



ORIGINAL ARTICLE

Infliximab in inflammatory bowel disease. Is premedication necessary? ☆



Paulina Nuñez F.^a, Rodrigo Quera^{b,*}, Daniela Simian^b, Lilian Flores^a, Carolina Figueroa^a, Patricio Ibañez^a, Udo Kronberg^c, Jaime Lubascher^a, Gonzalo Pizarro^a

^a Programa Enfermedad Inflamatoria Intestinal, Departamento Gastroenterología, Hospital San Juan de Dios Hospital, Universidad de Chile, Santiago, Chile

^b Clínica Las Condes, Santiago, Chile

^c Unidad de Coloproctología, Departamento de Cirugía, Clínica Las Condes, Santiago, Chile

Received 24 May 2020; accepted 13 July 2020

Available online 25 April 2021

KEYWORDS

Infliximab;
Adverse reactions;
Inflammatory bowel disease;
Crohn's disease;
Ulcerative colitis

Abstract

Background: The use of infliximab (IFX) in inflammatory bowel disease (IBD) has been associated with a 1–6% risk of infusion reactions. The usefulness of premedication with corticosteroids, paracetamol and /or antihistamines is controversial.

Aim: The aim of this study is to assess, in IBD patients on IFX, whether there are differences in secondary reactions to the infusion between those who use premedication or not.

Methods: A retrospective cohort study was performed identifying patients with a diagnosis of IBD who received IFX at our institution between January 2009 and July 2019. Acute reactions were defined as those that occurred in the first 24 h post infusion and late reactions for more than 24 h. Infusion reactions were classified as mild, moderate and severe. Descriptive and association statistics were used (χ^2 ; $p < 0.05$).

Results: Sixty-four patients were included with 1,263 infusions in total, 52% men. Median infusions per patient was 22 (2–66). All induction infusions were administered with premedication, and in maintenance in 57% of them. Premedication was given with hydrocortisone, chlorphenamine and paracetamol. Most of reactions were acute, mild or moderate in severity and no patient needed to discontinue IFX. In the maintenance group, there were 9/718 (1.2%) infusion reactions with premedication and 4/358 (1.1%) without it ($p = 0.606$). In the induction group, there were 8/187 (4.3%) infusion reactions, significantly higher when compared with both maintenance groups.

☆ Please cite this article as: Nuñez F. P, Quera R, Simian D, Flores L, Figueroa C, Ibañez P, et al., Infliximab en enfermedad inflamatoria intestinal. ¿Es necesario premedicar? Gastroenterol Hepatol. 2021;44:321–329.

* Corresponding author.

E-mail address: rquera@clc.cl (R. Quera).

Conclusions: In this group, premedication use during maintenance was not effective at reducing the rate of infusion reactions. These results suggest that premedication would not be necessary. © 2020 Elsevier España, S.L.U. All rights reserved.

PALABRAS CLAVE

Infliximab;
Reacciones adversas;
Enfermedad
inflamatoria
intestinal;
Enfermedad de
Crohn;
Colitis ulcerosa

Infliximab en enfermedad inflamatoria intestinal. ¿Es necesario premedicar?

Resumen

Introducción: El uso de infliximab (IFX) en enfermedad inflamatoria intestinal (EII) se ha asociado con un riesgo de 1–6% de reacciones a la infusión. La utilidad de premedicación con corticoides, paracetamol y/o antihistamínicos es controvertido.

Objetivo: Evaluar si en pacientes con EII que utilizan IFX hay diferencias en las reacciones secundarias a infusión entre aquellos que utilizan o no premedicación.

Métodos: Estudio descriptivo, observacional, retrospectivo en pacientes con EII, que han utilizado IFX entre enero 2009 y julio 2019. Se definieron como reacciones agudas aquellas ocurridas en las primeras 24 hrs.post infusión y tardías después de ese período, clasificándose en leves, moderadas y severas. Se usó estadística descriptiva y de asociación (χ^2 ; $p < 0,05$).

Resultados: Se incluyeron 1,263 infusiones en un total de 64 pacientes, 52% hombres. Mediana de infusiones por paciente 22 (2–66). El 100% de las infusiones en inducción fueron con premedicación y en mantenimiento el 57%. La premedicación fue realizada con hidrocortisona, clorfenamina y paracetamol. La mayoría de las reacciones fueron agudas, de gravedad leve a moderada y ningún paciente necesitó discontinuar IFX. En mantenimiento hubo 9/718 (1.2%) reacciones a la infusión con premedicación y 4/358 (1.1%) sin ésta, sin diferencias significativas ($p = 0.606$). En inducción hubo 8/187(4.3%) reacciones a la infusión, significativamente mayor al compararlas con ambos grupos de mantenimiento.

Conclusión: En esta cohorte de pacientes, el no usar premedicación en fase de mantenimiento de IFX no aumentó el número de eventos adversos a este fármaco. Estos resultados sugieren que su indicación no sería necesaria.

