Efficacy of infliximab in Crohn’s disease. Results of a retrospective multicenter study with a 15-month follow-up

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Introduction

Infliximab is a chimeric monoclonal antibody directed against tumor necrosis factor α (TNFα). It has demonstrated efficacy in patients presenting steroid-resistant or steroid-dependent Crohn’s disease (CD) as well as forms with perianal fistulae [1, 2]. After the initial randomized trials, several investigations conducted in routine clinical settings showed that the clinical response rate usually varies between 60 and 80%, about half of patients achieving remission after one or more infusions. In France, infliximab has had marketing approval since late 1999. Two studies carried out in western and eastern France examining 69 and 84 patients respectively with both active CD and also perianal fistulæ found very similar response rates close to 70% [3, 4]. In addition, Ouraghi et al. [5] reported a 71% response rate among patients requiring infliximab treatment for perianal fistulæ, with closure in 39% and sustained response of...
58% at six months. Follow-up in clinical trials conducted in French, European or American centers has varied from eight weeks to eight months after the last infusion [3-16].

The goal of this retrospective study was to evaluate prescription practices and short- and mid-term (> 1 year) outcome among adult CD patients who had received at least one infliximab infusion in the year 2000 and who were followed in the gastroenterology units of the university teaching hospitals of the Parisian hospitals group (AP-HP).

Patients and methods

The files of all the patients having received at least one infliximab infusion for CD in the adult gastroenterology units of the AP-HP between the 1st of January and the 31st of December 2000 were analyzed. Patients whose infliximab treatments were prescribed within the framework of an institutional protocol were not retained for this study. Demographic data, disease characteristics, treatments received, surgical interventions carried out before the first infliximab infusion, modalities of infliximab treatment, and associated treatments were noted.

A standard 5 mg/kg dose of infliximab was administered in a 2 hr infusion followed by surveillance for 2 hr in all patients except three who received 2.5, 7 and 10 mg/kg respectively.

Four categories of disease activity were defined. Patients with perianal or intestinal involvement which could not be controlled with usual treatments were considered to have active disease. Patients who were symptom-free or whose CDAI (Crohn's Disease Activity Index), when available or determined retrospectively, was less than 150, or whose perianal fistulae had closed at proctology examination, were considered to be in complete remission. Partial remission was defined as incomplete symptom improvement or a decrease of the CDAI of more than 70 points, when the CDAI was not available in the file or calculable retrospectively, or a decrease in the number of fistulae or fistular discharge of more than 50%. Relapse was defined as recurrent disease activity after complete or partial remission. Patients were considered to be responders if they achieved complete or partial remission during the first four weeks for intestinal-type disease, or in the first ten weeks in those with a perianal fistula. Steroid-resistance was defined as non-response after more than four weeks of corticosteroid therapy at 1 mg/kg/d (equivalence of prednisone). Steroid-dependence was defined as a dose of corticosteroids needed to maintain remission between 10 mg/d and 1 mg/kg/d (equivalence of prednisone). Three indications for treatment were identified: active disease (bowel involvement), perianal involvement and/or other type of fistulization, combined form associating both conditions.

Initial treatment was defined as the first series of one to three infliximab infusions. Re-treatment was defined as a new series of infusions (one to three infusions depending on the center). Maintenance therapy was defined as administration of at least two re-treatments. Time to relapse was defined as the time between the last infusion of the initial treatment and the appearance of clinical relapse.

Statistical analysis

Results are expressed as mean ± SD or percentage. The χ² test was applied to compare qualitative variables and Student’s t test for means. The Kaplan-Meyer method was used to establish relapse-free survival curves which were compared with the log-rank test to search for differences by age, gender, immunosuppressive treatment, smoking, and disease duration.

Results

One hundred fifty-eight patients received at least one infliximab infusion in one of the 15 gastroenterology units of AP-HP in predefined time period. The files of 147 (93%) of the patients could be consulted. Ten patients were excluded from the study due to the following: missing data or inclusion in an institutional protocol (N = 7), severe labial CD without intestinal involvement (N = 1), an enterocutaneous fistula not found to be associated with CD (N = 1), and a case of an anal squamous cell carcinoma mistaken for perianal CD. The 137 patients retained for study had been treated in 12 of the 15 participating units (two centers treated > 25 patients, three 10 to 20, and seven < 10). Patient characteristics and prior treatments are summarized in table I.

