

Received: 2018.09.11

Accepted: 2018.12.03

Published: 2019.03.27

Risk Factors Associated with Infusion Reactions to Infliximab in Chinese Patients with Inflammatory Bowel Disease: A Large Single-Center Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACEFG 1 **Xiaolei Wang**
BCD 2 **Jingli Cao**
BCD 1 **Haichao Wang**
BCD 3 **Chen Ye**

1 Department of Gastroenterology, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai, P.R. China
2 Department of Gastroenterology, Tongji Hospital, School of Medicine, Tongji University, Shanghai, P.R. China
3 School of Medicine, Soochow University, Suzhou, Jiangsu, P.R. China

Corresponding Author: Xiaolei Wang, e-mail: wangxiaolei@tongji.edu.cn

Source of support: This study was supported by a grant from the National Natural Science Foundation of China (# 81670476)

Background: This study investigated the risk factors of infliximab (IFX)-related infusion reactions (IR) in Chinese patients with inflammatory bowel disease (IBD).


Material/Methods: The medical records of 330 consecutive IBD patients treated with IFX between 2009 and 2017 were reviewed. The incidence of IR and adverse effects were recorded in detail, and the potential risk factors related to IR were analyzed by univariate and logistic regression analysis.

Results: The 330 patients received a total of 2108 IFX infusions, with a median follow-up of 29 months. Eighteen patients (5.5%) experienced IR: 15 were immediate (2 severe) and 3 were late (0 severe). The patients who were treated with episodic IFX without concomitant IM therapy and at the 2nd IFX series (all $P < 0.001$) had higher incidence of IR. Logistic regression revealed the 2nd IFX treatment series (OR=0.017, $P < 0.001$) and episodic use of IFX (OR=0.113, $P < 0.001$) as the significant predictors. Antibodies against infliximab (ATI) were highly positive in 10 of 14 patients (71%) with IR. Sixty-seven percent of patients finished infusions after IR through appropriate management.

Conclusions: IFX infusions were accompanied by IR in about 5% of Chinese IBD patients. Severe IR was rare. The patients with the 2nd series or episodic use of IFX should be monitored closely during infusion.

MeSH Keywords: **Drug-Related Side Effects and Adverse Reactions • Inflammatory Bowel Diseases • Risk Factors**

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/913152>

 3137

 4

 2

 25



Background

Infliximab (IFX) (Remicade, Centocor) is a chimeric monoclonal antibody designed to intercept and neutralize soluble and membrane-bound tumor necrosis factor alpha (TNF- α), consisting of human constant and murine variable regions. Since 1998, IFX has revolutionized the treatment of inflammatory bowel disease (IBD). It is effective in induction and remission of fistulizing Crohn's disease (CD) and steroid-dependent moderate-to-severe ulcerative colitis (UC) [1,2]. However, administration of IFX is associated with a well-recognized risk of infusion-related adverse events, such as infusion reactions (IR), autoimmune disorders, malignancies, opportunistic infections, and serious infections, including reactivation of tuberculosis and hepatitis B virus in patients with IBD in Western countries [3,4]. The exact etiology and pathogenesis of IR are unclear. The possible mechanisms may be related to cytokine release syndrome caused by massive and simultaneous release of cytokines from TNF-expressing immune cells affected by IFX [4], activation of neutrophils [5], degranulation of mast cells and basophils [6], or circulating IFX- antibodies to infliximab (ATI) complexes activating complement [7].

The majority of published IFX-related studies in Chinese IBD patients were related to the effectiveness of IFX [8–11]. However, few reports focused on adverse events. IFX is still the only available biological agent for IBD in China. After the occurrence of IR and other adverse effects, the continuing therapy of IFX and its clinical effectiveness may be challenged by both patients and doctors. Therefore, in this study, we investigated the tolerance and safety of IFX therapy in Chinese IBD patients. We found that the rate of IR (5.5%) in Chinese IBD patients was similar with the data previously reported in Western countries [12]. The patients with the 2nd IFX treatment series or episodic use of IFX had high risk of IR occurrence. Antibodies against infliximab (ATI) may contribute to IR (71%, 10/14). Although having IR, 67% of patients still finished infusions after IR through appropriate management. Short- and long-term IFX therapy was generally well tolerated in these Chinese patients.

