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Infliximab in inflammatory bowel disease: attention to adverse events

A. UYANIKOGLU, F. ERMIS[1], F. AKYUZ[2], B. PINARBASI[2], B. BARAN[2], T. AYDOGAN, K. DEMIR[2], F. BESISIK[2], S. KAYMAKOGLU[2]

Department of Gastroenterology, Harran University, Medical Faculty, Sanliurfa, Turkey
[1]Department of Gastroenterology, Duzce University, Medical Faculty, Duzce, Turkey
[2]Department of Gastroenterology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

Abstract. – OBJECTIVE: To assess the efficacy and adverse effects of infliximab in patients with Crohn's disease and ulcerative colitis who are resistant to conventional therapy or having fistulising type Crohn's disease.

PATIENTS AND METHODS: The patients with a diagnosis of inflammatory bowel disease received infliximab between 2007 and 2009 were followed-up prospectively. Infliximab 5 mg/kg was given at week 0, 2, 6, and every 8 weeks thereafter. Early and late adverse events occurring during the treatment were recorded for each patient.

RESULTS: There were 36 patients [mean age 35±12, 17 male] included in the study. Thirty-two (88%) patients were receiving concomitant long-term immunosuppressive therapy. Complete or partial response was obtained in 75% of all patients. At least one adverse event was observed in 10 (28%) patients. Anaphylaxis was seen in 2 (6%) patients, mild acute infusion reaction in 2 (6%) patients, hypotension in 2 (6%) patients, respiratory distress in 2 (6%) patients, skin rash and eruptions in 2 (6%) patients, one hypertension (3%) and one (3%) tightness in the chest. Treatment was continued in all except patients with anaphylaxis. No infection, tumour or cases of death were observed.

CONCLUSIONS: Several adverse events might be observed in patients who receive infliximab. Care should be given to patients whom treatment was restarted after a break in regard to anaphylaxis. No serious adverse event was observed during infliximab treatment except allergic events.

Key Words:
Infliximab, Inflammatory bowel disease, Treatment, Adverse event.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic, relapsing diseases that proceed with remissions and acute flare-ups. Symptoms of patients with inflammatory bowel disease (IBD) impair their quality of life. Although many drugs have been used in the treatment of IBD, none of them changed the natural progress of the disease or succeeded in providing long term remission[1]. The use of IFX in the last decade has changed treatment strategies and clinical outcomes significantly. Controlled trials support the use of IFX in treatment of luminal and fistulising CD, UC, paediatric CD, preventive therapy in postoperative CD and extra-intestinal manifestations of IBD[2,3].

New biologic therapies, which target specific cytokines in the inflammatory cascade leading to the intestinal lesions, including tumour necrosis factor alfa (TNF-α), have revolutionized the management of IBD by offering a therapeutic chance to patients whom conventional therapies failed. Infliximab is a chimeric monoclonal IgG1 antibody that almost completely suppresses the biological activity of TNF-α. The efficacy of IFX on active CD and fistulising CD has been demonstrated in many placebo controlled studies. Recently, IFX becames an alternative option in the treatment of UC disease. Clinical efficacy of IFX has been shown in patients with moderate to severely active, steroid resistant UC in randomized, placebo controlled studies[1,4].

Opportunistic infections, autoimmune diseases, infusion reactions might occur with IFX use. Despite no clear findings regarding reactivation of latent tuberculosis and solid cancer development, they remain important problems[5].

In this report, we aimed to evaluate the efficacy and adverse events of anti-TNF monoclonal antibody IFX which was used in the treatment of CD and UC that are resistant to conventional treatments and fistulising type CD.

Materials and Methods

Patients

Thirty-six patients with a diagnosis of IBD who received IFX between January 2007 and

Corresponding Author: Ahmet Uyanikoglu, MD; e-mail: auyanikoglu@hotmail.com

November 2009 were followed-up in Department of Gastroenterology, Istanbul Faculty of Medicine, Istanbul University. IBD was diagnosed with the combination of standard clinical, endoscopic, histological and radiological findings.

