Treatment of Crohn’s disease with anti-TNF alpha antibodies (infliximab)
Results of a multicentric and retrospective study

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SUMMARY

Objective — To evaluate the results of infliximab therapy, an anti-TNF-α antibody, in patients with severe and refractory Crohn’s disease or with fistulas, treated outside the setting of a therapeutic trial.

Methods — All Crohn’s disease patients treated at the Departments of Gastroenterology of the University Hospitals of Bordeaux, Nantes, Poitiers, Rennes and Tours were retrospectively analyzed.

Results — Sixty-nine patients were treated with a total of 170 infusions of infliximab, 32 patients being treated for refractory Crohn’s disease and 37 for fistulas. The median follow-up was 8 months (extremes 1-20). An objective response was observed in 79% of refractory Crohn’s disease patients and 78% of fistulizing patients. A remission was observed in 72% and 70% of the patients respectively. Forty-five percent of patients had relapsed within 4 months (extremes 2-7). Immunosuppressive therapy was associated with a lower relapse rate (18% versus 56% without, P = 0.004). Infliximab resulted in a steroid-sparing effect in 73% of patients. Forty adverse events, none of severe grade, were observed in 22% of the patients, without any influence of steroids or immunosuppressive therapy.

Conclusion — This study confirms that infliximab is very effective in steroid-dependent and fistulizing Crohn’s disease. Infliximab has a steroid-sparing effect and immunosuppressive therapy is associated with a reduced relapse rate. Although the tolerance is good in the short term, long term safety remains to be established by further studies.

RéSUMÉ

Traitement de la maladie de Crohn par anticorps anti-TNF alpha (infliximab). Résultats d’une étude multicentrique et rétrospective

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Objectif — Évaluer les résultats du traitement par l’infliximab, anticorps anti-TNF-α, chez les malades ayant une maladie de Crohn sévère et réfractaire et/ou fistulisante, en dehors d’un essai thérapeutique.

Méthodes — Les dossiers de tous les malades suivis dans les services de Gastroentérologie des CHU de Bordeaux, Nantes, Poitiers, Rennes et Tours pour une maladie de Crohn et traités par infliximab entre juillet 1999 et février 2001 ont été analysés rétrospectivement.

Résultats — Un total de 170 perfusions a été réalisé chez 69 malades, 32 traités pour maladie de Crohn sévère et réfractaire et 37 pour fistule(s). Le recul évolutif médian était de 8 mois (extrêmes 1-20). Une réponse objective a été observée chez 79 % des malades ayant une maladie de Crohn sévère et réfractaire et 78 % des malades ayant des fistules ; une remission a été observée respectivement dans 72 % et 70 % des cas. Quarante-cinq pour-cent des malades ont eu une rechute dans un délai médian de 4 mois (extrêmes 2-7). Un traitement immunosuppresseur était associé à une fréquence de rechutes significativement plus faible : 18 % versus 56 % sans immunosuppresseur (P = 0.004). L’infliximab permettait le sevrage des corticoïdes chez 73 % des malades. Un total de 40 effets secondaires non graves a été constaté chez 22 % des malades, sans influence significative des immunosuppresseurs et des corticoïdes.

Conclusion — Cette étude confirme l’efficacité de l’infliximab dans la maladie de Crohn sévère et réfractaire et/ou fistulisante, ainsi que sa bonne tolérance à court terme. L’infliximab favorise le sevrage en corticoïdes. Le traitement immunosuppresseur est associé à une diminution de la fréquence des rechutes. La tolérance à court terme est bonne, mais la sécurité à long terme demeure à établir.
the most effective with complete closure in 55% of patients and partial closure in 68% using an infusion protocol at 0, 2 and 6 weeks [3]. Significant improvement and even endoscopic proof of healing was achieved [4]. Furthermore, macroscopic evidence of healing was associated with a significant reduction in the histological activity score [5]. Infliximab thus appears to be an effective treatment for severe active Crohn’s disease refractory to classical treatment or causing fistulization, although the duration of the effect does not appear to exceed 8 to 12 weeks [1]. Prolonged remission can be achieved with repeated infusions [6] given when needed or every 8 weeks, as demonstrated by a multicentric controlled trial [7].

These promising results, which were obtained in controlled trials, remain to be confirmed in everyday clinical practice where outcome might be different. An example of this type of difference was illustrated by the Helicobacter pylori eradication percentages obtained in clinical practice: 56-84% in France [9, 10] compared with 90% in therapeutic trials [8]. There is very little data in the literature on response to infliximab in patients treated outside the setting of clinical trials, generally reported by North-American teams [11-14]. Only one French study has been published on the effect of infliximab treatment on anoperineal lesions in Crohn’s disease [15].