© 2020 Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

The advent of biological therapy signified a major advance in treating patients with immune-mediated inflammatory diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis, ankylosing spondylitis, psoriasis and psoriatic arthritis.¹ The first anti-tumour necrosis factor (anti-TNF) available as a therapeutic strategy in IBD was infliximab (IFX), an intravenously administered chimeric IgG1 κ anti-TNF- α antibody.²

However, administration of this biological drug has been associated with a risk of either acute or delayed infusion reactions.^{3,4} The acute reactions occur within 24 h of administration and affect somewhere in the region of 5–29% of patients and 6% of infusions.^{3–9} Symptoms can range from mild reactions such as erythema, pruritus, urticaria, fever, chills, myalgia, paraesthesia and asymptomatic hypotension, to severe reactions including anaphylaxis, seizures and symptomatic hypotension.^{3,9} The mechanisms that lead to these acute reactions are still not fully understood.^{4,10–13} Type 1 hypersensitivity reactions have been ruled out, as anti-IFX IgE levels are normal in patients who have had acute post-infusion reactions.¹¹ However, premedication continues to be widely used in clinical practice to prevent acute reactions.^{14–17} This strategy

generally includes the use of corticosteroids (prednisone, dexamethasone, hydrocortisone or methylprednisolone), antihistamines (diphenhydramine, loratadine or cetirizine) and antipyretics (paracetamol).^{7,8,15,18–21} Some have also added antiemetics (ondansetron) and prehydration (normal saline).^{22,23} In a survey that included 376 adult and paediatric gastroenterologists, 70% reported having prescribed an antihistamine, 64% paracetamol and 48% a corticosteroid before each IFX infusion.¹⁶

Delayed reactions appear from 24 h to 14 days after the administration of the biological drug and occur in up to 3% of infusions.^{3,4,9} The most common symptoms are itchy rashes, fever, myalgia and arthralgia.³ The pathogenesis of these reactions is due to a variety of local and systemic inflammatory responses caused by complement fixation and activation which would be triggered by the binding of IFX to anti-IFX antibodies.⁴ Given the lack of evidence to support the use of premedication or clearly define which group of patients this strategy would benefit, a number of studies have questioned its effectiveness, particularly in patients on maintenance therapy.^{7,8,22–25}

The aim of this study was to assess the effectiveness of premedication in the prevention of acute and delayed adverse reactions after IFX infusion, both in the induction and maintenance phases.

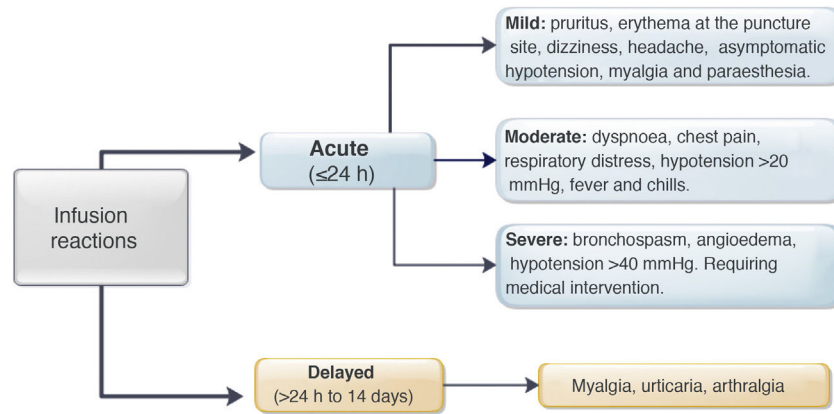


Figure 1 Post-infusion reactions.

Patients and methods

Observational, descriptive, cross-sectional, analytical study in patients ≥ 18 years of age with a confirmed diagnosis of Crohn's disease (CD), ulcerative colitis (UC) or IBD unclassified, who received IFX from January 2009 to July 2019 in induction and/or maintenance phases, and who were included in the Clínica Las Condes [Las Condes Clinic] Inflammatory Bowel Disease Programme. Patients who were administered the biological drug at another centre were excluded.

Demographic variables (age, gender and smoking) and clinical variables (diagnosis, Montreal classification, years since onset of disease, years since admission to the IBD Programme, current treatment with mesalazine, thiopurines (azathioprine/6-mercaptopurine) and methotrexate, induction or maintenance phase with IFX (dose, duration of infusion and number of weeks since the previous infusion), levels of IFX (measured by ELISA with upper limit $>12 \mu\text{g/mL}$) and anti-IFX antibodies, optimisation requirements (if necessary to increase the dose or shorten the frequency of IFX administration), history of previous IFX use (reason for discontinuation, including loss of response, lack of adherence, withdrawal of biological drug due to clinical remission and mucosal healing), history of surgery for IBD and drug allergies) were obtained from the Clínica Las Condes registry of IBD patients, which is kept for research purposes and was approved by the local Ethics Committee in April 2012.