Medical treatment at the time of the 1st infusion

Data concerning ongoing treatment at the time of the first infusion of infliximab were available for 130 patients. Twenty-one patients (16%) were without treatment, 5 (4%) were on salicylates derivatives, 79 (61%) on corticosteroids and 65 (50%) on immunosuppressive drugs. Regarding the patients receiving corticosteroids, 37% were steroid-dependent with an average dose of 28.0 ± 15.7 mg/d prednisone equivalent and 24% were steroid-resistant. Corticosteroids were continued in 68 patients. Among the 65 patients on immunosuppressive drugs, 31 (24%) were using a single immunosuppressive drug (excluding cyclosporine) alone, 30 (23%) received corticosteroids in combination with an immunosuppressive drug, 3 (2%) received salicylates derivatives in combination with an immunosuppressive drug, and one (0.8%) was given a corticosterol-salicylate derivative-immunosuppressive drug combination. Thirty-five patients were taking azathioprine or 6-mercaptopurine, with an average dose of 2.31 ± 0.40 mg/kg/d and remained at that level 12.3 ± 8.1 months.

Indications for infliximab

In 53 patients (39%), the indication for infliximab was fistulizing CD or perianal involvement. Nine patients (17%) had enterocutaneous fistulae and one a sigmoidovesceral fistula. Infliximab was prescribed for 62 patients (45%) with active intestinal CD: 15 of these patients (11%) had clinical and/or endoscopic signs of severe acute colitis. There were 22 patients (16%) who had both active intestinal disease and perianal involvement.

Number of infusions

An average of 3.6 ± 2.4 infliximab infusions were carried out per patient (range: 1-11, median: 3) (figure 1). The average follow-up after the first injection was 15.2 ± 7.2 months (median 14 months).

Overall response

Overall, 85% of patients responded to the first series of infliximab infusions. Median time to obtain remission was 33 days (figure 2). Clinical evolution in terms of time in the 123 responders (% of patients without relapse) is also presented in figure 2. There was no significant difference in duration of remission according to gender (P > 0.5), age (P > 0.5), indication for treatment (fistulization, active disease, both conditions) (P = 0.33), disease duration (more or less than 1 year) (P > 0.5), use of immunosuppressive drugs or not (P = 0.36), or smoking habit (P = 0.425).

In the group of sixty-five patients (47%) who received only the initial treatment (1 to 3 infusions without re-treatment or maintenance therapy), 11 (17%) were non-responders, 18 (28%) exhibited partial or transient remission, 32 (50%) achieved complete remission, and three were lost to follow-up. There was no difference regarding clinical or demographic variables or associated treatments between the 28 patients in complete remission without re-treatment and the group of treated patients (data not shown).
Average time to relapse, assessable in 82 patients, was 3.9 ± 3.1 months (median 3, range: 1-19).

Seventy-two patients (53%) were retreated with at least one infusion (average 3.1 ± 2.3) within an average delay of 5.7 ± 4.2 months after the initial treatment. A single series of re-treatment infusions was undertaken in 34 patients who received one (N = 24), two (N = 6) or three (N = 4) re-treatment infusions. At the end of the study period, the other 38 patients received maintenance therapy, given systematically every two to three months for 12 patients and treatment on demand for the remaining 26. Progressive loss of response to treatment was noted in 1.4 (37%) of these patients.

Response by indication

Therapeutic indication had no effect on response rate (P = 0.32). Fifteen patients were treated for acute severe colitis but according to no standard protocol. Remission was achieved in 9 patients but six of them relapsed within three months on average.

Three patients were treated for active intestinal disease with small bowel stricture and only one patient presented signs of intestinal occlusion.

Associated treatments

During the study period, immunosuppressive drugs were used in combination with infliximab in 78% of patients (79 given azathioprine, 6-mercaptopurine or thioguanine; 38 given methotrexate; 4 given moetyl mycophenolate). Certain patients were treated successively with different immunosuppressive drugs. Response to infliximab was not modified by addition of immunosuppressive drugs (P = 0.36).

Twenty-one patients (16%) received thalidomide following infliximab. This sequence was effective in 11 patients (52%) and failed in 6 (29%). Thalidomide was discontinued due to adverse effects before day 10 in two patients and had been introduced too late for evaluation in two others.