The purpose of the present study was to assess the effect of infliximab in patients with refractory or fistulizing Crohn’s disease treated outside the setting of clinical trials in five University Hospital Centers in western France.

Patients and methods

Study design

The hepatogastroenterology units of the Bordeaux, Nantes, Poitiers, Rennes, and Tours University Hospital Centers participated in this retrospective study. All patients included in the study were treated in these units for Crohn’s disease and had been given one or more infusions of infliximab between July 1999 and February 2001. Infliximab was administered at the dose of 5 mg/kg in a 2-hr infusion, in accordance with the recommendations of Centocor, Inc.

Diagnosis of Crohn’s disease was established on the basis of clinical, endoscopic, histological, and radiological findings [16]. The Crohn’s Disease Activity Index (CDAI) was determined for all patients [17].

Severe refractory Crohn’s disease was defined as active Crohn’s disease unresponsive to systemic corticosteroids or steroid-dependent Crohn’s disease unresponsive to immunosuppressive treatment with azathioprine or methotrexate. The presence of productive anoperineal and/or abdominal enterocutaneous fistulae defined fistulizing Crohn’s disease [18].

Two cohorts of patients were defined. The first cohort, designed to assess the efficacy of infliximab, included all patients who were followed more than one month after infusion. The second cohort, designed to assess tolerance, included all patients given at least one infusion of infliximab, irrespective of the duration of the subsequent follow-up.

Initial efficacy of infliximab infusion was assessed at 8 weeks on the average: 1) for patients with fistulizing Crohn’s disease, and at 5 weeks; 2) for those with severe and refractory Crohn’s disease. CDAI, proctology results, and serum C-reactive protein (CRP) (mg/l) were used to assess therapeutic response. Nutritional status was assessed with body weight. Anti-nuclear and anti-native DNA antibody titers were also determined. The daily prednisone-equivalent steroid dose was expressed in mg. Duration of follow-up was the time between the first infusion of infliximab and the last follow-up visit.

Expression of results

Initial response was defined as the response to the first infusion of infliximab for patients with severe refractory Crohn’s disease and as the response to three perfusions at 0, 2 and 6 weeks in patients with fistulae. A reduction of the CDAI of more than 70 points defined objective therapeutic response for patients with severe refractory Crohn’s disease. CDAI less than 150 points defined clinical remission [17].

For patients with fistulae, objective therapeutic response to infliximab was defined as closure of more than 50% of the initially productive fistulae and remission as closure of all fistulae [3].

Relapse was defined as resumed increase in CDAI of more than 70 points and CDAI greater than 150 points and/or redevelopment of productive fistulae.

Adverse effects occurring during and after the infusions were recorded in an open manner (without a pre-established chart). Severe adverse effects were defined according to the usual criteria: death or life-threatening events, hospitalization or prolongation of current hospitalization beyond the scheduled discharge, development of a permanent handicap, development of cancer, requirement of surgery to prevent serious course.

Statistical analysis

Results are largely presented as mean ± standard deviation (SD). The modified chi-square test was used to test differences between subgroups of patients. If data distribution was normal, Student’s t test was used to compare quantitative variables. The Mann Whitney U test was applied in case of abnormal distribution. Kaplan-Meier curves were plotted for patients given immunosuppressors or not and compared with the log rank test. Differences with P < 0.05 were considered significant.

Results

Demographic data and clinical features before treatment

Sixty-nine patients were included: 15 at Bordeaux, 17 at Nantes, 10 at Poitiers, 15 at Rennes, and 12 at Tours. There were no exclusions. Median follow-up was 8 months (range: 1-20). Demographic and clinical data as well as concomitant corticosteroid and immunosuppressor treatments are detailed in table I.

There was no significant difference between patients treated for severe refractory or fistulizing Crohn’s disease for age, gender, disease duration, history of intestinal resection, or immunosuppressor treatment before the first infliximab infusion. As expected, 88% of the patients treated for severe refractory Crohn’s disease were on steroid treatment at the time of the first infliximab infusion versus 57% of the patients with fistulae (P = 0.01). Steroid treatment had been discontinued just before the first infliximab infusion in two patients with severe refractory Crohn’s disease.

Nearly all the patients with fistulizing Crohn’s disease (98%) had been given metronidazole or ciprofloxacin before infliximab infusion. There was a history of anoperineal surgery in 79%. These patients had a single anal fistula (47%), multiple anal fistula (41%), and enterocutaneous fistulectomy (12%).

