at the time of the next infusion for minor reactions or when they occurred for more severe events. In addition, patients were asked to fill out a questionnaire with specific items on global satisfaction with the IV therapy and on interference of the treatment with activities of daily life. Patients scored the items on a 4 point Likert scale. All patients provided written informed consent for both parts of the study and the study was approved by the Leuven University Hospitals Ethics committee. Data sheets for the registration by nursing and medical staff were coded and patient questionnaires were anonymous. Descriptive statistics were used to analyze demographic data and for comparison between different patient populations non-parametric tests were used. For the analysis of times on unit and infusion reactions only infliximab patients were included in the analysis. For general satisfaction and other quality parameters all patients were included.

3. Results

3.1. Patients and therapies

Over 20 consecutive operating days 199 patients were treated and all gave written informed consent to participate. Infliximab (IFX) infusions predominated ($n=177$, 89%), 9% received IV iron (combined with IFX in 3%, $n=6$) and 3 received an experimental biological agent. More than one venopuncture was needed to establish an IV line in 5.5% ($n=11$) with a maximum of 3 attempts in one patient. Of note 72% of patients came from outside of the greater Leuven area (roughly more than 20 km radius). Demographics of those patients receiving IFX infusions are listed in Table 1. Crohn's disease patients predominated with 73.3%. The dose of IFX was 5 mg/kg in 97.2% (10 mg/kg in 2.8%). Concomitant immunosuppressives (azathioprine or methotrexate) were present in 35/177 of those patients (19.8%) and in 17/117 (14.5%) of patients with 1 h infusions. The median number of IFX infusions since start of the therapy was 19 (6–22) in the 177 patients and 18 (10–26) in the patients with 1 h infusions. Patients were followed up for infusion reactions until their next visit to our hospital (6–8 weeks).

3.2. Standard operating procedures for infusion therapy

Fig. 1 is a graphical representation of the standard operating procedures for infliximab infusions at our unit. All patients are now treated with scheduled maintenance infusions and we tailor the infusion times to the number of infusions patients have received and to previous infusion reactions. Briefly, infusion rates (all pump controlled) are slowed down initially

Table 1 Demographics of patients with IFX infusion.

Total number of patients on IFX	177
Female	49.7%
Age (median, range)	39 (17–72)
Crohn's disease	73.3%
Ulcerative colitis	26.7%
One hour IFX infusion	66.2%
Disease duration in years (median, IQR)	
All IFX patients	10 (5–18)
1 h infusions	11.5 (6–19) (ns)
Number of IFX infusions since start (median, IQR)	
All IFX patients	19 (6–22)
1 h infusions	18 (10–26) (ns)
10 mg/kg infliximab	2.8%
Prophylaxis	23.2%
Concomitant azathioprine/MTX with IFX	
All IFX patients	19.8%
1 h infusions	14.5% (ns)

Note: NS, not significant, $p>0.05$.