The indications for IFX treatment in patients with IBD were as follows: (1) fistulising CD, non-response to conventional treatment in CD (CD Activity Index (CDAI) of more than 150 or steroid-dependent CD), and steroid-resistant UC patients who had a Clinical Activity Index (CAI) of more than 10 points or extra-intestinal involvement.

Exclusion criteria included any cancer history, pregnancy, heart failure, history of tuberculosis, symptomatic intestinal stricture and presence of abscess.

The concomitant treatments with 5-aminosalicylates, immunosuppressive agents (azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate) and antibiotics were allowed.

Protocol Before Treatment

Clinical, laboratory and endoscopic evaluations were completed in inpatient and outpatient clinics. Complete blood count, CRP, erythrocyte sedimentation rate, biochemical work-up, HBsAg, anti-HCV, chest X-ray, PPD test were performed in all patients before the initial infusion; a PPD of more than 5 mm was accepted as positive and isoniazid prophylaxis of 300 mg/day was prescribed. The symptoms and signs of patients were assessed before, during and after every infusion.

Infliximab Administration

Infliximab 5 mg/kg was given at week 0, 2, 6, and every 8 weeks thereafter. A standard premedication including intravenous methylprednisolone (20 mg/dose) and antihistamine (pheniramine 45.5 mg) were administered before every infusion. Infusions were performed under physician control with a trained nurse who had daily admissions from outpatient clinics.

Efficacy was assessed in the 16th week after the 3rd infusion. In CD, a CDAI of < 150 was accepted as complete response, > 70 decline in non-remitting patients was accepted as partial response. Closing of the fistula was accepted as complete response; more than 50% decrease in the output was accepted as partial response. In UC, a CAI of < 10 and improvement of extra-intestinal symptoms and signs were accepted as complete response

Patients were followed for all kinds of adverse events in the clinic. Infusion reactions were classified as mild that did not require cessation, however depending on the symptoms and signs it might be classified as serious that requires cessation. Serious infection, cancer and death were classified as other serious adverse events.

Statistical Evaluation

Statistical evaluation was performed using SPSS 13.0 statistical package program. Correlation analyses were undertaken with Pearson and Spearman correlation tests. A "p score" of less than 0.05 was accepted as statistically significant.

Results

The mean age of 36 patients (17 male) recruited for the study was 35 ± 12 (range, 17 to 59). Mean body mass index (BMI) was 22 ± 5 (range, 16 to 35). Of all patients 29 were ileocolonic, 1 was ileal, 1 was colonic CD, 4 were pancolitic UC and 1 was UC pouchitis. Mean age and BMI of UC patients were 47.4 ± 13.1 years and 27 ± 6.4 kg/m^2 respectively while mean age and BMI of CD patients were 33 ± 11 years and 21.5 ± 3.3 kg/m^2, respectively. UC subjects were statistically significant older and had higher BMI when compared with CD ($p < 0.05$). Male/female ratio was similar between the two groups (Table I). 20% of all patients had a history of smoking.

Median disease duration was 5.5 years (range, 1 to 28 years). 32 (88%) subjects were receiving concomitant long-term immunosuppressive treatment. 24 (75%) patients were using azathioprine, 5 were using 6-mercaptopurin and 3 of them were using methotrexate. 21 patients (59%) either received or were still receiving corticosteroids. Median disease age 7 years (range, 3 to 28) vs. 5 years (1 to 17), concomitant steroid use (80% vs. 55%) and azathioprine use (80% vs. 64%) were statistically higher in the patients with UC than CD subjects ($p < 0.05$) (Table I).