When starting treatment with IFX, the patients received 5 mg/kg at week 0, week 2 and week 6 (induction phase). In the case of severe steroid-refractory UC, at the discretion of the treating gastroenterologist, an optimised scheme was indicated (10 mg/kg and/or administration at week 0, week 1 and week 4). During the maintenance phase, the dose was 5 mg/kg every eight weeks. Adjustments of doses (10 mg/kg) and intervals (every four or six weeks) in this phase were made according to clinical activity and, if available, levels of IFX and anti-IFX antibodies.

Regarding premedication, the type of drug (hydrocortisone, prednisone, paracetamol, chlorphenamine or other type) was recorded, along with its dose and route of delivery. All acute infliximab-related infusion reactions were recorded, including the symptoms, treatment provided,²⁷ and need for emergency medical assessment, hospitalisa-

tion and desensitisation. The severity of the reaction was classified according to the definitions identified as mild, moderate or severe (Fig. 1).^{3,9} In patients with delayed reactions (1–14 days), symptoms and required treatment were recorded.²⁷ Patients at high risk of infusion reaction were defined as those with a history of prior reaction to IFX, delay in infusions (≥ 10 weeks since the previous infusion) or reintroduction of the biological agent after a period of suspension (≥ 20 weeks between infusions).^{24,26–29} Low-risk patients were those who did not meet any of the above criteria.

This study was approved by the institution's Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

In view of the fact that a reaction could occur with one infusion and not subsequently occur again in the same patient, each infliximab administration was considered as a single event and both risk stratification and frequency of infusion reaction were determined. The results of the study were analysed using the R Commander software program. Categorical variables were analysed through absolute frequencies and percentages. Continuous variables were described in terms of measures of central tendency and dispersion depending on data distribution (mean and standard deviation for normal distribution, and median and interquartile range for non-normal distribution). Continuous variables were compared using the Mann-Whitney U test or Student's t test, depending on the distribution. Percentage relative frequency was used for categorical variables, and the chi-squared test was used for comparative statistical analysis. A p value ≤ 0.05 was considered statistically significant.

Results

Patients

The study included 1,263 IFX infusions in a total of 64 patients. The demographic and clinical data for the patients are shown in Table 1. Forty patients with a diagnosis of CD, 23 with UC and one with IBD unclassified participated

Table 1 Clinical and demographic characteristics of patients with infliximab.

n = 64 patients	n (%)
<i>Diagnosis</i>	
Ulcerative colitis	23 (36)
Crohn's disease	40 (63)
Chronic colitis, unclassified	1 (1)
<i>Age (years)</i> [≈]	34 (16–74)
<i>Gender</i>	
Male	33 (52)
Female	31 (48)
<i>Time since onset (years)</i> [≈]	5 (0–49)
<i>Surgery</i>	
Gastrointestinal	16 (25)
Perianal	11 (17)
<i>Time from diagnosis to use of infliximab (years)</i> [≈]	4.5 (0–38)
<i>Previous biological therapies</i>	
Naive	57 (89)
Previous use of Adalimumab	3 (5)
Previous use of Infliximab (more than 1 year)	4 (6)

[≈] (median; range).

in this study; 52% were male, with a median age of 34 (range 16–74), and a median time since disease onset of five years (range 0–49 years). Sixty-two patients had at some point been on combination therapy (IFX plus thiopurines/methotrexate). In relation to IFX, 89% of the patients had not used another biological drug and in four patients it was reintroduced as a strategy more than one year after the last dose (for non-medical reasons). None of the patients had a history of atopy, allergy or anaphylaxis to any drug.

Infusions

The median number of infusions per patient was 22 (range 2–66). All the patients received the original IFX (Remicade®) and 85% of the infusions were given in the maintenance phase. Both in induction and maintenance, the IFX dose most used was 5 mg/kg (89% and 79% respectively) (Table 2). In 74% of cases, the IFX infusions were administered over three hours, in 18% over two hours, and in 8% over more than three hours (up to eight hours). In two patients, IFX desensitisation was performed as per protocol,^{4,30} with the drug being administered over eight hours in one of them. All (100%) of the infusions in induction and 57% in maintenance were administered after premedication. The premedication consisted of hydrocortisone (100 mg in 95% and 200 mg 5%), chlorphenamine (10 mg) and paracetamol (1 g) in all patients. None of the patients received prehydration (normal saline or lactated Ringer's solution) or antiemetics (ondansetron or domperidone) as part of their premedication.

Of the 1,263 infusions analysed in this study, 64 (5%) were defined as high risk: 52 due to a history of an acute reaction after infliximab administration, eight due to a delay in the infusions, and four due to reintroduction of the biolog-

Table 2 Infliximab infusion characteristics.