Treatment with infliximab allowed steroid withdrawal in 82% of the patients on corticosteroids at the time of the first infusion. There was no significant difference in the rate of corticosteroid withdrawal between patients treated or not with immunosuppressive drugs (P = 0.28).

Adverse effects

Forty adverse events, potentially attributable to infliximab treatment, were noted in 32 patients (23% of patients, 8% of infusions). Twelve of these events (27% of events, 2% of infusions) occurred during the course of the infusion and resolved after discontinuation or reduction in rate of infusion. An anaphylactic reaction occurred in one patient and resolved with specific treatment. Twenty-eight events occurred late after the end of the infusion (5.5% of infusions) and are detailed in specific treatment. Twenty-eight events occurred late after discontinuation or reduction in rate of infusion. An ana-

### Table I

**Table I** – Patient characteristics and treatments before the first infusion of infliximab (mean ± SD).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36 ± 12.7</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>45/92</td>
</tr>
<tr>
<td>Smokers</td>
<td>54 (39%)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>30 (22%)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>10.0 ± 7.4</td>
</tr>
<tr>
<td>Disease localization:</td>
<td></td>
</tr>
<tr>
<td>esophagus</td>
<td>5 (3.7%)</td>
</tr>
<tr>
<td>stomach</td>
<td>15 (11.1%)</td>
</tr>
<tr>
<td>ileum</td>
<td>81 (59.3%)</td>
</tr>
<tr>
<td>caecum and right colon</td>
<td>109 (80.1%)</td>
</tr>
<tr>
<td>transverse colon</td>
<td>101 (74.1%)</td>
</tr>
<tr>
<td>left colon</td>
<td>107 (77.8%)</td>
</tr>
<tr>
<td>sigmoid</td>
<td>111 (80.7%)</td>
</tr>
<tr>
<td>rectum</td>
<td>99 (71.9%)</td>
</tr>
<tr>
<td>entire colon</td>
<td>73 (53.0%)</td>
</tr>
<tr>
<td>perianal</td>
<td>102 (74.5%)</td>
</tr>
<tr>
<td>Prior medical treatments:</td>
<td></td>
</tr>
<tr>
<td>salicylates</td>
<td>134 (98%)</td>
</tr>
<tr>
<td>corticosteroids</td>
<td>124 (91%)</td>
</tr>
<tr>
<td>azathioprine or 6-mercaptopurine</td>
<td>109 (80%)</td>
</tr>
<tr>
<td>methotrexate</td>
<td>47 (34%)</td>
</tr>
<tr>
<td>Prior surgery:</td>
<td></td>
</tr>
<tr>
<td>at least one procedure</td>
<td>90 (66%)</td>
</tr>
<tr>
<td>mean number of operations</td>
<td>2.6 ± 2.4</td>
</tr>
</tbody>
</table>

**Discussion**

This retrospective study reports prescription practices in the AP-HP during the first year of regular use of infliximab for the treatment of CD. Overall results in 137 patients show that two-thirds of patients benefited from the treatment.

Our study shows that the indications recommended in the marketing approval document were globally respected. The two cases of ulcerative colitis were diagnosed at the histological examination after colectomy, while the clinical diagnosis retained at the time of treatment was CD. The standard 5 mg/kg dose was prescribed for nearly all of the patients while the number of infusions for initial treatment was not strictly controlled. In a certain number of cases, treatment was interrupted when the patient achieved complete remission. Rapid improvement, particularly when complete remission was achieved before the end of the third infusion, raised the question of the usefulness of pursuing a costly treatment for which the average length of tolerance was poorly known. In other cases, patients whose CD was limited to luminal manifestations were given three infusions of infliximab,
The indications recommended in the 2004 authorization appear to be common practice during this first year of regular use. Such practices, which were not mentioned in the 1999 authorization, offer some insight into current use of maintenance protocols which will not be finalized until the ACCENT I [16].

This probably explains in part the high rate of corticosteroid reversioning to corticosteroids. All the same, a certain number of patients were treated despite the fact that their conditions were not retained for treatment in the initial trials (patients with a history of colectomy, patients with a series of intestinal strictures, patients with ulcerated or stenotic perianal lesions which had not fistulated) [1, 7]. This is probably related to two potential biases in the order of two to eight months [3-5, 7-16]. Thirty-four percent of the patients treated for fistulae achieved complete remission and 36% partial or transient remission; a maintenance schedule was prescribed for 17%. These results are comparable with those obtained in randomized studies [2] or retrospective studies [5, 6, 12, 14].

