Long-term Durability of Infliximab Treatment in Crohn’s Disease and Efficacy of Dose “Escalation” in Patients Losing Response

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Background: The efficacy of infliximab therapy in patients with Crohn’s disease (CD) is unknown beyond 12 months. For patients who lose their initial response, consideration can be given to dose “escalation” to regain therapeutic benefit.

Aim: Our primary goal was to evaluate the long-term durability of maintenance infliximab treatment. The secondary goals were to identify potential predictors of loss of infliximab efficacy, to evaluate the response to infliximab escalation, and to identify the safety of the treatment with infliximab with and without escalation of dose.

Methods: CD patients treated with infliximab with response to an induction regimen were evaluated. Maintenance of long-term response was estimated using Kaplan-Meier analysis. The effect of specific variables was calculated using logistic regression analysis. Efficacy of dose escalation in patients who lose response to infliximab was analyzed.

Results: Three hundred and nine CD patients were included. The mean follow-up time with infliximab treatment was 41 months, and the majority (95%) were on concomitant immunosuppressive therapy. The annual risk of loss of response to infliximab was 12% per patient-year of treatment. After loss of response, 41% of patients were managed with infliximab therapy escalation. After the first intensified dose, 56% of patients achieved remission and 40% partial response. Concurrent immunomodulators enhanced and smoking decreased the proportion of patients who maintained response (P < 0.05).

Conclusions: A relevant proportion of CD patients on long-term infliximab treatment lost response. After loss of response, a high proportion of these patients initially respond to infliximab dose escalation. Concurrent immunomodulators may increase and smoking may decrease maintenance of response.

Key Words: infliximab, intensification, dose escalation, loss of response, Crohn’s disease

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Infliximab, a chimeric monoclonal antibody to tumor necrosis factor (TNF)-α, has been demonstrated to be effective in the treatment of both luminal and fistulizing Crohn’s disease (CD). Initially, induction regimens with 1 (luminal disease) or 3 doses (fistulizing disease) were shown to be effective in the short-term treatment. Subsequently, studies have demonstrated that infliximab is also highly effective for maintenance of response and remission.

More than 50% of patients achieve initial response to infliximab. The duration of the response to a single infusion, however, is only 2 to 4 months, and at 12 months only 10% to 40% of patients have a sustained response. This response can be maintained with scheduled repeated dosing of infliximab. At present, infliximab infusions are commonly prescribed at 5 mg/kg body weight with induction infusions at weeks 0, 2, and 6, followed by maintenance therapy every 8 weeks.

There is paucity of data providing insight into the durability of response to infliximab in CD for periods longer than 12 months, as clinical trials have focused on efficacy and safety over the first year of treatment. However, infliximab is not typically discontinued at 12 months, and for many patients, is a treatment to be continued indefinitely.

Some “medium-term” follow-up studies have shown that although infliximab is initially effective in a high proportion of patients, over time, patients treated with a maintenance infliximab regimen may lose their initial therapeutic response. Nevertheless, durability of efficacy of infliximab maintenance therapy over multiple years has not been defined, and consequently, the true frequency of loss of efficacy and requirement of infliximab dose escalation needed in the long-term is not well known.

For patients treated with infliximab maintenance regimen loosing their initial response, consideration can be given to “dose escalation” to regain therapeutic benefit. Dose escalation can be achieved by either increasing the infliximab dose, generally from 5 to 10 mg/kg, or decreasing the frequency of infusion to as often as every 4 weeks.

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The primary aim of our study was to evaluate the long-term durability of efficacy during maintenance infliximab treatment. The secondary aims were to identify potential predictors of loss of response, to evaluate the response to infliximab escalation and the safety of this treatment strategy.

METHODS

Study Subjects

Patients who had received at least 3 induction doses of infliximab for CD (luminal or fistulizing/perianal CD) with primary response at a community-based gastroenterology practice, were evaluated in a historical cohort study. They were identified using a large Spanish database (ENEIDA), promoted by the Spanish Working Group in Crohn’s and Colitis (Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa), including patients with inflammatory bowel disease. The database prospectively records, use, effectiveness and adverse events of immunomodulators and anti-TNF therapy. The database at the time of the study includes 10752 patients, of whom 5467 had CD. Where necessary, additional clinical information was obtained by review of records. Patients were excluded from the study if: infliximab was initiated for treatment of a disease other than CD, infliximab was stopped because there was not primary response, or infliximab treatment was primary for extraintestinal manifestations of CD. Patients with strictures were not excluded.

