Safety and effectiveness of infliximab for inflammatory bowel diseases in clinical practice

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Abstract. – Background and Objectives: Our aim was to assess the efficacy and safety of infliximab (IFX) in clinical practice in three Primary Care, Hospital Centers.

Material and Methods: From September 2004 to December 2008 62 patients (28 males, 34 females, mean age 30.25 years, range 15-55 years), affected by ulcerative colitis (UC) (23 pts) or by Crohn’s disease (CD) (39 patients) were treated. Clinical efficacy, safety, mucosal healing and quality of life were assessed both in UC and CD.

Results: A total of 746 infusions were performed. IFX was administered for a mean of 26 months (range 8-44 months). 33/39 (84.61%) pts with CD were in remission under treatment with IFX for a mean time of 19 months (range 12-44 months). Mean Crohn Disease Activity Index (CDAI) score decreased from 295 (range 258-346) to 136 (range 98-136) (p<0.005). Inflammatory Bowel Disease Quality of Life (IBDQL) improved from 48 (at entry) to 198 (at the end of the study) (p<0.005). 20/23 (86.95%) patients with UC were in remission under treatment with IFX for a mean of 18 months (range 8-34 months). Mean Disease Activity Index (DAI) decreased from 11 (range 9-12) to <3 (range 2-3) (p<0.05). Mean Mayo Subscore for Endoscopy decreased from 3 to <1 (range 0-1). IBDQL improved from 56 (at entry) to 194 (at the end of the study) (p<0.005). Only 5 patients (8.06%) experienced side-effects.

Conclusions: Long-term outpatients treatment with IFX seems to be safe and effective in managing patients affected by IBD in clinical practice.

Key Words: Crohn’s disease, Infliximab, Mucosa healing, Remission, Ulcerative colitis.

Introduction

Crohn’s disease (CD) and ulcerative colitis (UC) are the commonest inflammatory bowel diseases (IBD), and are frequently disabling diseases. The introduction of infliximab (IFX), an anti-TNFα antibody, has greatly improved our treatment options in Crohn’s disease (CD), and its impact on the management of ulcerative colitis (UC) promises to be equally important.

In particular, IFX seems to be able in inducing and in maintaining remission in steroid-dependent or steroid-refractory CD or UC, reducing significantly complications1.

Despite the large information about the use of this drug, and despite IFX is used in clinical practice by at least 10 years, most of these data come from controlled studies and not from its use in outpatients in clinical practice. In particular, we don’t know if that patients should be managed as in-patients or as out-patients during the infusions.

This is an interesting point of discussion, since costs of infliximab infusions are very high2,3, and managing the patients as out-patients during infusions may be reduce the costs.

We report therefore our findings in managing IBD patients needing infliximab treatment as outpatients, looking at the safety of this approach.

Materials and Methods

Patients

From September 2004 to May 2008 sixty-two outpatients (28 males, 34 females, mean age 30.25
years, range 15-55 years), affected by UC (23 patients) or by CD (39 patients), were studied.

Patients reported a disease-history ranging from 3 to 8 years, and 47/62 (75.80%) were under continuative treatment with steroids from at least 6 months.

The demographic characteristics of the studied patients, as well as the colitis extension, and disease’s history are reported in Tables I and II.

All of them were under treatment with oral immunosuppressive drugs (azathioprine 1.5-2/mg/kg day: 52 patients; 6-mercaptopurine 1/mg/kg day: 13 patients) from at least 3 months.

At entry, all patients showed increased inflammatory indices (Table III).

All patients were eligible for infusion after exclusion of hepatitis B virus infection, Cytomegalovirus infection and TBC infection (by chest X-rays and by tuberculin skin test).

**Crohn’s Disease**

Disease’s activity was assessed by Crohn’s Disease Activity Index (CDAI)⁴, at entry, and at every IFX infusion.

Also Quality of Life, according to Inflammatory Bowel Disease Quality of Life (IBDQL) and ranging from 32 (worst quality of life) to 224 (best)⁵, was assessed. It assesses bowel, systemic, and emotional symptoms as well as social function, and was assessed at study entry and at the time of the last IFX infusion.

**Ulcerative Colitis**

Disease’s activity was assessed by Disease Activity Index (DAI)⁶, as well as the endoscopic activity was assessed by Mayo subscore for endoscopy⁷. Both scores was assessed at entry, after six month and therefore every year under treatment with IFX.

Also in these patients Quality of Life, according to IBDQL, was assessed at study entry and at the time of last infusion of IFX.

