

# Influence of previous corticosteroid treatment on the efficacy and safety of infliximab therapy in Crohn disease

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## Abstract

To determine the effect of prior corticosteroid treatment on the results of infliximab (IFX) therapy in patients with Crohn disease (CD). Patients with CD treated with at least 3 IFX infusions between March 2009 and April 2017 were divided into steroid group (n=43) and nonsteroid group (n=22) and analyzed retrospectively.

The cumulative probabilities of clinical remission and response to IFX at weeks 14, 30, 54, and 78 were higher in the steroid group, though this difference was not statistical significant. At the mean interval of 11.7 months following the initiation of IFX treatment, the mucosal healing rate was significantly higher in the steroid group (71.0% vs 22.2%,  $P < .01$ ). There was no statistical difference in the incidence of adverse reactions between the 2 groups.

In CD, patients with prior corticosteroid treatment may increase the response rate to IFX therapy.

**Abbreviations:** ATI = anti-infliximab antibody, AZA = azathioprine, CD = Crohn disease, CDAI = Crohn disease activity index, ECCO = European Crohn and Colitis Organization guidelines, HC = hydrocortisone, HGB = hemoglobin, hsCRP = high-sensitivity C-reactive protein, IFX = infliximab, IQR = interquartile ranges, LOR = loss of response, MH = mucosal healing, PLT = platelet count.

**Keywords:** corticosteroid, Crohn disease, infliximab, loss of response, therapy

## 1. Introduction

Crohn disease (CD) is a chronic disease caused by inflammation of the small bowel and/or colon in the form of mucosal ulcers, strictures, or fistulas, which has alternating phases of remission and relapse. Infliximab (IFX), a monoclonal IgG1 antibody against tumor necrosis factor alpha, has been shown to be effective in the induction, as well as maintenance, of remission in patients with CD.<sup>[1,2]</sup> However, according to meta-analysis, the pooled incidence of loss of response (LOR) in patients treated with IFX is 33% (95% confidence interval [CI] 27–40).<sup>[3]</sup> One of the key reasons for the high rate of LOR is the development of an

anti-infliximab antibody (anti-IFX Ab, ATI).<sup>[4]</sup> There are currently no effective strategies to reduce the formation of ATI and maintain the efficacy of IFX. In 2010, Ruffolo et al reported that combination therapy with IFX and azathioprine (AZA) has a greater efficacy than IFX or AZA monotherapy.<sup>[5]</sup> Additionally, a few studies have found that hydrocortisone (HC) premedication can potentially reduce ATI and prevent LOR.<sup>[6,7]</sup>

There is limited data regarding the effect of prior corticosteroid treatment on the efficacy and safety of IFX in Chinese patients. In addition, it has not been reported whether corticosteroid premedication can promote mucosal healing (MH) and increase the risk of infection. The purpose of this study was to investigate the influence of previous corticosteroid therapy on the efficacy and safety of IFX in patients with CD.

## 2. Methods

### 2.1. Study population

This is a single-center retrospective study of patients with CD who were administered IFX therapy between March 2009 and April 2017 at Peking Union Medical College Hospital. This study protocol was approved by the Ethical Committee of Peking Union Medical College Hospital (approval date: September 11, 2018) and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Written, informed consent was obtained from each patient included in the study.

Diagnosis of CD was performed based on the combined assessment of symptomatology, endoscopy, abdominal imaging, and histologic findings according to the European Crohn and Colitis Organization guidelines (ECCO). IFX therapy was indicated as the treatment of moderate-to-severe luminal and/or fistulizing CD in patients who had not responded to aminosalicylates, corticosteroids, and/or immunosuppressants.<sup>[4]</sup> All of the enrolled patients were treated with at least 3 IFX

Editor: Bülent Kantarçeken.

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This work was supported by the Health Research & Special Projects Grant of China (No 201002020).

The authors have no conflicts of interest to disclose.

