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BRIEF REPORT

Premedication prevents infusion reactions and improves retention rate during infliximab treatment

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Abstract Infliximab (IFX) is an anti-tumor necrosis factor-alpha antibody used to treat inflammatory joint diseases. Infusion reactions (IR) can occur during and after intravenous administration and often require discontinuation of IFX therapy. This retrospective study aimed at evaluating the incidence of IR in patients with joint inflammatory diseases receiving IFX with and without premedication. Clinical charts of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis patients receiving IFX from January 2002 to December 2014 were reviewed. Patients receiving only one premedication protocol over time were enrolled and clustered based on the type of premedication as follows: group 1 received no premedication; group 2 received paracetamol, esomeprazole, hydrocortisone, and chlorpheniramine maleate; group 3 received paracetamol, hydoxyzine, ranitidine, and 6-methylprednisolone. Adverse events were recorded during the infusion, in the following hours and at control visits. The charts of 105 patients treated with IFX were selected. IR were observed in 23/51 patients of group 1, in 7/35 patients of group 2, and none of 19 patients in group 3. IR incidence was significantly lower in the second ($p = 0.021$) and third ($p < 0.001$) compared to the first group. The incidence of IR was significantly lower in group 3 than group 2 ($p < 0.043$). Moreover, patients in group 1 had a relative risk of developing an IR 2.5 times higher than group 2. In our experience, the use of premedication significantly reduced the number of IR to IFX. In particular, the combination of paracetamol, hydroxyzine, 6-methylprednisolone and ranitidine was more efficacious than paracetamol, esomeprazole, hydrocortisone, and chlorpheniramine maleate combination protocol.

Keywords Ankylosing spondylitis · Infliximab · Infusion reaction · Premedication · Psoriatic arthritis · Rheumatoid arthritis

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Abbreviations

IFX	Infliximab
TNF	Tumor necrosis factor
IV	Intravenous
IR	Infusion reaction

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RA	Rheumatoid arthritis
PsA	Psoriatic arthritis
AS	Ankylosing spondylitis
DMARDs	Disease-modifying antirheumatic drugs
RCT	Randomized clinical trial
ATI	Antibodies to infliximab

Infliximab (IFX), a chimeric mouse-human antibody, targeting tumor necrosis factor (TNF) alpha, reduces the symptoms and induces the remission of joint inflammatory diseases [1]. During and after IFX intravenous (IV) administration infusion reactions (IR) may be observed. Acute IR may occur in 10–40 % of patients [2] and require discontinuation of IFX therapy. Reactions are defined as "acute" when "flushing," chest tightness, dizziness, shortness of breath, headache, hypo/hypertension, nausea, sweating, and a rise in temperature occur during infusion. Symptoms of anaphylaxis, like urticaria and bronchospasms can also be experienced by the patients. After the infusion, delayed reactions may occur between 24 h and 14 days and include arthralgia, myalgia, influenza-like symptoms, headache, tiredness, and "rash" or urticaria. The IR can also be subdivided according to sign and symptoms into mild, moderate or severe. Mild reactions are defined as those that are self-limiting and resolve spontaneously after temporary cessation of infusion or reduction of infusion speed. Moderate IR requires an extended observation period and often discontinuation of infusion. Severe IR may provoke respiratory symptoms or a symptomatic blood pressure drop, anaphylactic or anaphylactoid reaction and need tight monitoring, often for 24 h and occasionally requiring hospitalization [3]. In these cases, IFX should be stopped immediately. However, IFX is an effective therapy which is usually chosen after a range of other therapeutic agents turned out to be unsatisfactory or to cause serious side-effects. For this reason, in patients treated with IFX, treatment discontinuation should be prevented. The mechanisms of IR development may include anaphylactic/anaphylactoid reactions, serum sickness-like reactions and development of IgG antibodies against IFX (ATI) [4]. In practice, IR may be prevented or significantly attenuated using a premedication [5, 6].

The aim of this retrospective study was to evaluate the incidence of IR in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) receiving IFX with and without premedication.