Clinical features and demographic data were not significantly different between patients with and without immunosuppressor treatment. A total of 170 infusions of infliximab were administered, 146 first infusions and 24 secondary infusions administered to strengthen or prolong the effect. All infusions were dosed at 5 mg/kg in accordance with the recommendations of Centocor Inc. Among the patients treated for severe refractory Crohn’s disease, 22 (69%) were given one infliximab infusion, 4 (12%) were given two infusions, and six (19%) were given three infusions. Among the patients with fistulae, 28 (76%) were treated according to the recommended 3-infusion protocol, five
were given two infusions, and four (11%) were given one infusion.

**Initial therapeutic response**

The overall initial objective response rate was 79% and the remission rate was 70% (Figure 1). Response rate was not significantly different according to age, gender, disease duration, investigating center, or disease localization.

Among patients with severe refractory Crohn’s disease, the rate of objective response was 79% and the rate of remission after the first infusion of infliximab was 72% (Figure 1). Similar rates were observed for patients with and without immunosuppressor treatment. Objective response was observed in 65% of the patients with an ileocolonic localization versus 89% in those with isolated colonic involvement (P = 0.4). Ten patients with severe refractory Crohn’s disease were given two or three infusions of infliximab for acute treatment. Rates of objective response and remission were similar to those observed in patients given only one infusion: 80% and 70% versus 79% and 71%.

Among the patients with fistulizing Crohn’s disease, the rate of objective response was 78% and the rate of remission was 7% (Figure 1). Similar rates were observed for patients with and without immunosuppressor treatment. Objective response rate was 82% in patients given three infusions compared with 66% in those given one infusion, but the difference was not significant (P = 0.5). There was no significant difference in remission for this parameter. The four patients treated for an abdominal enterocutaneous fistula responded to the infliximab treatment, achieving closure of the oriﬁces without relapse during the follow-up (range 7-10 months after the last infusion). A significant reduction in the CDAI was observed in patients with severe refractory disease: 263 ± 18 before treatment and 96 ± 12 after treatment (P < 0.0001) (Figure 2a). For all patients, serum CRP fell from 34 ± 27 mg/L to 4 ± 4 mg/L (P < 0.0001) (Figure 2b). Significant weight gain was recorded after infliximab treatment, median weight increasing from 55 kg (range: 41-80) before infusion to 58 kg (range: 45-81) at last follow-up (P < 0.0001).

**Follow-up**

Median follow-up in patients with fistulizing Crohn’s disease was 7 months (range: 2-19). It was 6 months (range: 3-11) in those with severe refractory Crohn’s disease. The rate of remission was 65% at six months for patients with fistulizing Crohn’s disease and 63% for those with severe refractory disease (Figure 3).

For patients with fistulae, relapse was expressed by reopening of former fistulae in 64% of the patients and by a non-fistulizing ileal or colonic inﬂammatory flare-up in 36%.

Steroid treatment was successfully discontinued in 86% of the patients treated for severe refractory Crohn’s disease and in 57% patients with...
of those treated for fistulae, giving an overall steroid sparing effect in 73% (table II).

Prior immunosuppressor treatment was associated with a lower relapse rate: 18% versus 56% for patients without prior immunosuppression (P = 0.0004) (figure 4). This difference was observed both for patients with severe refractory disease (18% versus 53%; P = 0.10), and those with fistulae (18% versus 58%; P = 0.04). Median time to relapse was 6 months (range: 4-7) in immunosuppressed patients versus 4 months (range: 2-8) in others (p = 0.1).

Thirty-two percent of the patients given the recommended three infusions relapsed versus 55% of those given less than three infusions (NS).

Secondary infusions

The 10 patients who experienced relapse of their severe refractory disease after remission following a first infliximab infusion were given at least one secondary infusion. All exhibited an objective response and clinical remission was observed in 70%. Ten of the 13 patients who experienced relapse of their fistulizing disease were given secondary infusions. All exhibited objective response and clinical remission was observed in 60%.

Tolerance

Forty adverse effects were reported in 15 patients (22%), yielding one adverse effect for 4.34 infliximab infusions. Seventeen of these adverse effects occurred during or shortly after the infusion (two patients developed an urticarial rash which resolved after interruption of the infusion). Among the 23 late adverse effects, 9 were infections (table III).

