Intensification of infliximab therapy in Crohn's disease: Efficacy and safety

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KEYWORDS
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Abstract

Introduction: The response of Crohn's disease (CD) to infliximab is initially good, although a loss of efficacy is observed over time. Dose escalation has been recommended in such cases.

Aims: To study the response to an intensified infliximab regimen in patients with CD; and to evaluate the adverse effects associated with intensification of therapy and identify predictors of loss of response.

Methods: We performed a retrospective multicenter survey of all patients with CD who had been treated with at least the 3 induction doses of standard infliximab therapy, and for whom treatment had to be intensified due to loss of response. We analyzed the efficacy of the intensified regimen.

Results: Thirty-three patients were included. After the first intensification dose, 79% of patients had a clinical response (33.5% complete response, 45.5% partial response). In the long term, 83%, 69%, 47%, and 29% of patients who had an initial response to the intensification maintained the response at 6, 12, 18, and 36 months, respectively. The loss of efficacy after escalation was 43% per patient-year of follow-up. One patient had an infusion reaction after 36 doses. One patient developed a herpes zoster infection.

Abbreviations: CD, Crohn's disease; TNF, tumor necrosis factor; SD, standard deviation; IQR, interquartile range; CI, confidence interval; HR, hazard ratio; HBI, Harvey–Bradshaw index.

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1. Introduction

Infliximab, a chimeric monoclonal antibody to tumor necrosis factor alpha (TNF), has proven to be effective for the treatment of both luminal and fistulizing Crohn's disease (CD). Initially, induction regimens with 1 dose (luminal disease) or 3 doses (fistulizing disease) were shown to be effective in the short term. Subsequent studies have demonstrated that infliximab is also effective for maintenance of response. Current recommendations are to begin infusions at 5 mg/kg with induction infusions at weeks 0, 2, and 6, followed by maintenance therapy every 8 weeks. Some medium-term follow-up studies have shown that although infliximab is initially effective in a relatively high proportion of patients, the therapeutic response may be lost over time.

Low trough serum concentrations of infliximab have been associated with loss of response. Pharmacokinetic models indicate that higher trough serum concentrations might be achieved by escalating the dosage (increasing the dose, shortening the infusion interval, or both). Therefore, in patients who lose their initial response to the standard schedule of 5 mg/kg every 8 weeks, the dosage can be adjusted to regain therapeutic benefit.

The efficacy of infliximab dose intensification to overcome loss of response has been reported to be high in patients with CD, at least transiently, although data on the long-term efficacy of escalation are scarce. Consequently, it is still unknown whether the beneficial effect of this intensification is prolonged or transient.

The primary objective of our study was to evaluate the long-term durability of efficacy during intensified maintenance therapy with infliximab after loss of response to the standard dose. The secondary objectives were to evaluate the response to dose escalation, to identify potential predictors of loss of response, and to assess the safety of this intensified treatment strategy.

2. Methods

2.1. Patients

Patients followed-up in five University Hospitals from Madrid, Spain, with CD who had initiated and maintained treatment with infliximab at a community-based gastroenterology practice were evaluated in a historical cohort study. The study population comprised those patients who had received the 3 induction doses with at least a partial response and required their dosage to be intensified.

Patients were excluded if infliximab had been initiated to treat a disease other than CD, if infliximab had been initiated without the intention of long-term maintenance infusions, if the patient had previously received a TNF-antagonist, or if infliximab had been prescribed for extra-intestinal manifestations of CD.

2.2. Data collection

The data collected included sex, age, smoking status, duration of CD, primary anatomic location for CD, previous CD-related surgery, disease behavior (inflammatory, strictureting, or fistulizing), concurrent use of immunomodulators, predmedication with corticosteroids, time to dose escalation, time with the escalated dose, initial response to dose escalation, response to dose escalation at the last visit, and adverse events with the standard and escalated doses.

2.3. Definitions

2.3.1. Dosage escalation

Escalation was defined as either an increase in the dose of infliximab (e.g., from 5 mg/kg to 10 mg/kg), or a decrease in the infusion interval (e.g., from every-8-week infusions to every 4–7 weeks), or both.

2.3.2. Reason for escalation

The need for dose escalation was determined by the loss of response to the current dose and interval of infliximab. Loss of efficacy was defined as worsening of symptoms, together with endoscopic, radiographic, and/or serologic (elevated C-reactive protein) evidence of inflammation that made the physician escalate the dose.

2.3.3. Concurrent immunomodulator use

Concurrent immunomodulator use was defined as treatment with azathioprine, 6-mercaptopurine, or methotrexate when the infliximab infusions started.

