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Tolerability of one hour 10 mg/kg infliximab infusions in inflammatory bowel diseases: A prospective multicenter cohort study

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KEYWORDS

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Abstract

Background and Aim: In patients with inflammatory bowel disease (IBD) tolerating 2-h infusions of 5 mg/kg infliximab scheduled maintenance therapy, the infusion time can be shortened to 1-h with good tolerability. A retrospective study with small sample size demonstrated the feasibility of 1-hour infusion time for 10 mg/kg infliximab in IBD patients.

Methods: Between November 2011 and July 2012, 63 patients received 1-hour 10 mg/kg infliximab infusions under standard operating procedures and were enrolled in a prospective observational study. Intravenous steroid premedication was given to all patients.

Results: Sixty-three IBD patients on infliximab maintenance therapy (43 Crohn's disease, 34 males) received 1-hour 10 mg/kg infusions during the study period. A total of 182 infliximab infusions were administered. Seventeen (26%) patients were receiving concomitant immunomodulators. Two patients experienced (2/182, 1%) severe acute infusion reactions consisting on a cutaneous lupus and one severe anaphylactic reaction. We also observed one (1/182, 0.5%) severe delayed reaction after the first 1-hour infliximab infusion consisting on acne generalis. All 3 reactions led to infliximab discontinuation. No mild acute reactions and 6 mild delayed reactions (6/182, 3%) occurred.

Conclusions: In patients with IBD receiving infliximab scheduled maintenance therapy, 1-hour infusion time for 10 mg/kg infliximab seems to be well tolerated. This option might be considered in clinical practice in order to decrease the extra-burden of infliximab infusions in this patient population.

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1. Introduction

At the end of the 1990s, infliximab (IFX) (Remicade, Centocor, Malvern, Philadelphia, PA), was approved for the treatment of Crohn's disease (CD) and more recently for refractory ulcerative colitis (UC).^{1–6} IFX was usually administered intravenously at the dose regimen of 5 mg/kg as a 2-h infusion in patients with inflammatory bowel disease (IBD).^{1–6} Since 2006, IFX (3 mg/kg) can be administered as 1-h infusions for treatment of patients with rheumatoid arthritis (RA) who tolerated three initial 2-h IFX infusions.⁷ Recently, shorter infusion time of 1 h has been used in patients with IBD, who tolerated IFX 5 mg/kg administered on 2 h without any adverse event, with a good tolerability profile.^{8,9} Optimizing infusion procedures and accelerated infusion times with acceptable safety may offer perspectives for a decreased impact of the treatment on activities of daily life.⁸ Accordingly, a change in the label of IFX was made on August 2011 as follows: "in carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of Remicade (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 h". Tolerability of shortened infusions at doses over 6 mg/kg was unknown.¹⁰ We recently reported in a retrospective study enrolling only 8 IBD patients treated at Nancy University Hospital (France) that 1-hour infusion time for 10 mg/kg infliximab appeared to be well tolerated.¹¹ Following the publication of these results, 3 French University Hospitals (Nancy, Saint-Etienne, Nice) have started treating all IBD patients receiving IFX scheduled maintenance therapy with 1-hour 10 mg/kg IFX infusions for patients' convenience.

The aim of this prospective observational study was to assess the tolerability profile of 1-h IFX infusions in IBD patients receiving 10 mg/kg IFX scheduled maintenance therapy.

2. Methods

This was a prospective observational study of all consecutive IBD patients treated with IFX infusions on a scheduled maintenance basis between November 2011 and June 2012 at the IBD units of University Hospitals of Nancy, Saint-Etienne, and Nice (France). As previously described,¹¹ only patients receiving maintenance therapy, defined as at least 1 IFX infusion after induction therapy (weeks 0, 2 and 6) with no intervals longer than 8 weeks, were included. All data on the tolerability of IFX in patients who received one 1-hour 10 mg/kg infusions were collected prospectively. Standard operating procedures for infusions of IFX are used in these 3 IBD units. The infusion units were staffed by the same nurses since several years and direct medical supervision was always available. Hence, all 63 patients included in this study received a routine prophylactic pre-medication by intravenous (IV) corticosteroids (hydrocortisone 200 mg) before IFX treatment. The medical and nursing staff recorded any adverse event during and immediately after an infusion.