Material and Methods

Patients

A retrospective cohort study was conducted by collecting clinical data associated with 330 cases of patients diagnosed with IBD (including 309 CD cases and 21 UC cases) who received IFX treatment at the Department of Gastroenterology of the Shanghai Tenth People's Hospital affiliated with Tongji University (Shanghai, China) from January 2009 to May 2017. The diagnosis of CD and UC was confirmed in all

cases by reviewing patient's medical, endoscopic, radiological, and pathological records, in accordance with the diagnostic criteria published by the European Crohn's and Colitis Organization (ECCO) [13]. Patients who were younger than 70 years of age when they first received IFX injection were included in this study. Data collection started from the first injection of IFX and ended at the study endpoint or discontinuation of treatment (Table 1). The study protocol was reviewed and approved by the Institutional Ethics Committee of the Shanghai Tenth People's Hospital of Tongji University School of Medicine.

Data collection

Data were collected from all patients' medical records and safety records. General demography data (age of disease onset, gender, diagnosis), age of the first IFX injection, schedules of infusions, IR (immediate or late), treatment after IR, pretreatment before IFX infusion, severity grades, IFX outcome after IR (stopped, continued, or switched therapy), outcome of infusion reactions (observation, attenuation of infusion rate, attenuation and medication management, or interruption of infusion and medication management), regular use of IFX infusion or episodically (reinitiation after >6 months), concomitant immunomodulators during treatment, other adverse reactions (viral infection, abscess, tuberculosis, perforation, upper-respiratory tract infection), and timing of follow-up were recorded in detail.

IFX induction remission treatment was administered at a dose of 5 mg/kg at 0, 2, and 6 weeks, as described previously [8]. Infusion was administered according to the initial rate schedule, and the maintenance remission was infused every 8 weeks. The initiation of maintenance therapy was based on an assessment of the induction of remission therapy.

IRs that developed during the course of the infusion or within 1–2 h of its completion were classified as immediate IR. IRs that first manifested more than 24 h after infusion were defined as late IR to IFX [12]. The reactions were divided into 5 severity grades, ranging from mild (requires observation only); moderate (minimal, usually oral, intervention is sufficient); and severe (vital organ involvement but nothing life-threatening; usually requires parenteral medication); to life-threatening (multi-system involvement of vital organs, urgent and critical care required); and death [12]. All potential complications of IFX were documented. Concurrent immunosuppressive therapy was azathioprine (AZA) and methotrexate (MTX) in this study.

The IFX infusion protocol was a graded dose-challenge protocol [12]. The initial infusions were administered in a highly controlled manner, beginning with small test doses, followed by gradual and stepwise escalation of the infusion rate until the full target rate was reached.

Table 1. Baseline characteristics of patients in this study.

Parameter*	Value
Gender (M/F)	330
Male	237 (71.8%)
Female	93 (28.2%)
Disease	
UC	21 (6.3%)
CD	309 (93.9%)
Duration of follow-up (m), mean (SD)	29.0±19.3
Age at first IFX infusion (yrs), mean (SD)	30.4±12.6
A1 (≤16 yrs)	43 (13.0%)
A2 (17–40 yrs)	196 (59.4%)
A3 (>40 yrs)	91 (27.6%)
Age on disease onset (yrs), mean (SD)	22.1±10.4
A1 (≤16 yrs)	66 (20.0%)
A2 (17–40 yrs)	213 (64.5%)
A3 (>40 yrs)	51 (15.5%)
Extension of UC	
E1	0 (0%)
E2	2 (9.5%)
E3	19 (90.5%)
CD patient location	
L1 (ileum only)	67 (20.3%)
L2 (colon only)	81 (24.5%)
L3 (ileocolonic)	182 (55.2%)
L4** (upper GI)	20 (6.1%)
Behavior	
B1 (nonstricturing, nonpenetrating)	156 (47.3%)
B2 (stricturing)	91 (27.6%)
B3 (penetrating)	83 (25.2%)
p# (perianal disease)	71 (21.5%)
Concomitant immunomodulators	
Azathioprine	205 (62.1%)
Methotrexate	28 (8.5%)

* All values: mean ±SD for continuous variables; ** a modifier that can be added to L1–L3 when concomitant upper gastrointestinal (GI); # added to B1–B3 when concomitant perianal disease is present.