Eight patients had extra-intestinal involvement (3 ankylosing spondylitis, 1 pyoderma gangrenosum, 1 uveitis, 1 seronegative arthritis, 1 uveitis with primary biliary cirrhosis). 15 patients had a total of 19 surgical interventions (8 abscess drainages, 6 resections, 2 total colectomies, 1 partial colectomy, 1 appendectomy, 1 fundoplication and malrotation) before infliximab was initiated.

Haemoglobin level before infusions was 11.57±2.03 (range, 6.40 to 15.10) mg/dl, leukocytes

Table I. Demographic and clinical characteristics of the patients (IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis, BMI: body mass index, AZA: azathioprine, 6-MP: 6-mercaptopurine, MTX: methotrexate).

Clinical Characteristics	IBD (CD+UC)	CD	UC
n	36	31	5
Gender (M/F)	17/19	15/16	2/3
Age	35 ± 12.18 (17-59)	33 ± 10.98 (17-59)	47.4 ± 13.1 (26-58)
BMI	22.22 ± 4.62 (16.2-30.89)	(16.20-34.90) 26.98 ± 6.4	21.46 ± 3.88 (18.30-34.90)
Median disease time	5.5 (1-28) years	5 (1-17) years	7 (3-28) years
Disease involvement n (%)			
Intestine/pouch	1	1	
Colon	1	4	
Ileocolonic	29		
Steroid use n (%)	21 (59%)	17 (55%)	4 (80%)
Concomitant immunosuppressive n (%)			
AZA	24 (75%)	20 (64%)	4 (13%)
6-MP	5 (15%)	3 (10%)	1 (20%)
MTX	3 (10%)	4 (80%)	

were 7400 ± 2992 (range, 3100 to 14,400)/mm^3, thrombocytes were 391956 ± 201193 (range, 228000 to 1146,000)/mm^3, CRP was 35.99 ± 44.58 (1-188) ng/ml, sedimentation rate was 94 ± 43.1 (range, 3 to 94) mm/h, albumin was 3.31 ± 0.81 (range, 1.70 to 4.50) g/dl.

Of these patients 22 were given IFX because of fistulising CD, 8 for non-responsive CD to conventional treatments and 1 for steroid dependent CD. For patients with UC 3 were given IFX for ankylosing spondylitis, 1 for pyoderma gangrenosum, 1 for pouchitis (Table II). Patients received a median of 6 (range, 2 to 19) doses, for a mean of 14 months (1-34 months). PPD of 16 (44%) patients were positive and they were given INH prophylaxis for 6 months.

In 75% of all subjects complete or partial response was achieved. In fistulising CD 7 were complete (30%), 7 were incomplete (30%) responders, in 8 (40%) treatment was ceased (5 operations, 3 non-responders). 9 patients who were resistant to conventional treatments and who were steroid dependent, 4 responded (43%) completely, 4 responded (43%) incompletely, 1 failed to respond (14%) and medication was discontinued (Table II). Regarding UC subjects, a complete response was achieved in 3 with ankylozing spondylitis, 1 with pyoderma gangrenosum and an incomplete response was achieved in a patient with pouchitis (Table II).

A total of 261 infusions were administered in 36 patients and adverse events occurred in 18 infusions (6.9%). Ten treated (28%) experienced at least one adverse event. These were as follows: Anaphylaxis in 2 patients (6%) (in the 2nd and 7th application; one developed in the second application that was initiated after the initial treatment period was over), mild acute infusion reaction in 8 patients, hypotension in 2 patients, respiratory distress in 2 patients, skin eruptions and macules in 2 patients, hypertension in 1 and tightness in chest in 1 patient. All adverse events developed in CD except one (hypotension in a patient with UC) (Table III). Treatment was continued except with 2 patients whom anaphylaxis developed. No infection, tumour or cases of death were observed in any patient.

Discussion

The data about the long term efficacy and adverse events of IFX are not abundant. IFX use and its indications are rising worldwide; importance of drug safety is also on the increase. This study which involves 3 years of clinical follow-up is important in this respect.