Methods

The clinical charts of patients affected by RA, PsA, and AS treated with IFX (5 mg/Kg), followed up at the therapeutic outpatient clinic of the Division of Rheumatology, Azienda Ospedaliera Universitaria Careggi—University of Florence from January 1st 2002 to December 31st 2014, were reviewed. Patients were enrolled in the study if they did not receive more than one premedication protocol over time. IV IFX was given at 0, 2, and 6 weeks and thereafter every 6–8 weeks depending on the condition of the patient. Those affected by RA and PsA, received IFX in combination with disease-modifying antirheumatic drugs (DMARDs), except when it was not possible due to patients intolerance. Before therapy, all patients underwent latent tuberculosis screening (TST, chest x-ray, and exposure history), hepatitis B, C, and HIV-screening tests, antinuclear and anti-double-stranded DNA antibodies; informed consent was obtained and the

Table 1 Clinical features of the study population

Clinical features	Group 1 (2002–2006)	Group 2 (2007–2011)	Group 3 (2012–2014)	Total (2002–2014)
Patients	51	35	19	105
Sex				
Females	27 (53 %)	19 (54 %)	13 (68 %)	59
Males	24 (47 %)	16 (46 %)	6 (32 %)	46
Median age (years)	54.4 ± 13.6	48 ± 13.9	43.1 ± 15.1	
Disease				
RA	26	9	2	37
PsA	6	6	5	17
AS	19	20	12	51
Concomitant DMARDs				
MTX	17	9	3	29
Leflunomide	6	1	0	7
Others DMARDs	5	16	6	27
Monotherapy	23	9	10	42

Table 2 Number and percentage of infusion reactions in three groups divided also by different diseases

Groups	Infusion reactions
I group (2002–2006): 51 patients	23 (45.1 %)
Rheumatoid arthritis	13 (56.5 %)
Psoriatic arthritis	2 (8.7 %)
Ankylosing spondylitis	8 (34.8 %)
II group (2007–2011): 35 patients	7 (20 %)
Rheumatoid arthritis	2 (28.6 %)
Psoriatic arthritis	2 (28.6 %)
Ankylosing spondylitis	3 (42.8 %)
III group (2012–2014): 19 patients	0
Rheumatoid arthritis	0
Psoriatic arthritis	0
Ankylosing spondylitis	0

study was approved by the Ethics Committee of Azienda Ospedaliera Universitaria Careggi.

Patients treated with IFX from 2002 to 2014, were divided into three groups based on the type of premedication:

- Group 1: received IFX without premedication (from 1 January 2002 to 31 December 2006);
- Group 2: prior IFX received medication with paracetamol (500 mg orally), IV esomeprazole 40 mg, IV hydrocortisone 5 mg/Kg, IV chlorpheniramine maleate 10 mg (from 1 January 2007 to 31 December 2011);
- Group 3: prior IFX received medication with paracetamol (500 mg orally), hydroxyzine (25 mg) orally, IV ranitidine 50 mg and IV 6-methylprednisolone 100 mg (from 1 January 2012 to 31 December 2014).

Blood pressure, body temperature and pulse were monitored before, during and immediately after the infusion of IFX. Adverse events were recorded during the treatment and in the following hours and weeks (reported at control visits). Patients with a history of atopy or previous allergic reactions to others drugs, foods or inhalants were not included in the study.

Continuous variables were described by mean and standard deviation. Qualitative variables were described reporting the number and the percentage for each category. The difference in the proportion of allergic reactions in the three groups was evaluated by Chi-square test. The difference in the retention rate curves to the therapy (Kaplan-Meyers curves) was assessed by log-rank test. The relative risk of developing an allergic reaction was estimated by Cox model.

Results

The charts of 169 patients treated with IFX were reviewed and 105/169 patients were selected according to inclusion criteria; clinical features of study population are reported in Table 1. Overall 42/105 (40 %) patients were treated with IFX monotherapy due to DMARDs intolerance. In the first group there were 51 patients (26 RA, 6 PsA, 19 AS): in these patients premedication was not employed and 23/51 patients (45.1 %) experienced IR to IFX (13 with RA, 2 PsA, and 8 AS) (Table 2). In the second group there were 35 patients (9 RA, 6 PsA, 20 AS) and 7/35 patients (20 %) experienced a reaction to IFX (2 RA, 2 PsA and 3 AS) (Table 2). In the third group (19 patients: 2 RA, 5 PsA, 12 AS) when premedication was further