Data Collection

Data collected included sex, age, smoking status, age at diagnosis, location, disease behavior (inflammatory, stenosing, or fistulizing), perianal disease, extraintestinal manifestations, previous surgery for CD, concurrent use of immunomodulators, starting date of infliximab therapy, infliximab dose, for example, from 5 to 10 mg/kg, or a decrease in infliximab infusion interval, for example, from every 8 week infusion to every 4 week, or both a dose increase and interval decrease.

Definitions

Evaluation of Response

For luminal disease, response to adalimumab and infliximab was evaluated using the Harvey-Bradshaw index (HBI) 4 weeks after the first dose. Owing to the retrospective nature of the study, an effort was made to obtain information on all components of this index. Partial response was defined as a decrease in the HBI of more than 3 points. Remission was defined as a HBI below or equal to 4 without steroids. In perianal CD, complete response was defined as closure of all fistulas and partial response as a 50% or more reduction in the number of draining fistulas.

Loss of Efficacy

Loss of efficacy was defined as impairment in patient’s symptoms coupled with endoscopic, radiographic, and/or serologic (elevated C-reactive protein) evidence of inflammation that made the physician escalate the dose of treatment or change to other drug.

Dose Escalation

Dose escalation was defined as either an increase in infliximab dose, for example, from 5 to 10 mg/kg, or a decrease in infliximab infusion interval, for example, from every 8 week infusion to every 4 week, or both a dose increase and interval decrease.

Reason for Dose Escalation

In clinical practice, the need for dose escalation was determined by the loss of response to the current dose and interval of infliximab. This required symptoms coupled with clinical (reopening of healed perianal or enterocutaneous fistula), endoscopic, radiographic, and/or serologic (elevated C-reactive protein) evidence of inflammation.

Disease Behavior and Location

Disease behavior was categorized based on Montreal classification as: (1) inflammatory (B1) or CD without fistulizing or strictureing complications, (2) strictureing (B2) disease was defined as the presence of clinical symptoms of partial or complete obstruction with fixed narrowing and/or narrowing with proximal dilatation, and (3) fistulizing (B3), which included the presence of enteric fistulas, intra-abdominal abscesses, or bowel perforation. The location of disease was established by identifying macroscopic evidence of CD in any part of the gastrointestinal tract. Possible categories of disease location included the ileum (L1), colon (L2), ileum and colon (L3), upper gastrointestinal tract (L4), and perianal/perineal area (p).

Smoking History

Smoking was defined as consumption of at least 1 cigarette daily for a period of at least 3 months before the first infliximab dose. Smoking at diagnosis was defined as consumption of at least 1 cigarette daily at the time of diagnosis.

Statistical Methods

For continuous variables, mean, median, and SD were calculated. For categorical variables, percentages and 95% confidence intervals (95% CI) were provided.

The Kaplan-Meier method was used to evaluate the long-term durability of maintenance infliximab treatment and any differences between survival curves were evaluated with the log rank test. Stepwise multivariate analysis using the Cox model was used to investigate factors potentially associated with loss of response. In the log rank test and in the multivariate analysis, a \( P < 0.05 \) was considered the level of significance.

RESULTS

Baseline Characteristics

A total of 309 CD patients were identified as having received at least 3 induction doses of infliximab with primary response. The main characteristics of the study patients are reported in Table 1. The mean (±SD) age was 39 ± 12 years. Fifty-five percent of all patients were female and the mean age at diagnosis was 29 ± 12 years. Sixty-two percent of patients had ileocolic disease, 57% inflammatory behavior, and 45% perianal disease. Thirty-three percent of the patients (95% CI 28%-38%) were current smokers and the majority (95%; 95% CI 92%-97%) were on concomitant immunosuppressive therapy (94.5% of them with azathioprine or mercaptopurine). Sixty-three percent of patients had at least one surgery previous to the treatment
with infliximab. The most common indication for inflixi-
imab initiation was active luminal disease.

**Maintenance of Response**

The mean time of follow up was 41 months (range: 4 to 104 mo) and the median was 33 months. Based on Kaplan-Meier survival estimates, 89%, 81%, 79%, and 72% of all patients who initiated scheduled infliximab treatments maintained response at 12, 24, 36, and 48 months, respectively (Fig. 1). The incidence of loss of response to infliximab was 12% per patient-year of follow up (95% CI 8%-15%).