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Medicine (2019) 98:15(e15189)

Received: 8 November 2018 / Received in final form: 13 March 2019 /

Accepted: 18 March 2019

<http://dx.doi.org/10.1097/MD.00000000000015189>

infusions. All patients received 5 mg/kg IFX intravenously at weeks 0, 2, and 6, as induction therapy. Patients then received 5 mg/kg IFX intravenously every 8 weeks, as maintenance therapy.

Based on the history of prior treatment with corticosteroid, the patients were divided into a steroid group and a nonsteroid group. Prednisone, at an initial dose of 0.75 to 1.0 mg/kg/d, was given for about 4 to 6 weeks. It was then tapered by 5 mg every 1 to 2 weeks to 5 mg/d.

## 2.2. Data collection

For all of the eligible patients, demographic data (sex, age, smoking status) and clinical characteristics were collected from the prospectively maintained database. Clinical characteristics include the time interval between the onset of symptoms and the initiation of IFX therapy, CD-related previous abdominal surgery, the Montreal classification (age, location, and disease behavior), presence of extra-intestinal manifestations, comorbidities, the dose and duration of steroids before IFX therapy, concomitant treatment (5-aminosalicylic acid, AZA, or methotrexate, thalidomide), dose and number of IFX infusions, and adverse events of IFX treatment.

## 2.3. Outcome assessment

For the evaluation of the disease activity and the response to IFX therapy, the Crohn disease activity index (CDAI) was calculated and laboratory indices were collected before starting IFX and at weeks 2, 14, 30, 54, and 78 after the 1st IFX infusion.<sup>[1,2]</sup> Laboratory indices included platelet count (PLT), hemoglobin (HGB), high-sensitivity C-reactive protein (hsCRP).

Definitions of the clinical response and remission were adopted from the ACCENT-I and II trials.<sup>[1,2]</sup> Clinical response to treatment was defined as a decrease in CDAI score by at least 70 points or 25% reduction in the total CDAI score. The disease was considered to be in clinical remission in case of CDAI score <150. MH was defined as the absence of mucosal ulceration in all of the previously involved segments on ileocolonoscopy.

## 2.4. Statistical analysis

Quantitative data are presented as median (interquartile ranges [IQR]) for nonparametric data and as mean  $\pm$  standard deviation for parametric data. Categorical data are shown as percentages or proportions. The Wilcoxon matched-pairs signed rank test and the Mann-Whitney *U* test were used to analyze paired and nonpaired data, respectively. The Chi-squared test or the Fisher exact test was applied to test for differences among the categorical variables. A Kaplan-Meier analysis was conducted to estimate the cumulative rates of clinical response and remission at weeks 2, 14, 30, 54, and 78. All statistical analyses were performed using the SPSS version 22.0 (SPSS, Chicago, IL). The differences were considered to be statistically significant if *P*-value <.05.

## 3. Results

### 3.1. Baseline characteristics and its comparison

Based on selection criteria, 65 patients with CD were analyzed in this study. Patients included 53 (81.5%) men and 12 (18.5%) women with a male-to-female ratio of 4.4:1. The mean age of disease onset and that of the 1st IFX infusion were  $22.4 \pm 9.6$

(range: 10–57) years and  $29.3 \pm 11.1$  (range: 13–64) years, respectively. The median age at diagnosis was 22.0 (IQR: 18.0–31.0) years. The mean duration of the disease prior to initiation of IFX therapy was  $6.9 \pm 5.7$  years.

Extra-intestinal manifestations were present in 18 patients (27.7%) (Table 1). Fifty-four patients (83.1%) had complications before IFX therapy (Table 1). A total of 20 (30.8%) patients had undergone previous CD-related abdominal surgery, excepting appendectomy, before IFX therapy.

The steroid group was composed of 43 patients. Corticosteroid treatment was given to the patients at a median time interval of 3.7 (IQR: 1.9–9.0) weeks before starting IFX therapy. The median dose of corticosteroid administered (equivalent to prednisone) was 40 (IQR: 40–50) mg. Corticosteroid was tapered after 4 to 6 weeks. Successful corticosteroid withdrawal was achieved in 33 patients. Corticosteroids were discontinued after a mean duration of  $7.4 \pm 4.6$  months.