Acute infusion reactions were defined as any adverse experience that occurred during or within 1 h after IFX infusion. A mild acute infusion reaction encompassed facial erythema, tightness of chest, paresthesia, dyspnea, headache or any new symptom occurring during the infusion

and judged to be probably or definitely related by the attending physician. A severe infusion reaction was defined as a decreased consciousness or a drop in systolic blood pressure by 30 mm Hg, or below a systolic blood pressure of 85 mm Hg, with or without any of the above symptoms. A delayed infusion reaction (serum sickness-like reaction) was defined as the occurrence of myalgia, arthralgia, fever, and/or rash between 1 and 14 days after the IFX infusion.^{8,9,12} Information about the Nancy IBD cohort is reported to the Commission Nationale de l'Informatique et des Libertés (no. 1404720), which supervises the implementation of the act regarding data processing, data files and individual liberties that came into effect on 6 January 1978, and was amended on 6 August 2004, to protect the personal data of individuals.^{13–15} Only descriptive statistics were used.

3. Results

3.1. Baseline Characteristics of the 63 Patients

A total of 63 patients with IBD were included in the study. A total of 182 1-h IFX 10 mg/kg infusions were administered to these patients. Characteristics of the patients are given in Table 1. The median age was 40 years (range, 21–77), 46% were females and two-third of patients had CD (68%). The median disease duration was 11 years (range, 1–51). The median number of IFX infusions since drug initiation was 22 (range, 5–74). Concomitant use of immunomodulators (azathioprine or methotrexate) was reported in 17 patients (26%). Only three patients received concomitant systemic steroids. Of the 43 patients with CD, 2, 35 and 6 patients were classified as A1, A2 and A3 according to the Montreal classification, respectively. 17% (n = 11) had pure ileal disease (L1), 7% (n = 5) had pure colonic disease (L2), and 41% (n = 26) had ileocolonic disease (L3). One individual had upper gastrointestinal disease. Uncomplicated behavior (B1) was reported in half (n = 32) of CD patients. Structuring and penetrating disease were observed in 11% (n = 7) and 6% (n = 4) cases, respectively. Perianal lesions were seen in 22% (n = 14) of patients. Of the 20 patients with UC, 7 had a left-sided disease (E2), while 13 had extensive colitis (E3). After losing response to IFX, all 63 IBD patients had IFX dose intensification: 5 patients had increased dose before shortening the interval, while 15 had shortened intervals before increasing the dose. A total of 15 patients had both increased dose and shortened interval at the same time, and 28 patients had only IFX dose intensification at 10 mg/kg without shortening the interval between infusions. All patients were followed for infusion reactions until their next visit to the hospital.

3.2. Tolerability of One Hour 10 mg/kg Infliximab Infusions

A total of 9 infusion reactions were observed (9/186, 4.8%); details are given in Table 2. No mild acute reactions occurred. Two severe acute reactions were observed. A 28 year-old woman with UC developed a severe anaphylactic reaction occurring immediately after the first 1-h IFX 10 mg/kg infusion. She was receiving concomitant treatment with azathioprine for one year. The outcome was

favorable a few hours after receiving treatment with intravenous antihistaminic and systemic steroids treatment. A 24 year-old woman with CD developed a cutaneous lupus after the second 1-h IFX 10 mg/kg infusion. She was not receiving any concomitant treatment. There was a complete resolution of skin lesions after intravenous steroids administration, but required four days of hospitalization and a dermatologic follow-up. The physician decided to stop IFX treatment in both cases and a switch to adalimumab was efficacious and well tolerated in both patients.