Pretreatment and clinical management after infusion reaction

All patients received premedication with dexamethasone 5 mg intravenously (IV), promethazine 25 mg intramuscular injection, and omeprazole 40 mg intravenously (IV).

Statistical methods

Mean and SD for continuous variables were used. Descriptive statistics were calculated to characterize continuous variables as percentages for discrete data, and medians with range or interquartile range (IQR). Odds ratios and 95% confidence intervals were calculated for the risk of IR. Univariate analysis was used to analyze the potential risk factors as disease type, gender, age at diagnosis, age at first IFX infusion, disease duration at first IFX infusion, number of infusions, IFX infusion, distribution of reactions during 1st and 2nd IFX series and concomitant immunosuppression agents during the last IFX treatment by Pearson chi-square or Fisher's exact test. Comparison of combined/monotherapy IFX infusion with different types or severity grades of IR was conducted by use of the chi-square test or Fisher's exact test. Variables possibly associated with reaction were further evaluated in a multiple logistic regression analysis (enter method; Wald test used for assessing *P*-values). *P*-value was <0.05 and two-sided *P*-values were considered statistically significant. SPSS 22.0 software (IBM, Somers, NY, USA) was used for statistical analysis.

Results

General patients characteristics

A total of 330 consecutive IBD patients (309 CD patients and 21 UC patients) who received IFX treatment at the IBD center of the Shanghai Tenth People's Hospital affiliated with Tongji University were evaluated in the study (Table 1). A total of 237 male patients and 93 female patients with a median age of disease onset was 22 years (range, 8–76 years years), with median age at the first IFX infusion 30 years (range, 13–78 years) were included in this study. Forty-six of the 330 patients (13.6%) were adolescents (age 18 years or younger). We followed up 311 patients (94.2%) after IFX treatment, and 19 patients were lost to follow-up. The median follow-up was 29 months (range, 1–82 months) with 19 patients having 1 month of follow-up. A total of 76 patients were followed for 1–12 months, 57 patients for 13–24 months, 63 patients for 25–36 months, 40 patients for 37–48 months, 38 patients for 49–60 months, 15 patients for 61–80 months, and 3 patients for over 80 months. Table 1 shows that 205 (70.6%) patients were treated with concomitant immunomodulators (IM) (205 AZA, 28 MTX).

Table 2. Characteristics of infliximab-related infusion reactions in patients with IBD.

Characteristic	N=330 (%)
Infusion reactions per patient	18 (5.5)
Immediate infusion reactions	15 (4.5)
Mild	9 (2.7)
Moderate	4 (1.2)
Severe	2 (0.6)
Late infusion reactions	3 (0.9)
Average IFX number of infusion reactions	5
Over 2 infusion reactions	6 (1.8)
Other adverse events	12 (3.6)
Outcome of infusion reaction (patients)	N=18
Observation	1 (5.6)
Attenuation of infusion rate	6 (33.3)
Attenuation and medication management	5 (27.8)
Interruption of infusion and medication management	6 (33.3)
Infusion reactions per infusion (numbers)	38 (2108)
Outcome of IFX after infusion reaction (patients)	N=18
Stopped	1 (5.6)
Continued	6 (33.3)
Switched therapy	11 (61.1)

Characteristics of infliximab-related infusion reactions

In Table 2, when assessed on a patient basis, IR and serious IR occurred in 5.5% (18/330) of patients and 0.6% (2/330) of patients, respectively. The incidence of immediate IR was 4.5% (15/330), and late IR was 0.9% (3/330). When assessed based on the number of infusions, a total of 2108 infusions with IFX were administered, and the IR rate was 1.8% (38/2108) and serious IR was 0.4% (9/2108) of infusions. The most IFX infusions were 28 times, and the least was 1. The average IFX infusion related to IR was about the 5th infusion. Six patients (1.8%) had 2 or more IRs. After IR, 6 patients (33.3%) had attenuated of infusion rate, 5 (27.8%) had attenuated infusion and were given medication management, and 6 (33.3%) stopped IFX infusion and needed medication therapy. Eleven patients (50.0%, 9/18) switched to other therapies after IR, 6 patients (33.3%, 6/18) continued IFX treatment, and 1 (5.6%, 1/18) stopped IFX. Among the 3 patients who had late IR, 1 had serum sick-like response with pruritic skin, eruptions, fever, malaise, and polyarthralgia.