All of the patients received 3 or more infusions of IFX. Of these, 59 patients received at least 4 infusions, 49 patients received at least 6 infusions, 30 patients at least received 9 infusions, and 14 patients at least received 12 infusions. The median number of IFX infusions administered was 8 (IQR: 5.5–11.0). The median duration of IFX therapy was 11.3 (IQR: 6.7–16.3) months.

The differences in the mean age of onset, mean age at 1st IFX infusion, disease duration, Montreal classification, smoking status, extra-intestinal manifestations, comorbidities, surgery, and concomitant medications between the steroid and the nonsteroid groups were not statistically significant (*P* > .05) (Table 1). The values of CDAI, PLT, HGB, hsCRP in the 2 groups were comparable (Table 2). The median number of IFX infusions between the steroid group and the nonsteroid group was similar (8.0 [IQR: 4.0–10.0] vs 9.0 [IQR: 6.0–12.3], *P* = .208).

### 3.2. Clinical response and its comparison

The cumulative probabilities of clinical remission at weeks 2, 14, 30, 54, and 78 were higher in the steroid group but not statistically significant (84.7% vs 83.6%, 68.9% vs 65.6%, 55.6% vs 46.7%, 43.3% vs 37.2%, 35.2% vs 27.0%, *P* = .206). Similarly, the cumulative probabilities of clinical response at weeks 14, 30, 54, and 78 were higher in the steroid group but not statistically significant (65.6% vs 64.9%, 51.3% vs 46.2%, 41.8% vs 35.7%, 34.0% vs 26.0%; Figs. 1 and 2).

Of 65 patients, 49 patients underwent follow-up ileocolonoscopies. A group of patients who underwent ileocolonoscopies were composed of 18 and 31 patients in the nonsteroid and steroid groups, respectively. The mean interval between the 1st IFX infusion and the follow-up ileocolonoscopy was  $11.7 \pm 9.1$  months. This interval in both groups were similar ( $10.9 \pm 8.3$  vs  $13.1 \pm 10.4$ , *P* = .40). MH was present in 26 (53.1%) patients. The rate of MH was significantly higher in the steroid group (22/31 [71.0%] vs 4/18 [22.2%], *P* < .01).

### 3.3. Adverse events

Adverse events were observed in 17 (26.2%) patients. Adverse events included infections (9/65, 13.8%), infusion-related reactions (7/65, 10.8%), leucopenia (1/65, 1.5%), and liver dysfunction (1/65, 1.5%). Infection events included 7 cases of viral infections (3 cytomegalovirus infections and 4 herpes zoster virus infections), 1 case of clostridium difficile, 1 case of pulmonary tuberculosis (TB), and 1 case of fungal esophagitis.