Seven patients experienced delayed reactions (7/186, 3.8%). Only one was severe and occurred in a 30 year-old woman after the first 1-h IFX 10 mg/kg infusion. She had CD and was also treated with methotrexate. She developed severe acne generalis taken in charge by the Dermatology Department and leading to IFX withdrawal. The outcome was favorable 6 weeks after initiation of antibiotics and retinoids. A switch to adalimumab was efficacious and well tolerated, with no recurrence of skin lesions. The 6 remaining patients experienced mild delayed reactions and none of them led to drug withdrawal (Table 2).

4. Discussion

This is the first prospective study formally investigating the tolerability of 1-hour 10 mg/kg IFX infusions in IBD

patients. The rheumatologists reported a good tolerability profile of 1-hour 3 or 5 mg/kg IFX infusions in rheumatoid arthritis (RA), psoriatic arthritis and ankylosing spondylitis patients.^{7,17,18} Therefore, a change in the label of IFX was made in 2006 for patients with RA. The well-tolerated 1-hour IFX infusions in rheumatology led the gastroenterologists to consider a shorter time of IFX infusion in IBD.^{8,9} Recently, two studies from the same group demonstrated that 1-h IFX infusions were well tolerated in IBD patients.^{8,9} Notably, among 4307 IFX infusions administered over 1 hour, no severe infusion reactions were observed.⁸ More recently based on our preliminary experience with 1-hour 10 mg/kg IFX infusions, this drug regimen appeared to be well tolerated in 8 patients.¹¹ However, no conclusions could be drawn due to small sample size.

Sixty-three IBD patients on IFX maintenance therapy (43 CD) received a total 182 1-hour 10 mg/kg infusions. Two patients experienced (2/182, 1%) severe acute infusion reactions consisting on cutaneous lupus and anaphylactic collapse. We also observed one (1/182, 0.5%) severe delayed reaction after the first 1-hour IFX infusion consisting on acne generalis. All 3 reactions led to IFX discontinuation. The two patients who developed severe anaphylactic reaction and acne generalis were on concomitant treatment with immunomodulators (azathioprine and methotrexate, respectively), while the patients who developed cutaneous lupus was receiving IFX monotherapy.

Data from Leuven (Belgium)^{8,9} and from a previous report from Nancy (France)¹¹ can be used as control groups to compare the safety and tolerability of 1-hour 10 mg/kg versus 5 mg/kg IFX infusions in IBD patients. In 2011, no severe infusion reactions were reported in a large retrospective study on patients treated in the same Belgian referral center.⁸ The rate of delayed infusion reactions was similar in 1-h and 2-h infusion group patients in Leuven,⁸ and is also similar to that reported in the present study when considering clinically significant events (0.5%).

Six mild delayed reactions (6/182, 3%) were observed in the 1-h 10 mg/kg IFX group. This is lower than in our previous report on 26 IBD patients treated with 1-h 5 mg/kg IFX infusions (7.7%),¹¹ and broadly similar to that reported in a prospective cohort study from Leuven, with an overall immediate infusion reaction rate of 2.2%.^{8,9} No mild acute reactions were reported in the French multicenter prospective study. Mild acute reactions were reported in 0.6% to 7.7% of IBD patients receiving 1-h 5 mg/kg IFX infusions.^{8,11}

In France, we often stop azathioprine in some IBD patients receiving combination therapy for more than one year, especially young males. Furthermore, we usually optimize anti-TNF treatment before adding azathioprine in patients receiving IFX monotherapy. This may explain the relative low percentage of patients receiving concomitant immunomodulators in our multicenter study (26%). In a landmark study from Leuven, concomitant immunosuppressive agent was not a predictor for acute or delayed infusion reaction.⁸ In our prospective observational study, we could not assess this parameter due to the low number of events. Other factor criteria such as induction therapy and scheduled maintenance therapy were protective factors¹⁶ although conflicting data existed in a prospective cohort from the same referral center.⁸ In our study, all patients received induction therapy

Table 1 Characteristics of the 63 patients (IFX: infliximab).