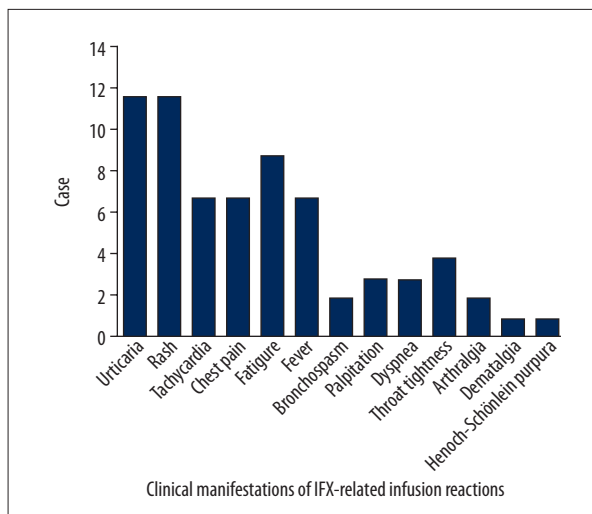


Figure 1. Clinical manifestations of infliximab-related infusion reactions.

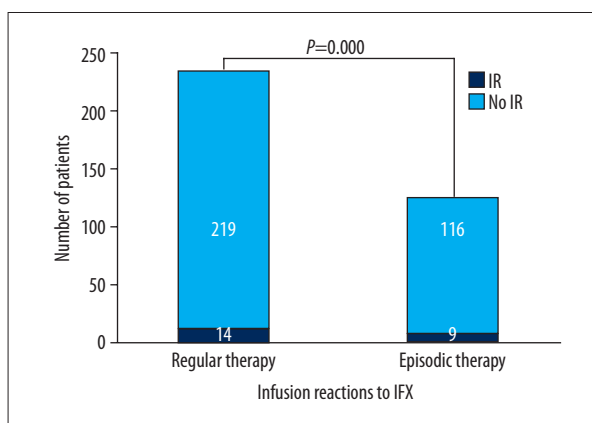


Figure 2. Patients with infusion reactions more often received episodic therapy than patients with regular treatment (P=0.000).

Outcomes of infliximab and patients with infusion reactions

Among the 18 patients with IR (Table 2), IFX infusion was continued in 1 patient having slight pruritus and dyspnea and kept under close observation. The symptoms disappeared after 5 h without any intervention. Six patients had urticarial and pruritus during the infusion, but the symptoms vanished after attenuating infusion rate. Three patients experienced arthralgia, fever, and tachycardia. Two patients had dermatalgia. These 5 patients recovered after attenuating infusion speed and were given transient steroid management. Five patients had palpitation, bronchospasm, throat tightness, and chest pain, and 1 patient had Henoch-Schönlein purpura (Figure 1). The infusions were interrupted immediately and these patients received methylprednisolone IV, oxygen uptake, and electrocardiograph monitoring. All the patients recovered after immediate management.

Table 3. Risk factors of infusion reactions of infliximab in patients with IBD in our study.