Anti-TNF treatment has markedly changed the treatment of patients with treatment resistant IBD. It is effective in moderate to severely active CD and for the remission and maintenance of the activation of UC, but 20-30% of CD subjects and 30-40% of UC patients are non-responsive to this treatment[6]. While 43% complete and 43% partial

Table II. Infliximab indications in CD (Crohn's disease), ulcerative colitis and response rates.

	Fistulising CD (n: 22)	Conventional-treatment-resistant and steroid dependent CD (n: 9)	Ulcerative colitis
Complete response	7 (30%)	4 (43%)	4 (80%)
Partial response	7 (30%)	4 (43%)	1 (20%)
Non-responsive	8 (5 operations)	1 (14%)	

Table III. Adverse events associated with infliximab infusion (IBD: inflammatory bowel disease, CD: Crohn's disease, UC: ulcerative colitis).

Adverse event	IBD	CD	UC
Serious infusion reaction	2	2	0
Mild infusion reaction	8	7	1
Hypotension	2	1	1
Respiratory distress	2	2	0
Skin eruptions	2	2	0
Hypertension	1	1	0
Tightness chest	1	1	0
Total	10	9	1

improvement was obtained in our CD patients who were resistant to conventional treatments, 14% remained non-responsive. The current reimbursement guideline for anti-TNF drugs in Turkey requires presence of fistulising disease or previous treatment failure to immunosuppressive therapy to start biologics in CD. Therefore, most of the subjects with CD who receive biologics had fistulising disease. UC subjects received the treatment with the indication of an extra-intestinal involvement, thus an assessment of response to UC activation was not carried out. The long term administration of IFX in UC is not reimbursed in Turkey. Instead, steroid-refractory patients with UC may receive induction therapy with IFX. Another strategy to provide reimbursement in patients with UC who require IFX therapy is to make use of the presence of an extra-intestinal disease (especially ankylosing spondylitis) as an indication for IFX therapy. Of the extra-intestinal manifestations of UC, 3 patients with ankylosing spondylitis and 1 with pyoderma gangrenosum improved completely and 1 with pouchitis improved partially.

In a study, Ferrante et al[7] evaluated the IFX treatment of 28 patients with pouchitis and reported 88% clinical response in 22 patients with refractory pouchitis (14 partial, 8 complete), and 86% clinical response in 6 patients with fistulising pouchitis (3 partial, 3 complete). Our only patient with pouchitis had a partial response. In 22 fistulising CD patients, 60% clinical response (7 partial, 7 complete) was obtained.

In a study[8] in which the efficacy of anti-TNF treatment in fistulising CD is evaluated by magnetic resonance imaging follow-up, it is found that in patients treated with IFX fistula closed in 50% to 68%, improved to a certain degree, and no change took place in 12%. In our subjects the most common IFX indication was fistulising CD, and 30% remission (closure of the fistula) and 30% improvement was achieved. 22% of the patients underwent surgery and 18% were accepted as non-responders. In Micheller et al's study[9] 363 patients were treated with IFX since 2000. Mean age was 33.5 ± 11.2 years and the mean duration of the disease was 6.7 ± 6.1 years. The population included 114 patients (31.4%) with therapy-refractory CD, 195 (53.7%) with fistulas, 16 patients (4.4%) with both therapy-refractory CD and fistulas, and 26 patients (7.2%) with steroid dependent CD. Overall response rate was 86.2% (313/363). It is reported that short disease duration and concomitant immunosuppressive treatment were related to high response rates. 34 allergic reactions (9.4%), 17 delayed hypersensitivity reactions (4.7%), 16 infections (4.4%) and 3 malignancies (0.8%) were observed as adverse events[9]. Similarly, the most common indication was fistulising CD in our study where total response to IFX was 75%. 88% of the patients were receiving concomitant immunosuppressive therapy. In another study conducted by Gonzaga et al[10], the treatment was stopped in the fourth dose of IFX; the most common reasons for cessation of the treatment were reported to be allergies/adverse events (44.2%) in those who previously used IFX episodically and had a decline in efficacy (38.2%). In our work during the third dose of IFX treatment was stopped due to operations in 5, non-responsiveness in 4 and severe allergic adverse events in 2 patients.