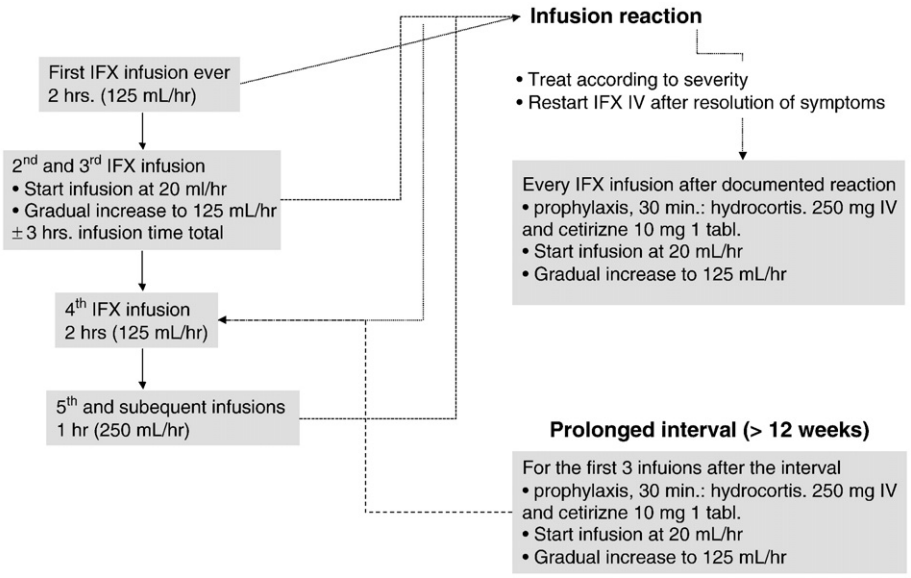

Figure 1 Standard operating procedures for infliximab infusions. The flow chart illustrates how the duration of infusions is gradually shortened and prolonged in patients with a documented reaction of a longer interval between infusions. For the 3 h infusions the infusion rate is gradually increased to 125 ml/h from an initial rate of 20 ml/h. Rates are only increased if patients show no sign of infusion reaction. Patients with prolonged intervals are those who stretched the pre-planned interval beyond 8 weeks for intercurrent events.

for the second and third infusion and the 4th infusion is given over 2 h. From the 5th infusion onwards IFX is administered over 1 h. All our patients are treated with maximal intervals of 8 weeks between infusions, but some patients prolong their interval due to intercurrent events (e.g. infection, pregnancy). In patients with a drug holiday of more than 3 months, prophylaxis is provided with 250 mg hydrocortisone and a slow infusion regimen is used with a slow initial infusion rate (20 ml/h) at the onset and gradual increase of the rate. In patients with a documented infusion reaction medical prophylaxis is administered first followed by IFX at a slower infusion rate. In patients with a mild or moderate infusion reaction the infusion is interrupted, medical therapy is administered, and only after complete resolution of symptoms the infusion is restarted at reduced speed. Vital signs (blood pressure, consciousness, heart rate) are obtained before and after the infusion in all patients and at 15 min time intervals in patients with a mild or moderate reaction. Severe reactions, defined as being associated with decreased consciousness, bronchospasm with wheezing, dyspnoea requiring ventilator support or hypotension with a systolic pressure below 80 mm Hg or a drop in systolic blood pressure with 40 mm Hg or more, lead to interruption of the infusion and of any further dosing of that therapy.

3.3. Safety and tolerability of infusion therapy

Infusion reactions were noted in 2.2% of patients treated with IFX (4/177, 2.2%) and in none of the other patients. Prophylaxis before the IFX infusion was administered to 23.2%. Two out of 4 infusion reactions occurred in patients with 1 h infusion, and 1 in a patient already receiving prophylaxis. All were mild and resolved with temporary interruption of the treatment and administration of an antihistaminic and/or hydrocortisone 250 mg IV. All other patients reported good tolerance.

3.4. Influence of infusion time on time spent in the unit

The median time in the unit for all patients was 1:50 h (IQR: 1:30–2:50) (Fig. 2). Patients with 1 h infusion were in hospital for a median 1:35 h (IQR: 1:25–1:50), which was significantly shorter than the time spent by patients with prophylaxis [3:20 h (IQR: 2:50–3:45), $p<0.001$ vs. 1 h infusion]. This time period also included venopuncture, blood drawing, preparation of infusion, physician's assessment and booking the next appointment.

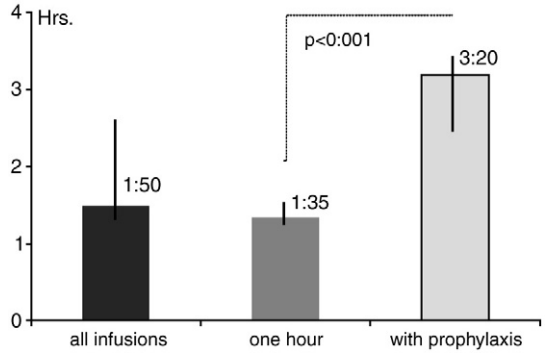

Figure 2 Times on the infusion unit for patients with 1 h infusions compared to all patients and patients who require prophylaxis. Data are represented as medians with IQR.