Variables	IR*, n=23	No IR, n=307	P value
Gender (M/F) – n (%)			0.489
Male	18 (78)	216 (70)	
Female	5 (22)	91 (30)	
Disease – n (%)			
UC	1 (4)	20 (6)	1.000
CD	22 (96)	287 (94)	
Age at disease onset (yrs), median (IQR)	15 (7–32)	26 (16–70)	0.289
<27	8	143	
≥27	15	164	
Age at first IFX infusion (yrs), median (IQR)	28 (16–42)	38 (19–72)	0.129
<28	6	132	
≥28	17	175	
Disease duration at the first IFX (m), median (IQR)	43 (5–128)	36 (1–98)	0.194
<32	7	140	
≥32	16	167	
IFX infusion – n (%)			
Regular	14 (61)	292 (95)	0.000
Episodic	9 (39)	15 (5)	
Number of infusions (times), median (IQR)	6 (1–12)	10 (4–25)	0.639
<10	8	91	
≥10	15	216	
Patients with concomitant IM** therapy – n (%)			0.000
With IM	14 (61)	219 (71)	
Without IM	9 (39)	116 (29)	
Infusion with concomitant IM therapy – n (%)	N=38	N=2070	
With IM	21 (55)	1684 (81)	0.000
Without IM	17 (45)	386 (19)	
IFX series – n (%)			
1 st IFX series	13 (57)	293 (95)	0.000
2 nd IFX series	10 (43)	13 (5)	

* IR – infusion reaction; ** IM – immunomodulator.

After IR, 1 patient stopped all the medications, and 11 patients switched to other medications, e.g., prednisone combined with MTX in active CD, or AZA in remission therapy. Six patients continued IFX therapy. Among them, 2 patients were given oral antihistamine and prednisone 20 mg 3 times 3 times a day 24 h prior to the infusion. Four patients did not receive special premedication before IFX administration. No IR was occurred in these patients thereafter.

Potential risk factors associated with infliximab-related infusion reactions

Table 3 shows potential risk factors for IFX-related IR, assessed using univariate analysis. Patients with IR more often received episodic therapy than regular treatment ($P=0.000$, Figure 2). Nine patients (9 of 15) had IR during episodic IFX therapy, and in 7 (78%) this occurred during the 2nd IFX series. A significant difference of IR was observed between patients who

Table 4. Summary of other adverse effects related to infliximab.

Types	Gender/ age	Infusion (n)	Time since last infusion	Clinical presentation	Concomitant treatment	Serious adverse event (death)	Treatment/ outcome
Viral infections							
Chicken pox	F/21	3	1 day	Chicken pox	No	No (no)	Acyclovir/healed
HBV	F/52	3	2 mo	HBsAg positive	MTX* 25 mg/wk	No (no)	Entecavir/controlled
Tuberculosis	F/39	3	2 mo	TB-IGRA positive	AZA** 50 mg/day	Yes (no)	Anti-tuberculosis/controlled
	M/28	2	1 wk	Pulmonary tuberculosis	No	Yes (no)	Anti-tuberculosis/controlled
Abscess	F/32	1	2 wk	Abdominal abscess	No	No (no)	Antibiotics/healed
	F/26	1	1 wk	Pelvic abscess	No	No (no)	Antibiotics/healed
	F/57	6	1 wk	Pelvic abscess	AZA 50 mg/day	Yes (no)	Antibiotics+surgery/healed
Perforation	M/34	2	4 wk	Acute abdominal pain and perforation	AZA 50 mg/day	Yes (no)	Antibiotics +surgery/healed
Upper respiratory tract infections	M/17	2	1 wk	Bronchitis	AZA 50 mg/day	No (no)	Observe/healed
	M/27	1	4 days	Influenza	No	No (no)	Observe/healed
	F/18	3	1 wk	Bronchitis	AZA 25 mg/day	No (no)	Observe/healed
	M/34	2	1 wk	Bronchitis	AZA 50 mg/day	No (no)	Antibiotics/healed

* MTX – methotrexate; ** AZA – azathioprine.

experienced the 1st and 2nd IFX series ($P=0.000$, Table 3), and the incidence of IR at 2nd IFX series was significantly higher than the incidence of IR at 1st IFX series.

Patients who were treated with concomitant IM had significantly lower incidence of IR compared with patients who received IFX treatment only ($P=0.000$, Table 3). Similarly, there were significantly fewer IR episodes in patients treated with concomitant IM than in those just treated with IFX ($P=0.000$, Table 3). However, multiple logistic regression analysis revealed the 2nd IFX treatment series ($OR=0.017$, $P<0.001$) and episodic use of IFX ($OR=0.113$, $P<0.001$) as the significant predictors of IR.