**Procedures**

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/i.v. at time 0, 2 and 6 weeks. Patients obtaining remission at the 6th week of treatment, underwent to scheduled treatment with infliximab 5 mg/kg/i.v. every 8 weeks in order to maintain remission.

**Statistical Assessment**

Data analysis was carried out by using Fisher’s exact test with Yate’s correction for small numbers, Student’s t-test for unpaired data, Mann-Whitney two samples U-test, as appropriate. Values of \( p<0.05 \) were considered as statistical differences.

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**Table I.** Characteristics of the Crohn’s disease’s (CD) patients studied.

<table>
<thead>
<tr>
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<th>18/21</th>
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<tbody>
<tr>
<td><strong>Males/Females</strong></td>
<td>18/21</td>
</tr>
<tr>
<td><strong>Indications for IFX treatment:</strong></td>
<td></td>
</tr>
<tr>
<td>Luminal CD (%)</td>
<td>32 (82.05)</td>
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<tr>
<td>Fistulizing CD (%)</td>
<td>7 (17.95)</td>
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<tr>
<td>Mean age at the time of diagnosis (years)</td>
<td>27.45 (14-51)</td>
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<tr>
<td>Mean age at the time of the first IFX infusion (years)</td>
<td>31.05 (15-55)</td>
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<tr>
<td>Mean duration of the disease prior to IFX treatment /years)</td>
<td>4 (1-7)</td>
</tr>
<tr>
<td>Mean follow-up under IFX treatment (months)</td>
<td>19 (12-44)</td>
</tr>
<tr>
<td><strong>Disease’s localization:</strong></td>
<td></td>
</tr>
<tr>
<td>Ileitis (%)</td>
<td>8 (20.51)</td>
</tr>
<tr>
<td>Colitis (%)</td>
<td>10 (25.63)</td>
</tr>
<tr>
<td>Ileo-colitis (%)</td>
<td>16 (44.45)</td>
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<tr>
<td>Perianal (%)</td>
<td>3 (7.69)</td>
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<tr>
<td>Upper GI tract (%)</td>
<td>2 (5.13)</td>
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<tr>
<td>Smokers (%)</td>
<td>17 (43.58)</td>
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<tr>
<td><strong>Drugs currently taken at the first IFX infusion:</strong></td>
<td></td>
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<tr>
<td>Amino-salicylates</td>
<td>29 (66.66)</td>
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<tr>
<td>Steroids</td>
<td>39 (100)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>76 (92.9)</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>11 (28.2)</td>
</tr>
<tr>
<td>Mean CDAI at the time of first IFX infusion</td>
<td>295 (258-346)</td>
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<tr>
<td>Mean PCR at the time of first IFX infusion</td>
<td>10.40 (7.0-19.0)</td>
</tr>
</tbody>
</table>
Results

Infliximab was administered for a mean of 26 months (range 8-44 months). A total of 746 infusions were performed.

60/62 (96.78%) patients underwent remission after the 3rd infusion at 6th week, and steroid was withdrawn within 4 weeks after starting treatment. Also immunosuppressive treatment was withdrawn within the 3rd month of treatment with infliximab to avoid the risk of malignancy. Patients in remission at the 6th week of treatment underwent scheduled treatment with infliximab 5 mg/kg/i.v. every 8 weeks, and maintained remission for a mean time of 26 months (range 8-44 months).

Crohn’s Disease

33/39 (84.61%) patients with CD were in remission under treatment with IFX for a mean time of 28 months (range 12-44 months).

Looking at the different localization of the disease, 23/27 (95.83%) patients with luminal disease, 4/5 (80%) patients with small bowel strictures, and 3/3 (100%) patients with perianal disease underwent long-term remission.

Two patients relapsed at 14th and 18th month of treatment respectively, and were successfully treated with adalimumab. Two patients loose the response to IFX at 16th and 20th month of treatment respectively, and also these patients were successfully treated with adalimumab. One patient with ileal stricture did not achieve resolution of the stricture at 6th week of treatment, and underwent surgery (Figure 1).

CDAI decreased from a mean score of 295 (range 258-346) to a mean score of 136 (range 98-136) ($p<0.005$). Finally, IBDQL improved from 48 (at entry) to 198 (at the end of the study) ($p<0.005$ (Figure 2).
Three patients (7.69%) experienced side-effects. Two patients (5.13% of the overall treated patients) experienced mild side-effects (one headache and one somnolence) not requiring suspension of the treatment; one patient (2.56%) experienced severe side-effects (cholestasis) at 12th month of treatment, requiring stopping treatment (Figure 1).