Number of patients (n)	63
Number of 1-h 10 mg/kg IFX infusion (n)	182
Age (median, range) (years)	40 (21–77)
Female (n, %)	29 (46%)
Crohn's disease (n, %)	43 (68%)
Ulcerative colitis (n, %)	20 (31%)
Disease duration (median, range) (years)	11 (1–51)
Number of infliximab infusions since treatment initiation (median, range) (n)	22 (5–74)
Concomitant steroids (n, %)	3 (4%)
Concomitant immunosuppressants (n, %)	17 (26%)
Adalimumab before IFX initiation (n, %)	5 (7%)
Acute reactions (n, %)	2 (3%)
Delayed reactions (n, %)	7 (11%)
Montreal classification (n, %)	
Crohn's disease (n = 43)	
A1	2 (3%)
A2	35 (55%)
A3	6 (9%)
L1	11 (17%)
L2	5 (7%)
L3	26 (41%)
L4	1 (1%)
B1	32 (50%)
B2	7 (11%)
B3	4 (6%)
P	14 (22%)
Ulcerative colitis (n = 20)	
E1	0
E2	7 (11%)
E3	13 (20%)

Table 2 Details on adverse events (IFX: infliximab).

Reactions	Intervention	Outcome
Severe anaphylactic reaction after one IFX infusion	IFX discontinuation and administration of intravenous steroids in association with an antihistaminic agent	Favorable; switch to adalimumab
Cutaneous lupus after two IFX infusions	IFX discontinuation, hospitalization and dermatologic management	Favorable; switch to adalimumab
Acne generalis a few days after one IFX infusion	Infliximab discontinuation and dermatologic management	Favorable; switch to adalimumab
Crust nose after the first IFX infusion	Local antibiotics	Favorable; continuation of IFX
Sinusitis after the first IFX infusion	Oral antibiotics	Favorable; continuation of IFX
Influenza-like illness after the fourth IFX infusion	Oral medical treatment	Favorable; continuation of IFX
Asthenia after 3 IFX infusions	No specific treatment (unknown etiology)	Favorable; continuation of IFX
Pharyngitis after the fifth IFX infusions	Oral antibiotics	Favorable; continuation of IFX
Mouth aphthae after six IFX infusions	Local treatment	Favorable; continuation of IFX

with IFX infusions at weeks 0, 2 and 6, all patients were on scheduled maintenance therapy according to current recommendations.

In the IBD units of Nancy, Saint Etienne and Nice, all patients received a routine prophylactic pre-medication by intravenous (IV) corticosteroids (hydrocortisone 200 mg) before IFX treatment even though the efficacy of premedication to prevent IFX infusion reactions has yet to be established.^{7,17,18}

A recent meta-analysis of 10 studies comprising 13 147 standard 2-to 3-h and 8497 <1-h IFX infusions in patients receiving IFX therapy for IBD, rheumatoid arthritis, spondyloarthropathy and psoriatic disease, demonstrated that rapid IFX infusions <1-h duration are not associated with an increased risk of IFX reaction in selected patients who previously tolerated three to four standard infusions.¹⁹ However all patients were treated at the standard dose of 5 mg/kg IFX infusions or less.¹⁹ In our study all patients received one hour 10 mg/kg infliximab infusions.

The strengths of our study are the prospective study design allowing us to systematically record all adverse events as well as the relatively high number of 1-h 10 mg/kg IFX infusions (n = 186).

In conclusion, our results suggest that in patients with IBD receiving IFX scheduled maintenance therapy, 1-hour infusion time for 10 mg/kg IFX is well tolerated. Even though all adverse events had a favorable outcome, before considering this option in clinical practice in order to improve patients' satisfaction by having a positive impact on work and quality of life, our findings need to be confirmed in large independent studies.

Conflict of Interest

LPB, consulting and/or lecture fees from Merck, Abbott, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pilège, BMS, UCB-

pharma, Hospira, Takeda; other authors declare no conflict of interests.

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