3.5. Impact of infusion therapy on quality of life

Of all 199 patients included in the audit, 197 (99%) returned their questionnaire. Eighty one percent was globally very satisfied with the care at our infusion unit, 13% rather satisfied, 3% rather unsatisfied and 5% very unsatisfied. The infusion therapy was felt to have a strong or considerable impact on studies or work in 37%, and on social and family life in 35%. Side effects associated with the treatment were scored as having a strong or considerable impact in 15% of patients (Table 2).

4. Discussion

In this first prospective study on the impact of 1 h infliximab infusions in a cohort exclusively composed of IBD patients we report that safety and tolerability of shortened infliximab infusions is comparable to longer infusions. Furthermore, we show that an infusion unit with a dedicated staff specializing in IV treatments with biologicals and IV iron can achieve high standards of care and good patient satisfaction.

In this cohort the patients were selected for 1 h infliximab infusions through standard operating procedures tailoring the duration of every infusion to the previous infliximab exposure and the occurrence of infusion reactions. Also, all patients were treated on a regularly scheduled maintenance base (q8 wks or less). It has been our experience that individuals receiving their second and third infliximab infusion ever or being treated after a drug holiday of more than 12 weeks are particularly vulnerable for infusion reactions and the operating procedures were designed accordingly.[6] However, for those patients tolerating at least 4 infusions of infliximab without an infusion reaction (66% of all patients treated in the predefined period) 1 h infliximab infusions are well tolerated and may decrease the impact of the treatment on activities of daily life. Infusion reactions were observed in only 2% of infusions and were all mild. There was no trend for a higher rate of infusion reactions in the patients treated with infusions over 1 h. The 2% risk of infusion reactions is clearly lower than the 17% reported before by our institution but the follow up in the current study was short and the population highly selected.

Data on 1 h and even 30 min infusions of infliximab have been reported in the literature.[8–10] However, most of these reports have been retrospective and from mixed cohorts or cohorts predominantly composed of patients with rheumatoid arthritis (RA). The infliximab dose in RA is 3 mg/kg and therefore could be theoretically better tolerated over 1 h than the standard dose of 5 mg/kg in patients with IBD. Data from the Leeds General infirmary in England,[8] indicate that shortened infusion times are safe also in patients with IBD with a low risk of infusion reactions and our prospective data add to this experience. In contrast to the data obtained in earlier cohorts, our patients were generally treated with IFX monotherapy (85% of patients). Since 2007, we have prospectively stopped concomitant immunosuppressives in all patients after 6 months of combined infliximab and immunosuppressive therapy, although combined therapy was still present in a small minority of patients on 1 h infusions (14.5%). Concomitant immunosuppression has been shown to downscale the risk of infusion reactions in patients with episodic therapy,[6] but our results indicate that shortened infusions can be safely administered in patients with IFX scheduled maintenance monotherapy. Another strength of our study is that we captured all consecutive patients over a predefined time period and this excludes any selection bias.

Finally, we also explored the patients' perspective on the care we deliver at our infusion center and on the impact of IV therapy on the daily life of patients with IBD. We deliberately opted for anonymous questionnaires to ensure patients would freely report their experience. As a drawback, we are unable to link the scores to the infusion times patients received. In general, 81% of patients were very satisfied with the care we provide and only 6% were unsatisfied. Also, two thirds of patients felt that the IV therapy they received did not have a major influence on their daily life including studies, work or social activities. Of note, however, for only half (53%) of the patients the side effects associated with IV therapy had no impact whatsoever on their quality of life and 15% rated the impact of side effects as strong or considerable. This illustrates that even if the infusion procedure is well tolerated by almost all patients, side effects during intervals between infusions can affect the quality of life.

In summary, this prospective cohort of unselected patients from a unit specialized in the treatment of IBD with infusions of biologicals and IV iron, shows that high standards of care can be achieved, and that adherence to strict standard operating procedures allows 1 h infusions in most patients with scheduled infliximab maintenance treatment.

Table 2 Influence of IV therapy on daily activities assessed by patient surveys.

$n=197$	No impact	Some impact	Considerable impact	Strong impact
Influence on social and family life	32%	31%	19%	18%
Influence on work/studies	43%	22%	16%	19%
Influence of side effects of IV therapy on quality of life	53%	32%	4%	11%

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