n = 1,263	n (%)
<i>Induction</i>	
<i>Dose</i>	
Standard or conventional	167 (89)
Optimised (10 mg/kg or accelerated 0–1–4 weeks)	20 (11)
<i>Induction concomitant therapies</i>	
Monotherapy	30 (16)
Combination therapy (thiopurines/methotrexate)	157 (84)
Premedication	187 (100)
<i>Infusion duration</i>	
2 h	23 (12)
3 h	156 (83)
More than 3 h (up to 8 h)	8 (5)
<i>Maintenance</i>	1,076 (85)
<i>Dose</i>	
Standard or conventional	845 (79)
Optimised (10 mg/kg every 4–6 weeks)	231 (21)
<i>Maintenance concomitant therapies</i>	
Monotherapy	312 (29)
Combination therapy (thiopurines/methotrexate)	764 (71)
Premedication	613 (57)
<i>Infusion duration</i>	
2 h	912 (85)
3 h	71 (7)
More than 3 h (up to 8 h)	93 (9)

ical agent more than 10 weeks after the last infusion. In this group, 46 doses were administered during the maintenance phase and in 57% the infliximab dose was 10 mg/kg. Premedication was indicated in 85% of the infusions in this group. There were 10 (16%) acute infusion reactions (four in induction and six in maintenance), all with premedication. All the adverse events in the induction phase occurred with the second dose of IFX, with the patients having been premedicated. In maintenance, three events occurred despite the patients having received premedication (Table 3).

The remaining 1,199 (95%) infusions were classified as low risk for an acute reaction to IFX; 169 (14%) were induction doses and in 97% the dose was 5 mg/kg. Premedication was given in 100% of these cases, with eight acute reactions occurring after IFX administration (three in induction and five in maintenance).

IFX levels were measured in 79 infusions, in a total of 32 patients (Table 3). Nine patients had two measurements and 13 more than three measurements during the study period. The levels ranged from 0.01 to 52.4 µg/mL. The presence of anti-IFX antibodies was measured in 14 infusions; two patients had two measurements. Antibody levels were elevated in five infusions (median 45.6 µg/mL, range 26.5–125).

Table 3 Acute post-infusion reactions.

Infusions 1,263	No reaction 1,245 n = (%)	Acute reaction 18 n = (%)
Induction* = 187 (16)	180 (96)	7 (4)
<i>Infliximab dose</i>		
5 mg/kg	162 (90)	7 (10)
10 mg/kg	18 (20)	0 (0)
<i>Combination therapy</i>		
Yes	156 (87)	3 (43)
No	24 (13)	4 (57)
<i>Infusion duration</i>	21 (12)	2 (29)
2 h	138 (76)	4 (57)
3 h	21 (12)	1 (14)
>3 h		
<i>Premedication</i>		
<i>Type of infusion</i>	180 (100)	7 (100)
High risk	14 (7)	4 (2)
Low risk	166 (89)	3 (1)
Maintenance = 1,076 (84)	1,065 (99)	11 (1)
<i>Infliximab dose</i>		
5 mg/kg	832 (78)	10 (91)
10 mg/kg	228 (22)	1 (9)
<i>Combination therapy</i>		
Yes	749 (70)	7 (64)
No	316 (30)	4 (36)
<i>Infusion duration</i>		
2 h	199 (19)	0 (0)
3 h	773 (72)	10 (91)
>3 h	93 (9)	1 (9)
<i>Premedication</i>		
Yes	709 (67)	9 (82)
No	356 (33)	2 (18)
<i>Type of infusion</i>		
High risk	40 (4)	6 (0.6)
Low risk	1,025 (95)	5 (0.4)
<i>Infliximab levels n = 79</i>		
Within range or high (>3 µg/mL)	56 (71)	0 (0)
Low (<3 µg/mL)	22 (28)	1 (1)
<i>Antibodies n = 14</i>		
High (>10 µg/mL)	4 (29)	1 (7)
Low (<10 µg/mL)	9 (64)	0 (0)

* Neither Infliximab nor antibody levels were measured during induction.

Acute reactions

Eighteen acute reactions occurred in this study (1.4% of the infusions), affecting nine patients (14%), with seven of the reactions being in patients with CD. A description of these events, their severity and management is given in Table 4. In terms of severity, 13 were classified as mild, two as moderate and three as severe. The three severe acute reactions were in the group that had received premedication (Fig. 2). In one of these patients, IFX had to be temporarily discontinued, and the desensitisation protocol was applied in two

of them, with a good response.^{4,30} Seven of the acute reactions occurred in the induction phase, six after the second dose. The other 11 reactions occurred during the maintenance phase, nine of them in patients who had received premedication (Fig. 2). The strategies most commonly used to manage acute reactions were decreasing the infusion rate (62%) and stopping the infusion (17%) (Table 4). It was not necessary to discontinue IFX and switch biological drug in any of the patients.

