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 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

SUMMARY

Objectives — To evaluate prescription practices and response to infliximab treatment for Crohn’s disease (CD).

Patients and methods — The files of CD patients treated with at least one infusion of infliximab treated in gastroenterology units belonging to university teaching hospitals of the Parisian hospitals group (Assistance Publique-Hôpitaux de Paris (AP-HP)) during the year 2000 were analyzed retrospectively.

Results — One hundred and thirty-seven patients (36.0 ± 12.7 years, 92 females) from 12 centers were studied. Indication for treatment was fistulæ or perianal disease in 39% of patients, active Crohn’s disease in 45% and mixed conditions in 16%. Mean follow-up was 15.2 ± 7.2 months. The overall response rate was 85%. No predictive factor of sustained remission could be identified. The mean time to relapse was to 3.9 ± 3.1 months. Thirty-eight patients were on maintenance therapy at the end of the follow up; 37% exhibiting progressive lost of response to treatment. Immunosuppressive therapy was added to infliximab in 78% of cases but response to infliximab was not modified by addition of immunosuppressive drugs. Adverse events, most frequently minor, were noted in 23% of the patients.

Conclusion — This retrospective study confirms the efficacy and safety of infliximab in CD.

RÉSUMÉ

Objectifs — Le but de cette étude était d’étudier les modalités d’utilisation du traitement et le devenir des malades traités par infliximab pour maladie de Crohn MC en 2000 à l’Assistance Publique-Hôpitaux de Paris (AP-HP).


Résultats — Cent trente-sept malades (36,0 ± 12,7 ans, 92 femmes) traités dans 12 centres ont été inclus. L’indication du traitement était une maladie fistulisée ou des lésions ano-périnéales dans 39% des cas, une maladie active dans 45 % et une forme mixte dans 16 %. Le nombre moyen d’injection administré a été de 3,6 ± 2,4 injections par malade. Le suivi moyen était de 15,2 ± 7,2 mois. Au total, 85 % des malades ont eu une réponse initiale. Aucun facteur prédicteur de durée d’efficacité n’a été retrouvé. Le délai moyen de rechute était de 3,9 ± 3 mois. Trente-huit malades étaient en traitement d’entretien à la fin du suivi, avec échappement progressif au traitement chez 37 %. Un traitement immunosupresseur a été associé au traitement par infliximab dans 78 % des cas. L’efficacité de l’infliximab n’était pas modifiée par l’adjonction d’un immunosupresseur (P = 0,36). Un effet indésirable, le plus souvent peu sévère, a été noté chez 23 % des malades.

Conclusion — Cette étude rétrospective confirme l’efficacité du traitement par infliximab dans la MC, son rôle d’épargne en corticoïdes et sa sécurité d’emploi.
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 those who received 2.5, 7 and 10 mg/kg/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 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 tubal CD without intestinal involvement (N = 1), an entero-cutaneous fistula not found to be associated with CD (N = 1), and a case of 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 derivates, 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 immunosuppressant drug (excluding cyclosporine) alone, 30 (23%) received corticosteroids and salicylates derivatives in combination with an immunosuppressive drug, 3 (2%) received salicylates derivatives in combination with an immunosuppressive drug, and one (0.8%) was given a corticosteroid-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 entero-cutaneous fistulae and one a sigmoidovesicular 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 methylprednisolone). 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 table II. Of the infectious complications involved pulmonary and bone-and-joint tuberculosis. Seven of the infectious complications arose in patients also given corticosteroids. The one case of lupus was diagnosed 3 months after the first infliximab infusion. Cancer, lymphoma, and serum sickness were not observed. None of the women became pregnant during the course of treatment. The adverse events were noted at the first (N = 14), second (N = 8), third (N = 10), fourth (N = 1), and fifth (N = 6) infusion.

Treatment with infliximab was also associated with the appearance of CD complications. Seven patients developed at least one perianal abscess; two developed an abscess complicating the closure of an enterocutaneous fistula, and nine exhibited manifestations secondary to one or more symptomatic bowel strictures. Anal incontinence was unmasked by the treatment in one patient.

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± SD</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,
anticipating the later marketing approval indications promulgated in 2004. In the event of relapse, re-treatment or maintenance therapy, either systematically or on a demand basis, did not 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 withdrawal: re-treatment with a new series of infusions or a maintenance schedule with infliximab being preferred over reverting 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 of this study: a recruitment bias (some of the participating units are secondary or even tertiary referral centers), and a selection bias since the first year of regular use would include a larger proportion of patients with long-term resistance to usual treatments. The indications recommended in the 2004 authorization document better define care for these patients.

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.

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]. 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 35% response rate among patients treated for active disease is similar to rates reported from Edinburgh [14] or Amsterdam [12]. There has been only one report by Ricart et al. [6] concerning patients treated for combined forms of CD: the response rate was 84.5% in the study but almost all patients also received an immunosuppressive drug from the beginning of the infliximab treatment. In our study, 32% of the patients treated for a combined form of disease achieved complete remission, 31.8% partial or transient remission, and 31.8% sustained remission while taking maintenance therapy.

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]. Twenty-eight percent of patients received maintenance therapy whereas its’ efficacy was subsequently reported in the literature [16]. Relapse occurred in 36.8% of
Infliximab for Crohn’s disease

Table II – Adverse events (N = 28) observed late after infliximab infusions.

<table>
<thead>
<tr>
<th>Late complications</th>
<th>N=28</th>
</tr>
</thead>
<tbody>
<tr>
<td>infectious</td>
<td>18</td>
</tr>
<tr>
<td>bacterial</td>
<td>10</td>
</tr>
<tr>
<td>viral</td>
<td>2</td>
</tr>
<tr>
<td>fungal</td>
<td>6</td>
</tr>
<tr>
<td>cutaneous</td>
<td>5</td>
</tr>
<tr>
<td>lupus</td>
<td>1</td>
</tr>
<tr>
<td>benign maculopapulosis eruption</td>
<td>3</td>
</tr>
<tr>
<td>aggravation of pre-existing psoriasis</td>
<td>1</td>
</tr>
<tr>
<td>neurologic</td>
<td>2</td>
</tr>
<tr>
<td>metabolic</td>
<td>2</td>
</tr>
<tr>
<td>thromboembolic</td>
<td>1</td>
</tr>
</tbody>
</table>

Among 147,000 patients treated with infliximab worldwide [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 response. 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