None of the adverse effects required prolonged hospitalization and none caused permanent handicap or death. The rate of
these effects was similar for patients with and without immunosuppression (22% versus 25%) and there was no significant difference for use of corticosteroids or not (20% versus 25%). Likewise, infections occurred at about the same rates with and without immunosuppression (11% versus 17%) and with and without corticosteroids (12% versus 15%).

Finally, adverse effects occurred more readily after a second infliximab infusion but the difference was not significant (Figure 5).

Anti-nuclear antibody titers were determined before and after infliximab treatment in 27 patients. All titers were negative or < 1: 50 before treatment. Eight patients (30%) had a titer > 1: 100 after infliximab. None of these 8 patients developed anti-native DNA antibodies. Two of the 8 patients who were positive for anti-nuclear antibodies after infliximab developed infliximab-related adverse effects: headache and fever during infusion for one patient and myalgia late after infusion for the others. No relationship was found between immunosuppressor treatment and development of anti-nuclear antibodies: 27% of the 15 patients given immunosuppressors were anti-nuclear antibody positive after infliximab versus 33% of the 12 patients not given immunosuppressors.

**Discussion**

These results confirm the efficacy of infliximab in the treatment of severe refractory and fistulizing Crohn’s disease. Objective therapeutic response was observed in 79% of the patients, all indications included. Immunosuppressor treatment with azathioprine or methotrexate in association with infliximab did not have any effect on therapeutic response. However, significant lower relapse rates were observed with immunosuppressor treatment and the delay to onset of relapse was also lengthened (although the latter was not significant). A steroid-sparing effect was also observed with infliximab treatment in 73% of the patients, all indications included. Finally, the adverse effects recorded were not serious and regressed.

The rate of objective response in patients with severe refractory Crohn’s disease observed in our patients was similar to that reported by Tragan et al. [2]. The remission rate was however higher in our patients: 72% versus 50% [2]. Possible explanations include: 1) 33% of the patients in the former study [2] were given immunosuppressor treatment compared with 44% in our study. Immunosuppressor treatment did not however demonstrate any influence on response rate in our study. 2) Patients included in the former study had more active Crohn’s disease for a longer time. Four other studies have recently reported clinical experience with infliximab [11-14]. All have demonstrated the efficacy of infliximab, although three reported response rates below ours [11, 12, 14]. But disease activity and therapeutic response of active disease were not reported in those studies.

Our fistulizing Crohn’s disease patients also exhibited response and remission rates above those reported by Present et al. [3]: greater than 50% closure in 78% and complete closure in 70%, compared with 68% and 55% [3]. Remission rates were also higher than those observed by Ouraghi et al. [15] despite comparable objective response and 6-month remission rates. Proctological response was not assessed with a pre-defined clinical score in all our investigating centers and the results reported were rather heterogeneous. An overestimation of response and an overly optimistic designation of remission may have resulted from insufficient use of a reproducible score comparable with other studies [11, 12].

Due to cost considerations and difficulty in procuring infliximab, 24% of our patients who exhibited a very good initial response were only given one or two infusions of infliximab. The rate of objective response was however higher (though not significantly) when the 3-infusion protocol was completed.

We did not find any evidence that immunosuppressors influence initial response to infliximab or median duration of remission. We did however observe that relapses were less frequent in patients given immunosuppressors (18% versus 56%, all indications included). Most of these patients had failed to respond to azathioprine. Similarly, Cohen et al. [11] and Farrell et al. [12] did not observe any effect of immunosuppressor treatment on rate of response or remission, or duration of response. Rutgeerts et al. [6] observed that clinical response was maintained 8 weeks after the last infliximab infusion in 75% of their patients given immunosuppressors versus 50% of those without immunosuppressors, but this difference was not significant. Moreover, Present et al. [3] suggested that concomitant immunosuppression could optimize response to infliximab: 44% clinical response in placebo-treated patients given immunosuppressors versus 18% without immunosuppressions, and no

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**Table III. Infliximab adverse events.**

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<tr>
<th>Intolerance reactions during or shortly after infliximab infusion (n = 17)*</th>
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<tbody>
<tr>
<td>— headache</td>
<td>6</td>
</tr>
<tr>
<td>— pruritus</td>
<td>2</td>
</tr>
<tr>
<td>— fever</td>
<td>3</td>
</tr>
<tr>
<td>— nausea</td>
<td>4</td>
</tr>
<tr>
<td>— urticarial rash</td>
<td>2</td>
</tr>
</tbody>
</table>

Adverse effects occurring late after infliximab infusion (n = 23)**:

- Infection (n = 9):
  - — atis | 1 |
  - — rhinopharyngitis | 5 |
  - — folliculitis | 1 |
  - — whooping cough | 1 |
  - — bronchitis | 1 |

Non-infectious events (n = 14):

- — arthralgia | 2 |
- — myalgia | 4 |
- — pruritus | 4 |
- — asthenia | 4 |

*These adverse effects were observed in 10 patients who developed intolerance reactions during or shortly after infliximab infusion and in 11 patients who developed late effects.