In the univariate analysis, being at high risk was associated with more acute reactions in both induction ($p < 0.0001$)

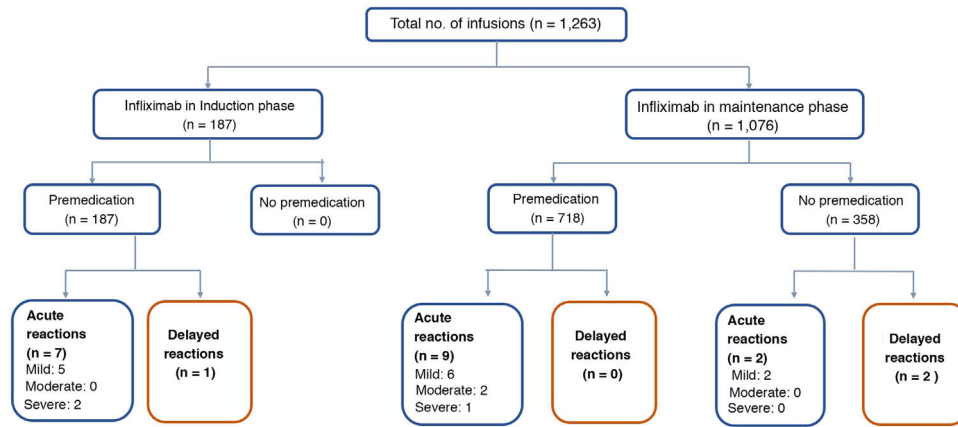


Figure 2 Type of reaction with or without premedication.

Table 4 Acute infusion reactions.

n = 18	n (%)
<i>Symptoms reported</i>	
Palpitations	4 (22)
Dizziness	3 (17)
Asymptomatic hypotension	3 (17)
Skin rash	3 (17)
Myalgia	2 (11)
Difficulty breathing	1 (5)
Severe hypotension	1 (5)
Anaphylaxis	1 (5)
<i>Symptom severity</i>	
Mild	13 (72)
Moderate	2 (11)
Severe	3 (17)
<i>Treatment</i>	
Infusion rate reduced	11 (62)
Infusion stopped	3 (17)
Blood volume restored	2 (11)
Oxygen	1 (5)
Emergency department	1 (5)

and maintenance ($p=0.00007$). The use of immunomodulators was associated with a lower rate of adverse reactions, but this was only in the induction phase ($p=0.0014$) (Table 3).

Delayed reactions

Only three delayed reactions (0.2% of infusions) were identified in this study. One patient reported myalgia during induction. The other two events occurred in the maintenance phase: one patient who received premedication had arthralgia, and the other, with no premedication, had urticaria. All three patients received chlorphenamine and paracetamol as treatment for these delayed reactions. In only one patient the IFX dose was decreased from 10 mg/kg to 5 mg/kg every eight weeks. None of the patients had elevated levels of anti-IFX antibodies.

Overall, in the maintenance phase, there were 9/718 (1.2%) reactions to the IFX infusion with and 4/358 (1.1%) without premedication, with no significant differences ($p=0.606$). In the induction phase there were 8/187 (4.3%) reactions to the infusion, significantly higher compared to both maintenance groups (without premedication $p=0.02$ and with premedication $p=0.008$).

Discussion

Advances have been made in the treatment of IBD over the last 30 years or so with the advent of biological therapy (anti-TNF, anti-integrins and anti-p40 IL-12/23) and, more recently, the use of small molecules. These developments have helped alter the course of the disease and, with that, the quality of life of these patients.³¹ IFX in particular, in an induction and maintenance regimen, has proven to be highly effective in reducing inflammation, achieving clinical and endoscopic remission, and reducing the number of hospital admissions and the need for surgery.^{32,33} Early use of IFX has also been shown to change the course of IBD.³⁴

IFX infusion reactions, although uncommon,³⁻⁹ are a concern to both the patient and the treating team due to the risk of having to discontinue therapy, especially considering the still limited therapeutic strategies available in the management of IBD. Our results confirm the low rates of acute reactions within the first 24 h (1.4% of infusions, 14% of patients) and delayed reactions from 24 h to 14 days (0.2% of infusions, 4.7% of patients).

In terms of the severity of the acute reactions, 87% were classified as mild to moderate, very similar to that described by other authors.^{9,14,23} In the study by Gold et al.,²³ which included 7,090 infusions, 83% of the reactions were mild to moderate. However, the rate of mild events was higher in our study (72% vs 57%). The reason for these differences may be the number of patients included, and thus the number of infusions. One recent study of patients who received IFX in an outpatient clinic confirmed that the percentage of serious reactions is low (11.5% of reactions, 0.2% of all infusions).⁹ The most common post-infusion symptoms in our study were palpitations, dizziness, asymptomatic hypotension and skin rash. Other studies have mentioned additional symptoms

such as itching, dyspnoea, myalgia, nausea, urticaria and headache.^{7,9,23}

Of the acute infusion reactions, 39% occurred during the induction phase. Some studies have pointed out that this percentage can reach 100% of events, especially after the second dose.^{3,14} In our study, six of the seven acute reactions in the induction phase occurred after the second dose.

Sixty-four (5%) of our infusions were defined as high risk and acute reactions occurred following six of those (9%). In a study that included 986 high-risk infusions, only 5.4% had an acute infusion reaction, unrelated to the use of premedication, regardless of the type of drug used as strategy.²³ In our study, however, there was a higher rate of acute infusion reactions both during induction and maintenance in the high-risk group. Prospective studies with a larger number of patients would help define the effectiveness of premedication in this scenario. In the low-risk group, premedication has been shown to have no protective effect, with adverse infusion reactions only occurring in 1% of cases.²³ Our results confirm this trend; only 1% of the infusions in this group caused an acute reaction.