Recently in many large retrospective investigations, severe adverse events and neoplasms in patients suffering from CD who were treated with

IFX were investigated[1]. In a study by Colombel et al[11] 500 CD subjects were followed for a median of 17 (range, 0 to 48) months and for a median of 3 IFX infusions; the rate of severe adverse event reported was 8.6%[11]. Moreover, Lönnkvist et al[12] referred that adverse event prevalence with IFX use was 32% and most were infusion reactions. A recent study from TREAT registry reported an overall percentage of infusion reaction of 3.0% in 53003 infusions[13]. In our research, the rate of adverse events among 261 infusions was 6.9% and 10 patients (28%) experienced at least one adverse event. Mild infusion reactions were observed in 8 patients (24%). Similarly the rate of severe adverse events was 6%. In our follow-up, no opportunistic infections or neoplasia were detected.

Hanuer et al[14] showed that production of IFX antibodies resulted in a decrease in the clinical response and an increase in the risk of infusion reactions. While the rate of infusion reactions with episodic treatment is 30%, it is reported to be 8% with regular treatment protocols. Regular treatment decreased the rate of infusion reactions and episodic treatment is shown to be more immunogenic in the ACCENT I (A Crohn's disease clinical trial evaluating infliximab in a new long-term treatment regimen) study[14]. Our patients mostly received regular treatment and developed severe adverse events (anaphylaxis); of these one developed in the second trial which was initiated after a break given after the 7th administration and was more severe which required hospitalization.

Activation of tuberculosis and disseminated tuberculosis may be seen in IBD during infliximab use[15]. This issue is especially important in our country where tuberculosis is frequent. No reactivation of tuberculosis was detected in our subjects in the 3 years follow-up. A routine PPD test was performed in all patients before treatment; in the cases of > 5 mm, a 6 months prophylaxis of INH was given. No reactivation of tuberculosis evidenced.

When Biancone et al[16] compared the rate of developing new neoplasm in 2 CD patient groups who were treated with or without IFX and found the rate to be 2.2% in IFX group and 1.73% in IFX naive group. Colombel et al[11] reported 3 newly diagnosed neoplasms in a total of 500 CD might be related to IFX[11]. In our study, we did not detect any new onset neoplasia. This might be due to limited number of patients and short duration of follow-up. Another important issue is the risk of hematological malignancies associated with biological agents used in the treatment of IBD. It has been reported that the risk of lymphoproliferative disorders increase with the long term use of immunomodulators. Although it has been thought that TNF alpha blockers increase the risk of lymphoma, this has not been confirmed[13,17]. We did not detect any hematological malignancies, but long term follow-ups are carried on.

In a study of 39 patients who were investigated for a rescue treatment due to acute severe UC, 2 severe adverse events(death from Pseudomonas pneumoniae infection and severe post-operative fungal infection) resulted in death were detected. Simple infections occurred in 4 patients. Acute and delayed infusion reactions were developed in 2 patients (after reinitiation of treatment following 9 months of a drug-free period). Spontaneously remitting elevation in aminotransferases was detected in 1 patient[18]. In our study which consisted of a similar number of subjects, lower rates of infections might be due to the differences in patient populations and the morbidity of patients in the UC study group. Higher rates of infusion reactions might be due to a longer term follow-up of our cohort. Although the rates of severe adverse events were similar, we did not encounter any cases of death.

Conclusions

As a result, IFX is effective in the treatment of IBD and results in partial or complete remission in three-fourths of patients. Several adverse events may occur in approximately one-third of subjects. Care should be given for the appearance of anaphylaxis especially if the treatment is reinitiated after a break. In the present study no serious adverse events were observed except allergic adverse events.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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