**Table 1****Baseline characteristics of the patients.**

	All patients (n=65)	Steroid group (n=43)	Nonsteroid group (n=22)	P
Male sex, n (%)	53 (81.5)	36 (83.7)	17 (77.3)	.521
Age of onset, yr (mean±SD)	22.4±9.6	22.7±10.3	21.8±8.1	.742
Age at diagnosis, yr, median (IQR)	22.0 (18.0–31.0)	22.0 (18.0–31.0)	22.5 (18.0–31.8)	.697
Age at 1st infliximab treatment (mean±SD)	29.3±11.1	28.8±11.4	30.1±10.5	.652
Disease duration at the IFX initiation, mo (mean±SD)	6.9±5.7	6.2±4.8	8.3±7.1	.163
IFX infusions, median (IQR)	8.0 (5.5–11.0)	8.0 (4.0–10.0)	9.0 (6.0–12.3)	.208
Duration of IFX therapy, mo, median (IQR)	11.3 (6.7–16.3)	11.0 (4.8–16.0)	13.3 (7.8–20.1)	.302
Montreal classification				
Age at onset, n (%)				
A1 (≤16 yr)	12 (18.5)	9 (20.9)	3 (13.6)	.737
A2 (17–40 yr)	47 (72.3)	30 (69.8)	17 (77.3)	.522
A3 (>40 yr)	6 (9.2)	4 (9.3)	2 (9.1)	1.000
Location, n (%)				
L1 (terminal ileum)	5 (7.7)	4 (9.3)	1 (4.5)	.655
L2 (colon)	15 (23.1)	10 (23.3)	5 (22.7)	1.000
L3 (ileocolon)	45 (69.2)	29 (67.4)	16 (72.7)	.662
L4 (upper gastrointestinal tract)	8 (12.3)	7 (16.3)	1 (4.5)	.248
Behavior, n (%)				
B1 (nonstricturing and nonpenetrating)	21 (32.3)	14 (32.6)	7 (31.8)	.952
B2 (structuring)	21 (32.3)	12 (27.9)	9 (40.9)	.289
B3 (penetrating)	12 (18.5)	8 (18.6)	4 (18.2)	1.000
B2+B3	11 (16.9)	9 (20.9)	2 (9.1)	.308
Smoking habit, n (%)	14 (21.5)	9 (20.9)	5 (22.7)	1.000
Extra-intestinal manifestations, n (%)	18 (27.7)	12 (27.9)	6 (27.3)	.957
Oral ulcer	13 (20.0)	9 (20.9)	4 (18.2)	1.000
Erythema nodosum	1 (1.5)	1 (2.3)	0	1.000
Arthritis	7 (10.8)	4 (9.3)	3 (13.6)	.681
Complications, n (%)	54 (83.1)	36 (83.7)	18 (81.8)	1.000
Intestinal fistula	20 (30.8)	16 (37.2)	4 (18.2)	.116
Abdominal abscess	2 (3.1)	2 (4.7)	0	.545
Intestinal stricture/intestinal obstruction	20 (30.8)	14 (32.6)	6 (27.3)	.662
Gastrointestinal hemorrhage	11 (16.9)	7 (16.3)	4 (18.2)	1.000
Intestinal perforation	5 (7.7)	4 (9.3)	1 (4.5)	.655
Surgery, n (%)	20 (30.8)	15 (34.9)	5 (22.7)	.315
Concomitant medication, n (%)				
ASA	30 (46.2)	21 (48.8)	9 (40.9)	.544
AZA	17 (26.2)	12 (27.9)	5 (22.7)	.653
MTX	1 (1.5)	0	1 (4.5)	.338
Thalidomide	2 (3.1)	1 (2.3)	1 (4.5)	1.000

5-ASA=5-aminosalicylic acid, AZA=azathioprine, IFX=infliximab, IQR=interquartile ranges, MTX=methotrexate, SD = standard deviation.

The frequency of adverse events was higher in the steroid group but not significant (32.6% vs 13.6%,  $P=.10$ ). The frequencies of infections and infusion-related reactions were higher in the steroid group though not statistically significant (16.3% vs 9.1%,  $P=.706$ ; 14.0% vs 4.5%,  $P=.408$ ).

#### 4. Discussion

This study found that prior corticosteroid treatment improved MH after IFX therapy without statistically significant increase in the risk of adverse events. It has been reported that both AZA

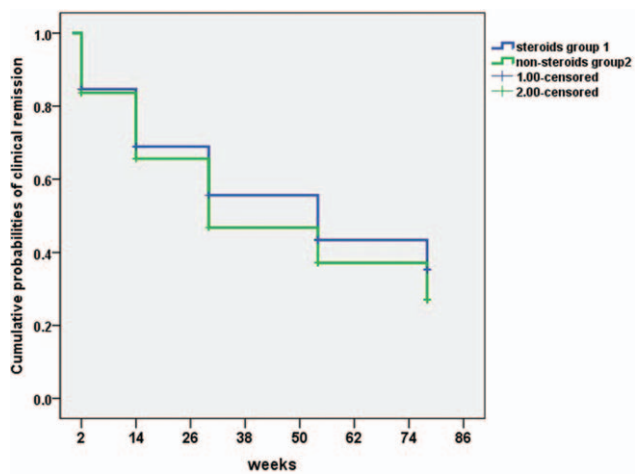
coadministration and HC premedication could prevent LOR.<sup>17</sup> However, taking safety, costs, and compliance into consideration, along with the results of this study, use of corticosteroid therapy before starting IFX may be a more attractive and safer option.