The average follow-up after the first infusion was 15.2 ± 7.2 months. This is an important feature of the present study in comparison with earlier work which reported follow-up to the order of two to eight months [3-5, 7-16].

The results of our study confirm the short-term efficacy of infliximab. The long-term results are more difficult to interpret because of important differences in disease course and treatment modalities between the different centers. The addition of an immunosuppressive drug was systematic in some centers but not in others and some patients were retreated after a long period of remission (average time to relapse 3.9 ± 3.1 months) as in earlier reports [8, 16, 17].

The CDAI and the Harvey-Bradshaw score are widely used to evaluate the effectiveness of therapeutic management in Crohn’s disease. Nevertheless, few physicians use them in routine clinical practice as demonstrated by our results from university hospitals. For the initial trials which demonstrated the efficacy of infliximab, variations in the CDAI were used as evaluation criteria [1, 8].

For our retrospective study, pragmatic clinical information readily available from the medical files — complete remission, partial improvement, relapse — were used as evaluation criteria.

Our study population was quite comparable with those reported in other clinical studies regarding demographic data, disease duration, proportions of the different clinical forms, and previous medical and surgical treatments [3-6, 10-12, 14]. During the study period, treatment with infliximab was reserved for patients with active disease resistant to usual treatments.

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Twenty-eight percent of patients received maintenance therapy whereas its’ efficacy was subsequently reported in the literature [16]. Relapse occurred in 36.8% of
patients on maintenance therapy and this is similar to those reported elsewhere [12, 13, 16]. The steroid-sparing effect appears to be one of the major benefits of infliximab treatment: prolonged steroid withdrawal was successful in 82% of our patients. This confirms steroid-sparing rates of 40 to 81% from earlier clinical practice reports [10-12] which could be partly attributable effects of anticipated re-treatment and maintenance therapy which were subsequently validated [16]. Considering the young age of the patients and the harmful effects of prolonged corticosteroid therapy, particularly for bone mass, this beneficial effect of infliximab treatment is important.

No factor predictive of response was identified. Smoking has been clearly identified as a factor associated with severity of CD [18, 19]. The smoking status of patients was not always well detailed in the randomized studies or routine practice studies. Parsi et al. did however demonstrate that non-smokers respond better than smokers among patients with predominantly inflammatory disease [21]. The smoking status was known for all of our patients, but this factor was not found to be significant. Other factors predictive of clinical response reported in earlier studies include recent disease onset [5], which was not found in our study, associated immunosuppressive treatment [9, 12] and exclusive colonic involvement [20]. In our study, response to infliximab was not better among patients given azathioprine. However, a recent prospective study confirmed this hypothesis among steroid-dependent patients [22]. The anti-TNF effect of thalidomide led to its use among 22 patients in the present study. This enabled sustained remission in slightly more than half of the treated patients but at the cost of non-negligible side effects. The report by Sabaté et al. [23] which included some of these patients demonstrated the beneficial effect of thalidomide in terms of sustaining remission.

In all, 23% of patients (8% of infusions) developed adverse effects related to infliximab treatment. This rate is less than in the initial studies [1, 2, 8], probably because of the retrospective nature of the data collection. In addition, several of the events recorded may not have been attributable to infliximab. For example, the absence of headache, almost never noted in the medical files, was rather surprising in light of the high frequency in earlier data [1, 8, 24]. Furthermore, we intentionally separated adverse effects related to CD itself. There was only one case of tuberculosis in this series; 70 cases have been reported among 147,000 patients treated with infliximab worldwide (for both CD and rheumatoid arthritis) [24-26]. Preventive measures instituted in 2002 should limit this risk [27]. We also had one case of cutaneous lupus [16], two cases of neurological disorders, and one case of liver anomalies, all adverse effects potentially attributable to infliximab [28-31]. Overall, the rate of adverse events observed in our patients (18%) was close to that observed in the first 500 patients treated at the Mayo Clinic [31].

In conclusion, this study conducted in a setting of routine clinical practice over a long follow-up period during the first year of regular prescription of infliximab in the Parisian hospital of the AP-HP group confirmed its efficacy and the safety. We were unable to identify factors predictive of short-term or long-term responses. Later changes in prescription recommendations, particularly concerning maintenance therapy, had been anticipated by the practitioners during the first year of use. These prescription practices merit further study.

**REFERENCES**