Relationship between infusion reactions and TNF- α , serum IFX concentration, antibodies (Ab) against infliximab (ATI)

ATI were highly positive in 10 of 14 patients (71%) who had anti-IFX IgG Ab after the IR (median 114 ng/mL, IQR 30–300 ng/mL). These patients had low serum IFX concentration (0.60 ± 1.08 $\mu\text{g/ml}$, range >0.5 $\mu\text{g/ml}$) and high serum TNF- α level (418.7267 ± 829.5 pg/ml , range <8.1 pg/ml). In the 10 patients with ATI, 7 had acute IR in the 2nd IFX series with reinitiation of IFX after therapy discontinued over 6 months, and 3 had IR in the 1st IFX series. Furthermore, levels of ATI

after IR in patients with IR were significantly higher than in the patients without IR to IFX maintenance therapy (median 0 ng/mL, IQR 0–0 ng/mL, $n=21$, $P<0.0001$).

Other adverse events

Twelve patients (3.6%) had the other adverse effects, possibly related to IFX (Table 4). Two patients had viral infections: 1 had chicken pox and recovered after anti-viral therapy for 2 weeks; another had HBV activation and was given Entecavir. Two patients had tuberculosis infection: 1 patient who received IFX combined with AZA therapy had fever again after the 3rd IFX infusion, and then her repeated tuberculosis-interferon gamma release assay (TB-IGRA) result was positive. Another patient had severe acute military pulmonary tuberculosis 1 week after methylprednisone 40 mg infusion for 7 days combined with IFX. The patient was given anti-tuberculosis therapy immediately and stopped the anti-TNF and steroid.

Three patients had abdominal or pelvic abscess 1–2 weeks after IFX infusion. All the patients stopped IFX and IM therapy and received antibiotics. Four patients had upper-respiratory tract infection with clinical manifestations of influenza or bronchitis, with 3 of them having AZA simultaneously.

All the adverse effects resolved or were controlled eventually. No patients developed other autoimmune disorders or malignancies during the follow-up (Table 4).

Discussion

No previous studies have focused on the safety of IFX in Chinese IBD patients, but this is an important topic because of its increasing use and it is the only available biologic for IBD patients in China. The main results in this study at our IBD center showed infusion reactions (IR) occurred in 5.5% of 330 IBD patients with 2108 infusions. Severe IR were rare. The 2nd IFX treatment series and episodic use of IFX were significant predictors of IR. Positivity of antibodies against infliximab (ATI) (71%, 10/14) may be related to IR occurrence.

Immediate IR to IFX are reported in 5–23% of IBD patients in large randomized controlled trials, with some comparable rates in unselected patient populations from Western countries [12]. In our center, acute (including immediate and late) IR occurred in 5.5% of Chinese patients. This percentage is similar to the results reported in previous uncontrolled multicenter studies from the USA (3.8–19.7%) [3,14–17]. The various methods used to record levels of IR may have contributed to the different IR rates observed in clinical practice. We recorded all the IR in our clinical practice. More than half (66.7%, 12/18) of them led to the permanent discontinuation of the infusion and IFX treatment, and 11 patients transferred to other treatment. According to the combined safety data from all clinical trials with IFX, 2.6% of USA patients had IR leading to discontinuation [15], which is slightly lower than our results (3.6%, 12/330). The decision to stop permanent IFX treatment usually was made by doctors for safety consideration, although the incidence of severe IR was only 0.6% (2/18), which is comparable to a previous study from USA [15]. Severe IR with clinical symptoms, including bronchospasm, laryngeal/pharyngeal edema, palpitation, and Henoch-Schönlein purpura [18], were observed during IFX infusion in our study.

Use of immunomodulators such as AZA, 6-mercaptopurine (6-MP), and MTX at the time of anti-TNF therapy was associated with a decreased likelihood of anti-TNF discontinuation in both CD and UC, as it reduces the immunogenicity of IFX and therefore the incidence of IR [19–20]. In our study, the low incidence of acute IR is consistent with previous results that concomitant treatment with IM may reduce the frequency of IR. Over 70% of our patients who received concomitant AZA or MTX started either before or at the time that they received their first infusion of IFX, and showed significantly lower incidence of IR than those without combined IM. However, this concomitant treatment with IM was not a predictor of IR in our study, and 17 of 45 patients with IR who did not receive

immunosuppressive medications also had IR risk. Studies with larger samples are needed to investigate the relationship between IFX-related IR and concomitant therapy with IM.