**In our study. Immunosuppressor treatment did not however influence initial response to infliximab. 2) Patients included in the former study had more active Crohn’s disease for a longer time. Four other studies have recently reported clinical experience with infliximab [11-14]. All have demonstrated the efficacy of infliximab, although three reported response rates below ours [11, 12, 14]. But disease activity and therapeutic response of active disease were not reported in those studies.

<table>
<thead>
<tr>
<th>Adverse events frequency according to the perfusion rank of infliximab.</th>
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<tr>
<td>perfusion (n=69)</td>
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<tr>
<td>11</td>
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*Fig. 5 – Adverse events frequency according to the perfusion rank of infliximab.*
significant difference in clinical response among patients given immunosuppressors between the placebo group and the infliximab group (44% versus 59%). Controlled clinical trials are therefore needed to determine the efficacy, in terms of prolonged remission, of immunosuppressors given in combination with infliximab.

There is only a limited amount of data available on the steroid-sparing effect of infliximab, particularly from controlled trials. Complete withdrawal was achieved in 73% of our patients, 86% of those treated for severe refractory Crohn’s disease and 57% of those treated for fistulizing disease. Ricart et al. [14] reported similar findings. Other non controlled trials also suggest infliximab might have a steroid-sparing effect [11-13].

Because of its chimeric composition and immunomodulating properties, it has been suggested that infliximab could induce immune sensitization and immunodepression. An analysis of all the controlled trials on the use of infliximab for the treatment of Crohn’s disease and rheumatoid polyarthritis has shown that adverse effects are frequent but non-specific and mild to moderate in the majority of the cases [19]. Our findings (40 adverse effects in 22% of the patients) are in agreement with these data. Most of the events we observed were intolerance reactions. Infections did account for 23% of our adverse effects, but none of our patients developed serious infection (there were no opportunistic infections and no cases of tuberculosis). It has been demonstrated that treatment with infliximab increases the risk of tuberculosis and that its use requires a rigorous analysis of the patient’s history and systematic search for suggestive symptoms [20]. There were no serious adverse effects. All side effects observed were mild to moderate and reversible, either spontaneously or after medical treatment. Analysis of the different clinical trials has demonstrated that concomitant immunosuppressor treatment could have a protective effect by decreasing production of anti-chimeric antibodies (HACA), development of anti-double-stranded DNA antibodies, and frequency of intolerance reactions. In our study, adverse reactions were not different between patients with or without immunosuppressor or steroid treatment.

We did not search for the presence of HACA. We did however prospectively assay anti-nuclear and anti-DNA antibodies in 27 patients before and after infliximab infusion. Anti-nuclear antibodies developed in 8 of these patients (30%) without concomitant production of anti-DNA antibodies and without any detectable influence of immunosuppressor treatment. The sample size was however rather small.

None of our patients developed a late hypersensitivity reaction but the longest interval between two infliximab infusions was only 8 months. Late hypersensitivity reactions reported in the literature have concerned re-infusions administered 2 to 4 years after the last treatment [21].

Finally, we did not have any case of lymphoproliferative disease in our patients, but the follow-up was too short to draw any conclusions.

In conclusion, the results after the first year of use of infliximab at the Bordeaux, Nantes, Poitiers, Rennes, and Tours University Hospital Centers has confirmed its efficacy in the treatment of severe refractory and fistulizing Crohn’s disease. Results were similar to or even slightly better than those reported in the literature. Tolerance to infliximab was good with only mild to moderate adverse effects being observed. We also noted that infliximab had a steroid-sparing effect. Finally, there appears to be some beneficial effect from the infliximab-immunosuppressor combination, with a significant decrease in the rate of relapse. Further controlled clinical trials should be conducted with longer follow-up to confirm these beneficial effects and search for any possible long-term toxic effect.

REFERENCES

10. Lamouliatte H, Forestier S, Périé F. Lansoprazole 30mg or 60 mg with two antibiotics (amoxicillin-clarithromycin) for Helicobacter Pylori eradication (abstract). Gut 1998;43(suppl 2):A80.