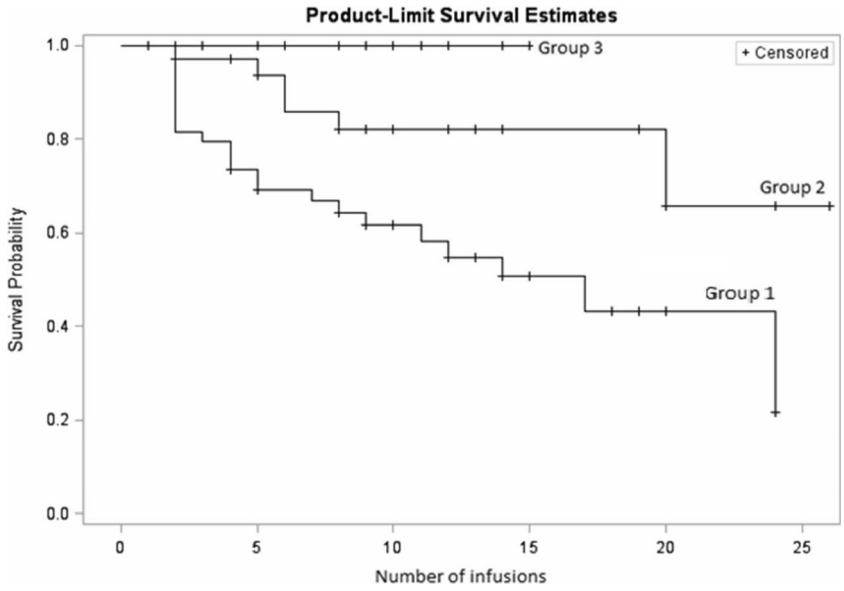

Fig. 1 Kaplan-Meyers curves of the retention rate of IFX in the three groups

implemented, none of the 19 patients experienced IR (Table 2). During the infusion, a total number of 25 (83.3 %) mild and 5 (16.7 %) moderate IR were observed, while no severe IR and no anaphylactic reactions occurred.

The number of IR to IFX was statistically significantly lower in the second ($p = 0.021$) and third ($p < 0.001$) group compared to the first. In the third group IR were absent and therefore it resulted significantly also lower when compared to the second group ($p < 0.043$). In the first group 3/23 moderate and 20/23 mild IR were observed; in the second group 6 mild IR and 1 moderate IR were developed. Delayed reactions were never reported by the patients.

Moreover, patients in the first group had a relative risk of developing an IR 2.5 times higher than in the second group. It was impossible to determine the relative risk of the third group because no IR was observed. In Fig. 1 the Kaplan-Meyer curves of the retention rate of IFX in the three groups are shown. Clearly, patients of the second and third group have a longer retention rate and have a significantly lower number of IR. The statistical analysis underlines a significant difference between the curves of the three groups (p value = 0.002). Actually, group 3 showed the best retention rate in comparison to the other two groups.

Conclusions

In clinical practice, IR to IFX are common and may occur in 10–40 % of patients [2], although serious events are rare. The premedication with antihistamine and corticosteroid is today considered the standard procedure to minimize the risk of IR [7, 8]. Before infusions, premedication (consisting of paracetamol, antihistamines and/or corticosteroids) is often routinely administered to prevent the occurrence of IR. However, solid evidence that prophylactic medication can prevent IR is lacking. No randomized clinical trial (RCT) has been conducted comparing patients treated with and without antihistamines and/or paracetamol as prophylactic premedication before infusion. One double-blind RCT compared the prophylactic administration of betamethasone (0.15 mg/kg) before infusion with placebo: number of IR was even higher in the betamethasone group, but the difference was not statistically significant [9].

In a RCT with IFX, 1 % of patients with psoriasis developed a severe IR and similar results are seen in patients treated with IFX for other indications [10, 11]. Also the symptoms [10, 11] and mechanisms of IR are thought to be comparable for all patients treated with IFX, independent from indication of use. The exact mechanisms of IR development are not yet clear, although several factors and possible mechanisms have been suggested. These include anaphylactic/anaphylactoid reactions, serum sickness-like reactions, and development of IgG antibodies against IFX [12]. Treatment with IFX may elicit the development of human antichimeric antibodies, mostly called ATI [12], that develop soon after initiation of treatment [13]. In a retrospective cohort study, a strong correlation between the concentration of ATI and the incidence of IR was shown [13]. It has clearly been demonstrated that when ATI are present the number of IR is significantly higher [14, 15]. Our retrospective study has some limitations due to the small sample size, the retrospective nature and the lack of another control groups.