**Ulcerative Colitis**

20/23 (86.95%) patients with UC were in remission under treatment with IFX for a mean of 24 months (range 8-34 months). One patient affected by left-sided colitis relapsed at 18th month of treatment, and was successfully treated with methotrexate. One patient affected by pancolitis relapsed at 10th month of treatment, and underwent surgery (Figure 3).

The DAI score decreases from a mean value of 11 (range 9-12) at entry to a <3 mean value (range 2-3) at the time of the last endoscopic assessment (p<0.05) (Figure 4).

The IBDQL score improved from 48 (at entry) to 198 (at the end of the study) (p<0.05) (Figure 4).

Also the endoscopic appearance improved dramatically. Colonoscopy showed diffuse loss of vascular pattern and edema in the mucosa, diffuse ulcerations and easy bleeding on contact with colonoscope at entry (all patients showed value 3 as Mayo endoscopic subscore). At the end of follow-up, colonoscopy showed complete disappearance of ulcers and edema in the mucosa, and reappearance of vascular pattern in all patients evaluated (Mayo endoscopic subscore 0-1). The Mayo subscore for endoscopy decreased therefore from mean value of 3 to mean value <1 (range 0-1) at the time of last endoscopic assessment (p<0.05).

Looking at the adverse events, two patients (8.69%) experienced side-effects. One patient (4.34%) affected by left-sided colitis experienced headache, not requiring suspension of the treatment; another-one patient (4.35%) affected by pancolitis developed sepsis by *Proteus* strain, requiring stopping treatment and colectomy (see Figure 3).

**Laboratory Indices**

The inflammatory indices were normal in all patients at the end of follow-up. Only the mean value of ESR persisted elevated during the follow-up but in absence of clinical recurrence of the disease. However, the mean values of inflammatory indices assessed in the study decreased statistically at the end of follow-up (see Table III).
Safety
Five (8.06%) of the overall treated patients experienced side-effects: Three patients (60%) experienced mild side-effects (two headache and one somnolence) after infusion, none of them requiring suspension of the treatment; two patients (40%) experienced side-effects requiring stopping treatment: one patient developed sepsis 18

Figure 2. Activity of the disease and quality of life before and at the end of follow-up in Crohn’s disease’s patients. CDAI: Crohn’s disease activity index; IBDQL: Inflammatory bowel disease quality of life.

Figure 3. Outcome of UC patients under treatment with infliximab.
months after starting therapy; another-one patient experienced cholestasis 16 months after starting therapy.

**Discussion**

Ulcerative colitis and Crohn’s disease are distinct entities, but an imbalance between pro-inflammatory and anti-inflammatory cytokine production is suspected in both conditions. In contrast to CD, UC has been traditionally associated with a dysregulated Th2 response. However, it has been shown that TNF-α may also play a role in its pathogenesis. In this respect, patients with UC, on severe flare-up, show pathological and clinical aspects similar to those of CD.

In the last years, several fine papers showed the effectiveness of infliximab in obtaining and maintaining remission both in CD and in UC. Although IFX is used in clinical practice by at least 10 years, most of these data come from controlled study and not from its use in outpatients in clinical practice. Only in the last year some papers have described the safety and the tolerability of the IFX treatment in clinical settings by nonacademic gastroenterologists or by general practitioners, confirming data coming from controlled studies. However, most of these new data in clinical practice did not show a long-term use over 1 year.

Our results showed that infliximab is effective in inducing and maintaining remission in CD in clinical practice in outpatients. In fact, 84.61% of patients with CD were in remission under treatment with IFX for a mean time of 28 months. This result is better than recently described by other Authors, who showed rate of maintaining long-term remission ranging from 63.4 to 78%. This approach seems to be effective in every type of the disease. In fact, 95.83% of patients with luminal disease, 80% of patients with small bowel strictures, and 100% of patients with perianal disease maintained remission up to the end of follow-up.