Combination therapy with IFX and thiopurines/methotrexate has been suggested as a strategy for decreasing the likelihood of post-infusion reactions.^{4,35} In our study, the combined use of immunomodulators in the induction phase was associated with fewer adverse events. Other studies have shown that patients who develop anti-IFX antibodies have twice the risk of developing an acute reaction and up to six times the risk of a serious IFX infusion event.^{13,37} One randomised controlled study showed that, although premedication with hydrocortisone decreased the formation of antibodies against IFX, it did not eliminate the risk of developing an infusion reaction.²² However, other studies have not managed to confirm this effect in patients receiving IFX treatment in a maintenance regimen.³⁶ In our study, only one of the patients who had antibodies had an infusion reaction. It is important to point out that the technique used to measure the presence of antibodies only allowed them to be measured when IFX levels were low or absent.³⁸

Although there are no specific guidelines for the management of acute post-IFX reactions, according to treatment recommendations based on case studies^{3,8,9,23} and expert opinion,^{4,39} decreasing the infusion rate, temporary discontinuation of IFX, use of normal saline or lactated Ringer's solution and the use of drugs are the measures most often suggested, similar to those that were applied in our patients. Unlike other studies,^{9,14,39} definitive suspension of biological therapy was not required in any of our patients.

Delayed reactions after IFX administration only occurred on three occasions (0.2% of infusions), confirming the low frequency shown in other studies.^{3,4,9} In the Cheifetz et al. study³ only 0.6% of patients had a delayed reaction within 14 days after administration of infliximab. As described by other authors,^{3,4,9} the most common symptoms were urticaria, arthralgia and myalgia. The suggested treatment for these reactions is paracetamol and antihistamine,^{3,4,9} and this is what was used in our patients.

Although premedication with corticosteroids, antihistamines and antipyretics is frequently used to prevent the development of an IFX infusion reaction, adequate validation of the use of these treatments is lacking.¹⁶ Our study

confirms that premedication with corticosteroids, paracetamol and chlorphenamine during the maintenance phase does not reduce the risk of developing an acute infusion reaction (nine of the 11 events were in the group premedicated prior to IFX administration). Studies have shown that premedication, either with hydrocortisone²² or the combination of intravenous steroids, antihistamines and paracetamol, does not prevent the development of acute IFX infusion reactions.^{7,9} When classifying the groups according to risk, our results also failed to show that premedication reduced the risk of an acute infusion reaction in the high-risk group, confirming the findings reported by others.²³ Moreover, also in line with other authors,⁴⁰ premedication did not reduce the risk of developing a severe acute reaction. The three severe acute reactions occurred in patients who had received premedication. We did not assess the use of normal saline as premedication, but Gold et al.²³ showed that the use of prehydration, alone or in combination with other drugs, could reduce the risk of an acute IFX infusion reaction in high-risk patients. However, validation of these results is obviously required before such an indication can be suggested.

It is important to bear in mind that, like any drug, corticosteroids and antihistamines can also cause undesirable effects. Those associated with corticosteroids include drowsiness, blurred vision, abdominal pain and decreased alertness.⁴¹ Moreover, the use of corticosteroids as premedication is not optimal considering that patients with IBD have more exposure to these drugs as a treatment strategy for their underlying disease, along with the accompanying complications.³¹ Antihistamines can be associated with drowsiness and decreased alertness, which can prolong the patient's stay at the infusion clinic or make it necessary for the patient to be accompanied.⁴² Interestingly, in a prospective study that included 1,632 patients with rheumatological conditions and IBD, the use of diphenhydramine was associated with an increased incidence of infusion reactions (OR 1.58; $p = 0.0007$).⁷

Prospective studies have confirmed the effectiveness of biosimilar drugs in inducing and maintaining remission in patients with CD and UC.³⁹ Although the biosimilar Remsima® is available in Chile, no patients received it during the time of this study. There is evidence that biosimilars would have a low immunogenicity and a similar rate of acute infusion reactions to the original drug, being higher in patients with previous exposure to an anti-TNF who developed antibodies during the induction phase.⁴³

Our study has certain strengths. As it is a cross-sectional study and shows the experience of a tertiary hospital with an established IBD programme, it provides insight into routine clinical practice. Unlike other studies,^{9,16,23} the premedication was standardised in all the patients; the use of corticosteroids, paracetamol and chlorphenamine in this group means that real conclusions can be drawn about the effectiveness of this strategy in preventing the development of infusion reactions. Nevertheless, we know there are also limitations. The number of patients included in this study is low compared to other studies. However, from the number of infusions in the maintenance phase, with or without premedication, we are able to conclude that, in patients without risk factors for developing adverse events, the use of premedication may not be effective in preventing acute

or delayed IFX infusion reactions. Secondly, as all patients in the induction phase were premedicated, we cannot confirm its effectiveness in this scenario and advise whether or not to use this strategy. Thirdly, we were not able to accurately define the time between the administration of the premedication, the start of the IFX infusion and the timing of the infusion reaction. The pharmacokinetics of the drugs used in premedication have to be considered when defining their role in the development of infusion reactions, especially when acute. In the Gold et al. study, the majority of acute reactions occurred within 15 min of starting the infusion (data not shown).²³ Last of all, in this study it was not possible to assess the presence of levels and antibodies in all the patients who developed acute or delayed IFX infusion reactions.