The prevention of IR is very important in clinical practice both for patient safety and for drug retention. In our experience, the use of premedication reduced significantly the number of IR to IFX. In particular, the combination of oral paracetamol, hydroxyzine, 6-methylprednisolone and IV ranitidine was more efficacious than the use of paracetamol, esomeprazole, hydrocortisone and chlorpheniramine maleate. Likely, the role of ranitidine (as H2 blockers) could have contributed to the further reduction of IR. However, our data may be helpful in practice to guide the choice of the drugs that can be used as premedication to prevent or at least limit the number of IR.

Authors' contributions Francesca Bartoli participated in the design of the study, participated in the draft of the manuscript.
Cosimo Bruni participated in the draft of the manuscript.
Laura Cometi participated in the draft of the manuscript.
Jelena Blagojevic participated in the draft of the manuscript.
Ginevra Bruni participated in the draft of the manuscript.
Lorenzo Tofani performed statistical analysis and participated in the draft of the manuscript.
Felice Galluccio participated in the draft of the manuscript.
Daniel E Furst participated in the draft of the manuscript.
Marco Matucci-Cerinic conceived the study and participated in the draft of the manuscript.

Compliance with ethical standards The study was approved by the Ethics Committee of Azienda Ospedaliera Universitaria Tareggi.

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Disclosures None.

References

1. Furst DE, Keystone EC, So AK, Braun J, et al. (2013) Updated consensus statement on biological agents for the treatment of rheumatic diseases. Ann Rheum Dis 72(Suppl 2):ii2–i34
2. Lecluse LL, Piskin G (2008) Review and expert opinion on prevention and treatment of infliximab-related infusion reaction. Br J Dermatol 159:527–536
3. Steenholdt C, Svenson M, Bendtzen K, et al. (2011) Severe infusion reactions to infliximab: aetiology, immunogenicity and risk

factors in patients with inflammatory bowel disease. Aliment Pharmacol Ther 34:51–58

4. Okuyama A, Nagasawa H, Suzuki K, Kameda H, Kondo H, Amano K, Takeuchi T (2011) Fcγ receptor IIIb polymorphism and use of glucocorticoids at baseline are associated with infusion reactions to infliximab in patients with rheumatoid arthritis. Ann Rheum Dis 70:299–304
5. Lequerré T, Vittecoq O, Klemmer N, et al. (2006) Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. J Rheumatol 33:1307–1314
6. Antoni C, Kalden JR (1999) Combination therapy of the chimeric monoclonal anti-tumor necrosis factor alpha (infliximab) with methotrexate in patients with rheumatoid arthritis. Clin Exp Rheumatol 17:S73–S77
7. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, et al. (2003) The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol 98:1315–1324
8. Bermejo F, Lopez San Roman A, Algaba A, Van Domselaar M, Carneros JA, Rivero M, et al. (2008) Efficacy of premedication with intravenous corticosteroids and antihistaminics in preventing infusion reactions to infliximab. Gastroenterol Hepatol 31:629–632
9. Sany J, Kaiser MJ, Jorgensen C, et al. (2005) Study of the tolerance of infliximab infusions with or without betamethasone premedication in patients with active rheumatoid arthritis. Ann Rheum Dis 64:1647–1649
10. Gottlieb AB, Evans R, Li S, et al. (2004) Infliximab induction therapy for patients with severe plaque type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 51:534–542
11. Reich K, Nestle FO, Papp K, et al. (2005) Infliximab induction and maintenance therapy for moderate to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 366:1367–1374
12. Wolbink GJ, Vis M, Lems W, et al. (2006) Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis Rheum 54:711–715
13. Baert F, Noman M, Vermeire S, et al. (2003) Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. N Engl J Med 348:601–608
14. Farrell RJ, Alsahli M, Jeen YT, et al. (2003) Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. Gastroenterology 124:917–924
15. Hanauer SB, Wagner CL, Bala M, et al. (2004) Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol 2:542–553