Premedications are commonly given to patients with IBD before intravenous IFX administration. All the patients in our study were given pretreatment routinely with intravenous corticosteroids before each IFX infusion. However, high inter-practice and intra-practice variability for premedication use exists before IFX administration in different centers in Western countries [21]. The clinical rationale for premedicating patients seems to be driven by individual preference or group practice habit [21]. In contrast, data from the Mayo Clinic found that in the adult population, premedication was not associated with a reduced risk of recurrent IR [15].

The main argument in favor of premedication with antihistamines, antipyretics, and/or corticosteroids is that it may be justified in patients with a history of moderate infusion reactions [13]. Better knowledge of the evidence may help in understanding the significance of premedication in preventing IR.

The presence of antibodies to IFX (ATIs) has been associated with a significantly higher risk of acute IR in some studies of patients with IBD, especially in patients receiving episodic or on-demand IFX for resuming treatment after a long interval, who suffer increased chances of infusion responses with high ATI titers [19,22]. Our results also showed the patients who were treated with episodic IFX had higher incidence of IR. At the same time, the patients at the 2nd IFX series also had high IR rate. These 2 factors were significant predictors for IR. Similar to the reported data, episodic regimens, resumption of IFX infusions after a prolonged drug-free interval, and administration of IFX to patients with high ATI titers increased the risks of IR [22]. Ten of 14 patients (71%) after the IR had the high anti-IFX IgG Ab in this study. All the patients with 3 late IR and 7 of immediate IR detected ATI and had positive results. Other possible etiologies are cytokine-release syndrome, anaphylactic reaction, and complement activation [16,23]. The majority of reactions can be predicted by the appearance of anti-IFX antibodies, according to a previous report [24].

The other adverse events associated with IFX treatment were infections such as abscess, upper-respiratory tract infection, and viral infection (including HBV infection), but none were fatal. Five of 9 cases of infections were treated with concomitant immunosuppressive therapy. It has been reported that combination therapy with IFX and IM increases the occurrence of infections [23]. Recent published data emphasize the risk of tuberculosis associated with IFX [25]. In our study, 2 cases of tuberculosis were observed in this series, although chest computerized tomography (CT) screening and TB-IGRA were applied in all patients before initiating IFX therapy.

Many recent studies have shown that the incidence of tuberculosis reactivation during IFX infusion is still very low [25]. However, in countries at high risk for hepatitis B virus and *Mycobacterium tuberculosis*, such as China, it is still necessary to regularly monitor patients for hepatitis B virus infection and IGRA during IFX infusion. One patient had acute perforation after 2 IFX infusions. This is a very rare adverse event and happened after a long interval (2 years) of reuse IFX. Small bowel stricture and fibrosis in this patient with long disease duration may have led to poor effectiveness of IFX and could have caused the emergent complication.

References:

- Rutgeerts P, Sandborn WJ, Feagan BG et al: Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*, 2005; 353: 2462–76
- Sands BE, Anderson FH, Bernstein CN et al: Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*, 2004; 350: 876–85
- Lees CW, Ali AI, Thompson AI et al: The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. *Aliment Pharmacol Ther*, 2009; 29: 286–97
- Aubin F, Carbonnel F, Wendling D: The complexity of adverse side-effects to biological agents. *J Crohns Colitis*, 2013; 7: 257–62
- Khodoun MV, Strait R, Armstrong L et al: Identification of markers that distinguish IgE- from IgG-mediated anaphylaxis. *Proc Natl Acad Sci USA*, 2011; 108: 12413–18
- Puchner TC, Kugathasan S, Kelly KJ, Binion DG: Successful desensitization and therapeutic use of infliximab in adult and pediatric Crohn's disease patients with prior anaphylactic reaction. *Inflamm Bowel Dis*, 2001; 7: 34–37
- van der Laken CJ, Voskuyl AE, Roos JC et al: Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. *Ann Rheum Dis*, 2007; 66: 253–56
- Liu C, Xia X, Wu W et al: Anti-tumour necrosis factor therapy enhances mucosal healing through down-regulation of interleukin-21 expression and T helper type 17 cell infiltration in Crohn's disease. *Clin Exp Immunol*, 2013; 173: 102–11
- Yu L, Yang X, Xia L et al: Infliximab preferentially induces clinical remission and mucosal healing in short course Crohn's disease with luminal lesions through balancing abnormal immune response in gut mucosa. *Mediators Inflamm*, 2015; 2015: 793764
- Zhou Y, He H, Wang P et al: Infliximab for the treatment of Crohn's disease: Efficacy and safety in a Chinese single-center retrospective study. *Eur J Gastroenterol Hepatol*, 2015; 27: 1270–75
- Zhou YL, Xie S, Wang P et al: Efficacy and safety of infliximab in treating patients with ulcerative colitis: Experiences from a single medical center in southern China. *J Dig Dis*, 2014; 15: 483–90
- Lichtenstein L, Ron Y, Kivity S et al: Infliximab-related infusion reactions: Systematic review. *J Crohns Colitis*, 2015; 9: 806–15
- Gomollon F, Dignass A, Annesse V et al: 3rd European Evidence-Based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and medical management. *J Crohns Colitis*, 2017; 11: 3–25
- Cheifetz A, Smedley M, Martin S et al: The incidence and management of infusion reactions to infliximab: A large center experience. *Am J Gastroenterol*, 2003; 98: 1315–24
- Colombel JF, Loftus EV Jr, Tremaine WJ et al: The safety profile of infliximab in patients with Crohn's disease: The Mayo clinic experience in 500 patients. *Gastroenterology*, 2004; 126: 19–31
- Hamzaoglu H, Cooper J, Alsahli M et al: Safety of infliximab in Crohn's disease: A large single-center experience. *Inflamm Bowel Dis*, 2010; 16: 2109–16
- Keshavarzian A, Mayer L, Salzberg B et al: A multicenter retrospective experience of infliximab in Crohn's disease patients: infusion reaction rates and treatment persistency. *Gastroenterol Hepatol (NY)*, 2007; 3: 381–90
- Song Y, Shi YH, He C et al: Severe Henoch-Schonlein purpura with infliximab for ulcerative colitis. *World J Gastroenterol*, 2015; 21: 6082–87
- O'Meara S, Nanda KS, Moss AC: Antibodies to infliximab and risk of infusion reactions in patients with inflammatory bowel disease: A systematic review and meta-analysis. *Inflamm Bowel Dis*, 2014; 20: 1–6
- Targownik LE, Tennakoon A, Leung S et al: Factors associated with discontinuation of anti-TNF inhibitors among persons with IBD: A population-based analysis. *Inflamm Bowel Dis*, 2017; 23: 409–20
- Picoraro J, Winberry G, Siegel CA et al: Premedication use before infliximab administration: A cross-sectional analysis. *Inflamm Bowel Dis*, 2017; 23: 174–80
- Hanauer SB, Wagner CL, Bala M et al: Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol*, 2004; 2: 542–53
- Steenholdt C, Svenson M, Bendtzen K et al: Severe infusion reactions to infliximab: Aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*, 2011; 34: 51–58
- Vultaggio A, Matucci A, Nencini F et al: Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions. *Allergy*, 2010; 65: 657–61
- Carpio D, Jauregui-Amezaga A, de Francisco R et al: Tuberculosis in anti-tumour necrosis factor-treated inflammatory bowel disease patients after the implementation of preventive measures: Compliance with recommendations and safety of retreatment. *J Crohns Colitis*, 2016; 10: 1186–93

Conclusions

Our single-center study details the short- and long-term safety profile of IFX in a large group of Chinese patients. IFX was well tolerated in the majority of patients. Whether concomitant IM had a protective effect against IR or increased infections needs further observation in clinical practice. Clinicians should weigh the benefits and risks of anti-TNF therapy in all patients according to the risk factors, e.g., the 2nd IFX series or episodic use. Monitoring HBV, IGRA, and other infections during IFX therapy may be recommended. Furthermore, a prospective study to establish a standardized protocol for optimal IR prophylaxis is needed.