In conclusion, our study suggests that acute and delayed IFX infusion reactions are rare, mostly mild to moderate, and can be managed successfully without suspending the biological therapy. Although during the maintenance phase there may be scenarios where premedication should be considered, we suggest not using it routinely. Prospective studies have yet to define the role of this strategy in the induction phase.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

- Melsheimer R, Geldhof A, Apaolaza I, Schaible T. Remicade® (infliximab): 20 years of contributions to science and medicine. *Biologics*. 2019;13:139–78.
- Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's disease cA2 Study Group. *N Engl J Med*. 1997;337:1029–35.
- Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol*. 2003;98:1315–24.
- Lichtenstein L, Ron Y, Kivity S, Ben-Horin S, Israeli E, Fraser GM, et al. Infliximab-related infusion reactions: systematic review. *J Crohns Colitis*. 2015;9:806–15.
- Wasserman MJ, Weber DA, Guthrie JA, Bykerk VP, Lee P, Keystone EC. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. *J Rheumatol*. 2004;31:1912–7.
- Kellsall J, Rogers P, Galindo G, De Vera MA. Safety of infliximab treatment in patients with rheumatoid arthritis in a real-world clinical setting: description and evaluation of infusion reactions. *J Rheumatol*. 2012;39:1539–45.
- Choquette D, Faraawi R, Chow A, Rodrigues J, Bensen WJ, Nantel F. Incidence and Management of infusion reactions to infliximab in a prospective real-world Community Registry. *J Rheumatol*. 2015;42:1105–11.
- Duron C, Goutte M, Pereira B, Bommelaer G, Buisson A. Factors influencing acute infusion reactions in inflammatory bowel disease patients treated with infliximab in the era of scheduled maintenance therapy. *Eur J Gastroenterol Hepatol*. 2015;27:705–11.
- Checkley LA, Kristofek L, Kile S, Bolgar W. Incidence and management of infusion reactions to infliximab in an alternate care setting. *Dig Dis Sci*. 2019;64:855–62.
- Vultaggio A, Matucci A, Nencini F, Pratesi S, Parronchi P, Rossi O, et al. Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions. *Allergy*. 2010;65:657–61.
- Steenholdt C, Svenson M, Bendtzen K, Thomsen OØ, Brynskov J, Ainsworth MA. Severe infusion reactions to infliximab: aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2011;34:51–8.
- Vultaggio A, Maggi E, Matucci A. Immediate adverse reactions to biologicals: from pathogenic mechanisms to prophylactic management. *Curr Opin Allergy Clin Immunol*. 2011;11:262–8.
- O'Meara S, Nanda KS, Moss AC. Antibodies to infliximab and risk of infections reactions in patients with Inflammatory Bowel Disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2014;20:1–6.
- Bermejo F, López San Román A, Algaba A, van Domselaar M, Carneros JA, Rivero M, et al. Efficacy of premedication with intravenous corticosteroids and antihistaminics in preventing infusion reactions to infliximab. *Gastroenterol Hepatol*. 2008;31:629–32.
- Bartoli F, Bruni C, Cometi L, Blagojevic J, Fiori G, Tofani L, et al. Premedication prevents infusion reactions and improves retention rate during infliximab treatment. *Clin Rheumatol*. 2016;35:2841–5.
- Picoraro J, Winberry G, Siegel CA, El-Matary W, Moses J, Grossman A, et al. Premedication use before infliximab administration: a cross-sectional analysis. *Inflamm Bowel Dis*. 2017;23:174–80.
- Ricart E, Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. *Am J Gastroenterol*. 2001;96:722–9.
- Jacobstein DA, Markowitz JE, Kirschner BS, Ferry G, Cohen SA, Gold BD, et al. Premedication and infusion reactions with infliximab: results from a pediatric inflammatory bowel disease consortium. *Inflamm Bowel Dis*. 2005;11:442–6.
- Keshavarzian A, Mayer L, Salzberg B, Garone M, Finkelstein W, Cappa J, et al. A multicenter retrospective experience of infliximab in Crohn's disease patients: infusion reaction rates and treatment persistency. *Gastroenterol Hepatol*. 2007;3:381–90.
- Mantzaris GJ, Viazis N, Petraki K, Papamichel K, Theodoropoulos I, Roussos A, et al. A pilot study comparing hydrocortisone premedication to concomitant azathioprine treatment in preventing loss of response to infliximab. *Eur J Gastroenterol Hepatol*. 2009;21:1042–8.
- Lee TW, Singh R, Fedorak RN. A one-hour infusion of infliximab during maintenance therapy is safe and well tolerated: a prospective cohort study. *Aliment Pharmacol Ther*. 2011;34:181–7.
- Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology*. 2003;124:917–24.
- Gold SL, Cohen-Mekelburg S, Schneider Y, Shen Y, Faggen A, Rupert A, et al. Premedication use in preventing acute infliximab infusion reactions in patients with Inflammatory Bowel Disease: a single center cohort study. *Inflamm Bowel Dis*. 2017;23:1882–9.
- Hutsell SQ, Wu M, Park KT. Frequency of severe infusion reactions associated with outpatient infusion of infliximab without premedications. *J Pediatr Gastroenterol Nutr*. 2017;65:430–1.
- Fumery M, Tilmant M, Yzet C, Brazier F, Loreau J, Turpin J, et al. Premedication as primary prophylaxis does not influence the risk of acute infliximab infusion reactions in immune-mediated