Few studies have investigated the effect of corticosteroid premedication on the efficacy and safety of IFX, especially in Chinese patients. In addition, there is no clear definition of corticosteroid premedication. Farrell et al<sup>16</sup> observed that patients in a HC group (who had received intravenous HC premedication immediately before the 1st IFX infusion) had

**Table 2****Comparison of CDAI and laboratory indexes (median [IQR]) before IFX therapy between the 2 groups.**

	Best CDAI	PLT, ×10 <sup>9</sup> /L	Hgb, g/L	hsCRP, mg/L
Steroid group (n=43)	210.0 (164.3–300.8)	261.5 (204.8–309.5)	122.5 (102.0–133.3)	7.4 (1.8–18.7)
Nonsteroid group (n=22)	220.5 (160.3–250.5)	275.5 (227.3–314.3)	129.5 (110.3–145.0)	8.5 (4.3–27.9)
P	.347	.441	.179	.343

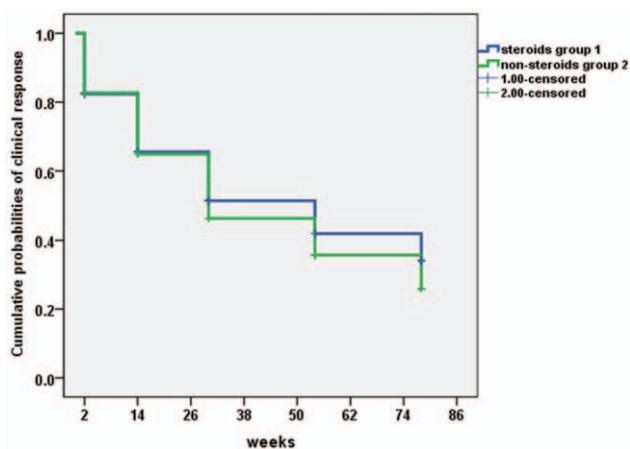
CDAI=Crohn disease activity index, HGB=hemoglobin, hsCRP=high-sensitivity C-reactive protein, IQR=interquartile ranges, LT=platelet.



**Figure 1.** Cumulative probabilities of clinical remission comparing patients with and without steroids.

higher clinical response and remission rates at weeks 8 (56% vs 46%, 31% vs 24%) and 16 (54% vs 44%, 28% vs 24%) than the placebo group. They also found ATI levels to be lower at week 16 in HC-treated patients than the placebo group (1.6 vs 3.4  $\mu\text{g}/\text{mL}$ ,  $P = .02$ ). Farrell and colleagues concluded that intravenous HC premedication significantly reduces ATI levels and lowers the risk of LOR. Mantzaris et al<sup>[7]</sup> performed a prospective 2-year pilot study comparing HC premedication (250mg intravenously immediately before each infusion of IFX) to concomitant AZA treatment (2–2.5 mg/kg/d) in the prevention of LOR. They showed no significant difference between the 2 groups in the clinical remission rates, LOR, or the cumulative probability of remission maintenance. They concluded that both AZA coadministration and HC premedication are equally effective in the prevention of LOR.

In the present study, corticosteroids was given to the patients for a median time period of 3.7 (IQR: 1.9–9.0) weeks before starting IFX therapy. The median dose of corticosteroid administered (equivalent to prednisone) was 40 (IQR: 40–50) mg. Corticosteroids were discontinued after a mean duration of  $7.4 \pm 4.6$  months. Previous studies have reported that young age, a short history of disease, nonsmoking, disease limited to the



**Figure 2.** Cumulative probabilities of clinical response comparing patients with and without steroids.

colon and concomitant immunosuppressive therapy to be associated with favorable response to IFX.<sup>[8–11]</sup> In our study, the age of the patients at the start of IFX treatment, duration of illness, smoking history, Montreal classification, disease activity or concomitant medication between the 2 groups were similar. On comparing the outcomes of these well-matched groups, we found that the cumulative probabilities of clinical remission and response at weeks 14, 30, 54, and 78 were higher in the steroid group. Although these differences were statistically insignificant, we propose it may be partly related to the small sample size of the study. Furthermore, the results were compatible with those of previously reported randomized controlled trials and prospective studies.