Patients treated with immunomodulators had lower risk of loss of response to infliximab compared with patients without immunomodulators, and the log rank test was statistically significant ($P = 0.046$) (Fig. 2). Cigarette smoking at the time of diagnosis was associated with shorter duration of response to infliximab compared with nonsmokers, differences reaching statistical significance ($P = 0.029$) (Fig. 3). However, no statistical significance in loss of response was observed depending on the following variables: age at diagnosis, sex, months from CD diagnosis to first infliximab infusion, indication for infliximab (luminal or perianal), disease location, disease behavior, presence of perianal disease, family history, current smoking habit, and prior surgery related to CD.

**Management of Loss of Response to Infliximab**

After infliximab response was lost, 53% of patients received adalimumab and 41% were managed with infliximab therapy escalation (51% increased doses to 10 mg/kg, and 49% decreased infusion interval to each 4 wk). Ninety-six percent (95% CI 83%-99%) of patients receiving infliximab dose escalation achieved initial response after the first intensified dose (36% remission and 40% partial response).

**Multivariable Analysis**

In the Cox regression analysis, concurrent use of immunomodulators and smoking at diagnosis were significantly and independently associated with risk of loss of response to infliximab. Patients concomitantly treated with immunomodulators had lower risk of loss of response [hazard ratio = 0.37, $P = 0.02$]. On the other hand, cigarette smoking at the time of diagnosis was significantly associated with loss of response.
with higher rates of loss of response to infliximab (hazard ratio = 2.05, \( P = 0.019 \)). Other baseline characteristics had no impact on maintenance of response to infliximab.

**Safety**

Thirteen percent of patients (95% CI 9%-17%) had adverse events during infliximab treatment with standard doses and 7.8% of all patients required discontinuation of infliximab therapy for this reason. Most of the adverse events registered were immediate or delayed hypersensitive reactions, as is shown in Table 2. The median time from the beginning with infliximab therapy to the infusion reaction was 12 months (range: 9 to 40 mo) and the median time since the treatment with infliximab was started until the delayed hypersensitive reaction occurred was 21 months (range: 14 to 34 mo).

Only 1 patient had a delayed hypersensitive reaction after the first intensified dose of infliximab (3% of patients with intensified treatment), requiring the cessation of therapy. In this patient, the treatment had been intensified shortening the administration of 5 mg/kg of infliximab from 8 to 4 weeks.

The incidence of adverse events was lower in patients receiving concurrent immunomodulators than in those not on immunomodulator therapy (12% vs. 33%, \( P = 0.016 \)).

**DISCUSSION**

Infliximab is effective for the induction and maintenance of remission of inflammatory and fistulizing CD.\(^2,5,6,9,10\) Infliximab clinical trials have focused on efficacy and safety over the first year of treatment. However, in clinical practice, most patients who have responded to 1 year of infliximab are continued on this therapy. Although it has become standard practice to increase the infliximab dose or decrease the interval in CD patients losing response to standard doses, there are few data about the proportion of patients who require dose escalation after 1 year and the efficacy of this therapeutic manoeuvre.

We found that 72% of patients maintained response to infliximab after a median of 3 years of follow up. As might be expected, our maintenance of response rates were higher than those reported in prospective randomized studies,\(^5,11\) which used rigorous CD activity index criteria for the loss of response. In this study there were also no predefined treatment initiation criteria with respect to disease activity and conceivably patients with less severe disease, but inadequate response to other treatment options, receive infliximab in real world clinical practice.

The annual risk for loss of infliximab response in our study was 12%, similar to the overall risk calculated in a recent review performed by Gisbert and Panes.\(^8\) These authors included 16 studies evaluating the incidence of loss of response to infliximab in patients with CD, and the annual risk for loss of infliximab response was estimated to be 13.1% per patient-year.