- inflammatory diseases: a systematic review and meta-analysis. *Dig Liver Dis.* 2019;51:484–8.
26. van Wassenae EA, Meester VL, Kindermann A, Koot BGP, Benninga MA, de Meij TGJ. Premedication with intravenous steroids does not influence the incidence of reactions following infliximab infusions in pediatric Inflammatory Bowel Disease patients—a case-control study. *Eur J Clin Pharmacol.* 2019;75:1445–50.
 27. Lecluse LL, Piskin G, Mekkes JR, Bos JD, de Rie MA. Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. *Br J Dermatol.* 2008;159:527–36.
 28. Domenech E, Zabana Y, Manosa M, Garcias-Planella E, Cabré E, Gassukk MA. Infliximab reintroduction is not associated to a higher rate of immune-related adverse effects in patients with inflammatory bowel disease initially treated with a three-infusion induction regimen. *J Clin Gastroenterol.* 2010;44:34–7.
 29. Rubin DT. Restarting biologic agents after a drug holiday. *Gastroenterol Hepatol (NY).* 2019;15:612–5.
 30. Mourad AA, Boktor MN, Yilmaz-Demirdag Y, Bahna SL. Adverse reactions to infliximab and the outcome of desensitization. *Ann Allergy Asthma Immunol.* 2015;115:143–6.
 31. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of Inflammatory Bowel Disease in adults. *Gut.* 2019;68:s1–106.
 32. Papamichael K, Lin S, Moore M, Papaioannou G, Sattler L, Cheifetz AS. Infliximab in inflammatory bowel disease. *Ther Adv Chronic Dis.* 2019;10, 2040622319838443.
 33. Hossain A, Lördal M, Olsson AE, Stortåhls A, Aleman S, Eberhardson M, et al. Sustained clinical benefit, improved quality of life, and reduced intestinal surgery from maintenance infliximab treatment in Inflammatory Bowel Disease. *Scand J Gastroenterol.* 2020;55:178–83.
 34. Ungaro RC, Aggarwal S, Topaloglu O, Lee WJ, Clark R, Colombel JF. Systematic review and meta-analysis: efficacy and safety of early biologic treatment in adult and paediatric patients with Crohn's disease. *Aliment Pharmacol Ther.* 2020;51:831–42.
 35. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet.* 2002;359:1541–9.
 36. Larsen L, Jess T, Drewes AM, Dige A, Fallingborg J, Jacobsen BA, et al. Premedication with corticosteroids does not impact the pharmacokinetics of infliximab in Inflammatory Bowel Disease irrespective of azathioprine cotreatment. *Eur J Gastroenterol Hepatol.* 2019;31:964–7.
 37. Baert F, Drobné D, Gils A, Vande Casteele N, Hauenstein S, Singh S, et al. Early trough levels and antibodies to infliximab predict safety and success of reinitiation of infliximab therapy. *Clin Gastroenterol Hepatol.* 2014;12:1474–81.
 38. Franca R, Curci D, Lucafò M, Decorti G, Stocco G. Therapeutic drug monitoring to improve outcome of anti-TNF drugs in pediatric Inflammatory Bowel Disease. *Expert Opin Drug Metab Toxicol.* 2019;15:527–39.
 39. Al Sulais E, AlAmeel T. Biosimilars to antitumor necrosis factor agents in Inflammatory Bowel Disease. *Biologics.* 2020;10:1–11.
 40. Shivaji UN, Sharratt CL, Thomas T, Smith SCL, Iacucci M, Moran GW, et al. Review article: managing the adverse events caused by anti-TNF therapy in Inflammatory Bowel Disease. *Aliment Pharmacol Ther.* 2019;49:664–80.
 41. Fardet L, Kassir A, Cabane J, Flahault A. Corticosteroid-induced adverse events in adults: frequency, screening and prevention. *Drug Saf.* 2007;30:861–81.
 42. Simons FE, Simons KJ. Histamine and H1-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol.* 2011;128:1139–50.
 43. Bálint A, Rutka M, Végh Z, Kürti Z, Gecse KB, Banai J, et al. Frequency and characteristics of infusion reactions during biosimilar infliximab treatment in Inflammatory Bowel Disease: results from Central European nationwide cohort. *Expert Opin Drug Saf.* 2017;16:885–90.