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Original Article

Managing ambulatory ulcerative colitis patients with infliximab: A long-term follow-up study in primary gastroenterology centers

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ABSTRACT

Background: Infliximab (IFX) is the key treatment for ulcerative colitis (UC) unresponsive to standard treatments. The aim of the present study was to assess the efficacy and safety of IFX in treating ambulatory UC patients in primary gastroenterology centers.
Methods: One hundred and eighteen patients (65 M, 63 F, median age 34 years, range 19–71 years), affected by UC, were treated with IFX. Clinical efficacy, safety, mucosal healing (MH), and histological healing (HH) were assessed at a scheduled follow-up of 42 months.
Results: Percentage of patients with clinical remission persistence at 42-month follow-up was 70.4%. Colectomy occurred in only 3 patients (2.7%). At 42-month follow-up percentage of patients with MH was 44.6%, and percentage of patients with HH was 24.3%. HH at 6-month follow-up occurred in 13 out of 34 patients (38.2%) with C-reactive protein (CRP) <3 and in 8 out of 76 patients (10.5%) with CRP ≥3 ($p = 0.002$).
Side effects were reported in 16 patients (13.6%): infusion reactions occurred in 7 patients, other severe side-effects occurred in 3 patients, and opportunistic infections occurred in 3 patients (2.5%). Finally, 3 cancers (2.5%) occurred during the follow-up period (1 breast, 1 kidney and 1 rectal cancer).
Both univariate and multivariate analyses showed Hb <11.5 g/dL and HH at 6-month follow-up to be significantly associated with treatment failure during follow-up.
Conclusions: IFX seems to be effective and safe in long-term treatment of outpatients affected by UC.

1. Introduction

Ulcerative colitis (UC) is a lifelong disease arising from an interaction between genetic and environmental factors, observed predominantly in the developed countries of the world [1]. It is characterized by a relapsing and remitting course, sometimes requiring an aggressive therapeutic approach in order to prevent complications [2]. The introduction of infliximab (IFX), an anti-TNFα antibody, has greatly improved our treatment options in UC [2,3]. At present, national and international guidelines recommend IFX as an effective and safe drug in inducing and maintaining remission in steroid-dependent or steroid-refractory UC, reducing complications significantly [2–6].

Mucosal healing (MH) is becoming one of the most important goals in the treatment of CD, since it has been associated with more sustained clinical remission and reduced rates of hospitalization and surgical resection [7]. Finally, UC histology is becoming an important goal of treatment [8]. Studies describing the IFX effect on histology are now becoming available [9,10]. However, no study has been conducted in primary gastroenterology centers. Moreover, we should consider that it is still needed to standardize both the histological assessment and the severity grading of these disorders [8].

We report a clinical practice experience in managing ambulatory UC patients with IFX by primary gastroenterology centers, focusing the attention to efficacy, safety, and ability to obtain MH and HH.

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2. Patient and methods

2.1. Patients

We performed a retrospective cohort study. Patients with UC were identified from 6 general hospitals and one ambulatory service in central-southern Italy. Patients were enrolled between January 2004 and December 2012. Diagnosis was based on clinical, endoscopic, and histological features. Patients were defined as "ambulatory" if they had active UC based on clinical and/or endoscopic grounds and IFX was decided upon and initiated as an outpatient. Inclusion of patients with indeterminate colitis or inflammatory bowel disease-unclassified was not allowed. Patients on IFX treatment were included if they met the following criteria: [1] cases were recorded on computer and paper, [2] patients were anti-TNFα-naïve, and [3] complete clinical, endoscopic and histological data were available during a scheduled 42-month follow-up. All centers involved used the same clinic, endoscopic, and histological approach in treating and managing UC patients. Disease extent was classified according to the Montréal Classification [11].

Azathioprine or mercaptopurine use, continued after the initiation of IFX, was considered "concomitant". Data on MH and HH after therapy were not uniformly recorded using standardized criteria, so that it was not considered as an end-point.

2.2. Clinical assessment

Disease activity was assessed by Disease Activity Index (DAI) [12]. This score was assessed at entry and thereafter at every endoscopic control. Patients were categorized as having been "responders" to IFX based on their gastroenterologist's global assessment within 6 weeks of initiation of IFX, and their progression to maintenance therapy after induction.

2.3. Endoscopy

Colonoscopy was performed in all the enrolled patients.