Also the safety was optimal. Side-effects were recorded in only three patients (7.69%), two of them experiencing mild side-effects not requiring suspension of the treatment and only one patient (2.56%) experienced severe side-effects at 12th month of treatment, requiring stopping treatment. These data are better than described by recent literature. The TREAT registry found 30.8% of moderate-to-severe side-effects and 2.5% of severe-fulminant side-effects. Two very recently surveys on 620 patient-years follow-up in clinical practice and of 614 patients coming from a sin-

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**Figure 4.** Disease’s activity and quality of life before treatment with IFX and at the end of follow-up under scheduled treatment with IFX in ulcerative colitis patients. DAI: Disease activity index; IBDQL: Inflammatory bowel disease quality of life.
gle-centre experience found 28% (with 36 serious adverse events) and 12.8% (all severe adverse events requiring stopping treatment) of side-effects respectively\textsuperscript{16,19}.

We obtained the same interesting results also in treating UC. Although IFX was found effective both versus steroids and versus placebo in obtaining remission in steroid-dependant and steroid-resistant UC\textsuperscript{12}, most of these data described the infliximab efficacy in short-term treatment. We treated UC patients with infliximab for mean time of 24 months (range 8-34 months): 20/23 (86.95%) patients with UC were in remission under treatment with IFX, and only 1/23 (4.35%) required colectomy under treatment. Literature data about long-term infliximab treatment on UC are unclear. A recent review\textsuperscript{12} found that overall long-term response to infliximab was 53%, and long-term remission was achieved in 33% of patients. The larger studies, ACT-1 and -2, treated patients for 46 (ACT-1) or 22 weeks (ACT-2), and therefore followed-up clinically up to 54 (ACT-1) or 30 weeks (ACT-2). In both cases the long-term efficacy was 52% and 35% respectively\textsuperscript{12}. More recent long-term studies obtained similar results. A recent Italian survey on 83 patients\textsuperscript{21} showed that only 53 patients (69.87%) avoided colectomy after a median time of 23 months under treatment with IFX. Similar results were described by a recent Spanish multicenter survey\textsuperscript{22}, while a more recent study\textsuperscript{23} found that 73.6% of UC patients maintained an ongoing response for a mean duration of 16.8 months, with 55.3% being in remission. In both of the larger studies adverse events occurred from 11% to 13.2\%\textsuperscript{21,22}, whilst we recorded adverse events only in 8.69% of patients. Finally, also mucosal healing was obtained in most of our patients, with statistical reduction of Mayo score. Looking at the ACT-1 and ACT-2 studies\textsuperscript{20}, the active treatment resulted in complete endoscopic healing (meaning endoscopic Mayo subscore equal to 0) in 27% of cases, compared to only 8% in the placebo group. On the contrary, a recent Italian multi-centre experience\textsuperscript{24} showed that mucosal healing was maintained in 76% at week 54.

Several important points may explain our results. First of all, we adopted scheduled treatment, and this approach seems to be superior to episodic treatment in maintaining remission and in obtaining mucosal healing\textsuperscript{25,26}.

Another important point was the combined treatment with azathioprine for at least 3 months. This approach reduce the risk of anti-IFX antibodies, which is a cause of loosing response to drug\textsuperscript{27}. Moreover, this combined approach seems to be the best approach in naïve patients, as showed by a recent Belgian research\textsuperscript{28}.

Also the optimal selection of patients may explain our data. The lower mean age at the time of the first infusion and the absence of concomitant autoimmune or infective diseases may be an important point to obtain remission and maintain the remission in IBD\textsuperscript{29}. From this point of view, an early combined approach in these patients may be the best approach, bearing in mind that azathioprine should be withdrawn after some months to avoid the risk of T-cell lymphoma in young adults taking combined therapy\textsuperscript{30}.

Finally, the lower adverse events recorded may be related not only to the optimal selection of the patients, but also to pre-treatment prior to IFX infusion. We pre-treated the patients with methylprednisolone 20 mg intravenously, or chlorphenamine 10 mg intramuscular in patients intolerant to steroids, at every infusion. Very low severe side-effects were recorded, as well as no death were recorded during a mean 26 months follow-up. As showed by two recent wide clinical experiences\textsuperscript{30,31}, pre-treatment with anti-histamine and/or prednisone is one of the most important good clinical practices that may reduce the frequency of infliximab reactions and to increase safety.

In conclusion, this long-term, clinical experience in treating outpatients with infliximab confirms that infliximab is able to obtain remission in CD and UC outpatients, as well as to obtain mucosa healing, and maintain remission. Moreover, our study confirms that a good clinical selection of the patients, a combined treatment with azathioprine and IFX, and the pre-treatment seem to be a useful strategy to increase the rate of remission, to improve mucosal healing, to reduce the frequency of infliximab reactions and to increase safety also in outpatients.

References


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