Growing evidence suggests that achieving MH can improve patient outcomes and alter disease progression.<sup>[12,13]</sup> The SONIC trial and the study of “Top-Down” strategy demonstrated that early IFX and combined immunosuppression could result in a higher rate of MH.<sup>[15,14]</sup> In the present study, the rate of MH in 65 patients with CD was up to 53.1%, with the rate of the MH being significantly higher in the steroid group (71.0% vs 22.2%,  $P < .01$ ). These results suggest that corticosteroid premedication could promote MH. Corticosteroids can alleviate the inflammatory response to a great extent, which may contribute to the promotion of MH.

Infection is one of the major adverse events occurring after IFX therapy. In the TREAT registry,<sup>[15]</sup> the rate of serious infections related to IFX was 43%. One of the factors independently associated with serious infections was concomitant prednisone therapy (HR = 1.57, 95% CI = 1.17–2.10;  $P = .002$ ). A systematic review and network meta-analysis indicated that biologic agents increase the risk of opportunistic infections in inflammatory bowel disease (IBD).<sup>[16]</sup> In the present study, the frequency of infections was higher in patients treated with corticosteroid premedication, but this difference did not reach statistical significance. Our results imply that corticosteroid premedication may increase the risk of infection. It has been emphasized that once clinical remission is achieved, the corticosteroid dose should be reduced and withdrawn as soon as possible in order to reduce the risk of infection.

It has been reported that infusion reactions after IFX therapy are strongly related to ATI formation and its levels; corticosteroid premedication can prevent this infusion reaction.<sup>[6]</sup> However, Sany et al<sup>[17]</sup> found that the incidence of infusion reactions was higher in patients with betamethasone premedication (5% vs 2.5%,  $P = .05$ ). Choquette et al<sup>[18]</sup> reported that 201 (12.3%) patients had at least 1 infusion reaction out of the 1632 patients treated with IFX for rheumatologic conditions and IBD. They demonstrated that corticosteroid premedication did not influence the risk of infusion reactions. However, the authors believe that the difference in the risk of infusion reactions may not be significant due to the selection bias. In the present study, the usage of corticosteroid was different from those of the previous reports. However, consistent with that of most other previous reports, our results demonstrated that the corticosteroid premedication did not decrease the risk of infusion reactions.

In clinical practice, CD and intestinal TB frequently show similar clinical and endoscopic features and it is difficult to differentiate between the 2 diseases, especially in areas with a high prevalence of TB such as Asia. The natural history and treatment options of the 2 diseases are distinct. Therefore, misdiagnosis or delayed diagnosis can not only affect the treatment outcomes but also health care costs and economic losses. In TB-endemic Asian countries, for the modest-to-severe

CD, corticosteroid therapy can be considered to be given as a 1st line treatment to induce remission. Subsequently, as per the patients' response to the steroid therapy, the immunosuppressive drugs or IFX can be administered. Moreover, if the patient shows the signs and symptoms of infection such as fever during the steroid therapy, then the diagnosis of CD should be questioned and IFX should be avoided, potentially preventing serious infections.

This study has some limitations, Firstly, being a single-center retrospective study, the corticosteroid usage prior to IFX therapy was not predetermined and was slightly different for each patient. Secondly, the number of the patients enrolled in this study was small. However, apart from the confirmation that prior corticosteroid treatment before IFX therapy may reduce LOR, we also found that corticosteroid premedication promotes MH in Chinese patients. Future prospective studies and randomized controlled trials are required to validate the findings of this study.

### Author contributions

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