As a standard protocol in our centers about patients under treatment with biologics, colonoscopy was performed at entry, after 6 and 12 months and every 12 months thereafter during treatment.

Endoscopic severity was assessed by Mayo Subscore for Endoscopy [13]. Score 0 suggested inactive, 1 mildly active, 2 moderately active, and 3 severely active disease [13].

2.4. Histology

At least four biopsy samples were taken during every colonoscopy in every colonic district.

Histological severity was re-evaluated by two expert histopathologists according to the Geboes grading system for UC at the time of each endoscopic control [14]. Scores range from 0 to 5.4, with higher scores indicating more severe histological inflammation. A total Geboes score was assigned to biopsy specimens from each colonic segment and the highest score (most inflamed segment at histology) was used as the total histology score for each patient.

2.5. Endpoints

All outcomes were assessed using strict definitions and during a follow-up period of 42 months.

As stated, primary end-point was to assess efficacy and safety of IFX in treating UC in real clinical practice during a 42-month follow-up. Efficacy was defined as clinical remission rate under treatment with IFX. Clinical remission was defined as follows: 1) DAI score was ≤ 3 points; 2) steroid-free clinical response; and 3) hospitalization for exacerbations or UC-related surgery was avoided. Clinical remission was assessed by the primary gastroenterologist during follow-up after the patient's initial IFX infusion. In addition, any patient who had undergone colectomy for UC, had discontinued IFX due to loss of response, or required systemic steroids at the time of the scheduled visit, was considered as a treatment failure. Finally, "escalation" was defined as either an increase in maintenance IFX to 10 mg/kg at least every 8 weeks, or 5 mg/kg every 4–6 weeks.

Safety of IFX was defined as the absence of adverse events. They were subdivided as early (occurring during infusion) and late (occurring at least one week after the infusion) events, and graded as mild (not requiring stopping treatment) and severe (requiring stopping treatment). Occurrence of opportunistic infections was also considered as adverse event. It was defined as any infection caused by microorganisms that have limited pathogenic capacity under normal circumstances, but that have been able to cause disease as a result of the predisposing effect of another disease or its treatment.

Secondary endpoints assessed in this study were:

a. MH under treatment with IFX. It was defined as Mayo score 0 during the follow-up.
b. HH under treatment with IFX. It was defined as Geboes grade ≤ 1 during the follow-up.

2.6. Treatment

All patients were eligible for infusion of IFX after exclusion of active hepatitis B virus infection, active Cytomegalovirus infection, and TBC infection.

Fifty-four patients were under treatment with oral immunosuppressive therapy (azathioprine 1.5–2/mg/kg day) from at least 3 months before starting IFX. Azathioprine was started in further 42 patients too, in order to improve the efficacy of the induction of the remission [15].

After pre-treatment with methyl-prednisolone 20 mg intravenously (or chlorphenamine 10 mg intramuscular in patients intolerant to steroids) at every infusion, the patients underwent scheduled treatment with infliximab 5 mg/kg/e.v. at time 0, 2 and 6 weeks in order to obtain remission.

According to the above reported definition, responders to IFX at the 6th week of treatment underwent scheduled treatment with IFX 5 mg/kg/e.v. every 8 weeks in order to maintain remission. Finally, azathioprine was suspended 6 months after starting therapy in order to reduce the risk of developing fatal complications [16]. Patients were assessed at the end of the induction regimen and every two months during the follow-up.

2.7. Statistics

The collection and analysis of data were performed by using the SPSS® Release 13.0 (SPSS, Inc., Chicago, IL). Statistical analysis was performed by using the χ^2 test for categorical variables. We analyzed the probability of persistence of clinical remission using the Kaplan–Meier method. The potential prognostic factors for clinical remission, screened in univariate analysis, were further analyzed by multivariate analysis using the Cox regression model, and hazard ratios were calculated with 95% confidence interval (95% CI). Interobserver agreement was assessed by weighted kappa value and was classified as follows: poor, 0–0.20; fair, 0.21–0.40; moderate, 0.41–0.60; good, 0.61–0.80; and excellent, 0.81–1.00. A p-value of <0.05 was considered statistically significant.

3. Results

One-hundred and eighteen patients were enrolled from January 2004 to December 2012. Characteristics of patients at enrolment are shown in Table 1.