We found that the concurrent use of immunomodulators is associated with a significant improvement of maintenance of infliximab response. Concurrent use of immunomodulators has been associated with a significant reduction in the proportion of patients that develop anti-infliximab antibodies,\(^5,12-15\) which might be expected to enhance the efficacy of infliximab long term. Rudolph et al.\(^16\) in a recent study, found that concurrent immunomodulators enhance maintenance of response to infliximab, particularly if started more than 3 months before the initiation of infliximab therapy. More recently, Corman et al.\(^17\) performed a retrospective observational study for all CD patients who were treated with maintenance infliximab for longer than 12 months, and concluded that concomitant immunomodulator use appeared to protect from requiring dose escalation. However, the beneficial impact of concomitant immunomodulators on maintenance of response is still unclear because it has not been demonstrated in many other studies.\(^4,5,10,18-21\)

The negative impact of smoking on the clinical course of CD is well known but the effect of smoking on infliximab response rates is unclear.\(^22-24\) In our study, we found that smoking cigarettes at the time of diagnosis was significantly associated with a higher rate of loss of response to infliximab, but this difference did not reach statistical significance when we compared the rates of loss of response between “current” smokers and current nonsmokers. One of the plausible explanations for this apparent discrepancy could be that smoking cigarettes has a deleterious effect on the clinical course of CD from the early beginning, making it more severe and worse responder to treatment. Several studies have been consistent with our results, showing that smoking decreases the effectiveness of maintenance infliximab therapy.\(^16,18,25\) However, this trend contrasts with other studies which found that cigarette smoking did not show an impact on response rates or duration of response of infliximab.\(^4,26,27\)

A high proportion of patients in our study (96%) initially responded to the escalation of infliximab. Our results are consistent with that reported by several investigators. As an example, Rutgeerts et al.\(^28\) found that 80% to 90% of CD patients who had lost response to infliximab were able to regain response with an escalation of dose. Similar results were reported in the ACCENT I study,\(^5\) where the increase of infliximab dose from 5 to 10 mg/kg in patients with luminal CD restored response in 90% of the patients who had lost response to 5 mg/kg. This suggests that most patients who loose response to infliximab are able to regain response with an increase in dose or decrease in dosing interval.

In our study, 59% of patients who lost response to infliximab were switched to another anti-TNF antibody. Nowadays, it is unknown which is the best strategy of treatment for these patients. Randomized controlled trials comparing clinical efficacy and cost effectiveness of switching to a second anti-TNF antibody versus infliximab dose escalation have not been undertaken, but a cost-effectiveness analysis performed by Kaplan et al.\(^29\) suggests that
infliximab dose escalation strategy yields more quality-adjusted life year compared with the switch strategy.

Treatment with infliximab was safe in our experience, as adverse events were reported in only 13% of the cases, and the side effects forced a discontinuation of the infliximab treatment in only 7.8% of all patients. The majority of them had to stop infliximab because of immediate and delayed hypersensitivity reactions. We also found that patients on concomitant immunomodulators had significantly lower rates of adverse events related to infliximab therapy. This finding, added to the fact that concomitant immunomodulator use appears to protect from loss of response to infliximab, suggest that immunogenicity mechanisms may be involved in both processes. Only 1% patients on intensified infliximab regimen presented a delayed reaction that forced the interruption of treatment. This shows that infliximab dose escalation is a safe option in patients who have previously tolerated the treatment with the standard dose.

The main strength of this study is that it reflects real-life experience with infliximab treatment in CD daily clinical practice, but it also has several limitations. First, the Spanish ENEIDA project prospectively records response to infliximab and the requirement of dose escalation, but the response to escalation had to be analyzed retrospectively from clinical records. Also, the database categorizes patients as smokers or nonsmokers with precise criteria, but does not record tobacco consumption, and we were not able to categorize patients into light or heavy smokers; this distinction would have been important because the effect of tobacco in CD may be dose dependent. In addition, there was a lack of data on antibody to infliximab or infliximab plasma levels, which has been associated with infusion reactions and loss of response to infliximab. In this respect, prior studies suggest that patients with concomitant immunomodulator administration have a decreased likelihood of forming anti-infliximab antibodies, but its clinical significance remains unclear.

In summary, we conclude that the efficacy of infliximab treatment in CD seems to be reasonably durable beyond 12 months. However a considerable number of patients will, over time, lose benefit from infliximab treatment. Our findings suggest that the concurrent use of immunomodulators contributes to optimize the maintenance of response, whereas smoking at diagnosis has a negative impact. The majority of patients loosing response to infliximab are able to regain response with an increase in the dose or a decrease in the interval, suggesting that dose escalation is an effective and safe option for these patients.

REFERENCES