2.3.4. Disease behavior

Diagnosis of CD was established by standard clinical, radiological, histological, and endoscopic criteria. We used the Montreal classification of CD, which classifies patients according to age at diagnosis (A1, ≤16 years; A2, 17–40 years; A3, >40 years), location of disease (L1, terminal ileum; L2, colon; L3, ileum–colon; upper gastrointestinal tract [L4]), and disease behavior (B1, inflammatory; B2, strictureting; B3, penetrating; and p, perianal modifier).

2.3.5. Evaluation of response

The response to infliximab was determined by a chronological review of the prescribing clinician’s notes in the medical record. The response to the escalated regimen in the case of luminal disease was evaluated using the Harvey–Bradshaw index (HBI) four weeks after the first escalated dose. As the study was retrospective, information was obtained on all the components of this index. Partial response was defined as a
decrease in the HBI of more than 3 points. Remission was defined as an HBI below or equal to 4 without corticosteroids. In perianal CD, complete response was defined as closure of all fistulas, and partial response as a ≥50% reduction in the number of draining fistula. Response to treatment was evaluated after the first and last escalated doses.

2.3.6. Adverse events
Adverse events included infusion reactions (occurring within an hour after the infusion), infections, serum sickness-like reactions (within 1–14 days, after re-infusion), drug-induced lupus, other autoimmune diseases, cardiovascular complications, cancer, and death.

2.4. Statistical analysis
For continuous variables, data are presented as the mean and standard deviation (SD) or the median and the interquartile range (IQR). For categorical variables, data are presented as percentages and 95% confidence intervals (95% CI).

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

3. Results

3.1. Baseline characteristics
We identified 197 patients with CD that at least achieved partial response after the three induction doses of infliximab. Of these patients, 33 (17%) required dose escalation due to loss of response, and these patients were included in our analysis. Median age was 43 years (range, 20 to 76 years) (Table 1). The median time of evolution of the disease was 15 years (IQR=11 years). Fifty-one percent of patients were male, 37% were current smokers, and most (76%) were taking concomitant immunomodulators (mainly thiopurines, 69%). The median length of follow-up with infliximab therapy (either standard or escalated dose) was 22 months (IQR=12 months) and the median length of follow-up with the escalated dose was 11 months (IQR=10 months).

3.2. Short-term efficacy of the escalated dose
The median time on infliximab before escalation was 12 months (IQR=13.5 months). After the first escalated dose, 26 (79%) of patients responded. Fifteen patients (45.5%) had a partial response and 11 patients (33.5%) reached remission.

The therapy was escalated by increasing the dose from 5 to 10 mg/kg in 25 patients and by shortening the interval between infusions in seven patients. In one patient the escalation was made by increasing the dose from 5 to 10 mg/kg and shortening the interval from eight to six weeks. Among patients who increased the dose from 5 to 10 mg/kg 80% responded (28% remission and 52% partial response). Among the seven patients who shortened the interval between infusions 72% had response (57% remission and 15% partial response). No predictive factors of response to the escalated treatment were found. From the 11 patients who achieved remission with the first intensified infusion, seven lost response after a median of 48 weeks (range 20–95).

3.3. Long-term efficacy of the escalated dose
Of the 26 patients who had an initial response to the escalated dose of infliximab, 13 lost efficacy. The mean time of follow-up with the escalated dosage was 14 months (range 4–39 months) and the median was 33 months. Based on Kaplan–Meier survival estimates, 83%, 69%, 47%, and 29% of all patients who had an initial response to the intensified regimen maintained response at 6, 12, 18, and 36 months, respectively (Fig. 1). The risk of loss of efficacy with the escalated treatment was 43% per patient-year of follow-up.

No statistically significant differences were observed for loss of response with the following variables (log-rank test): age, gender, indication for infliximab (luminal or perianal disease), disease location, disease behavior, presence of perianal disease, premedication with corticosteroids, concomitant use of immunomodulators, time from first infliximab infusion at the standard dosage to the loss of efficacy, smoking habit, and prior surgery related to CD. Finally, in the Cox regression analysis, no variables were independently associated with the risk of loss of response to the escalated dosage.

From the 13 patients who lost response during the follow-up, seven had achieved remission after the first intensified infusion and six of them had partial response. From the seven

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics.</th>
</tr>
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<tbody>
<tr>
<td>Age, years (SD)</td>
<td>43 (13)</td>
</tr>
<tr>
<td>Time of disease, years (IQR)</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Follow-up with IFX therapy, months (IQR)</td>
<td>22 (12)</td>
</tr>
<tr>
<td>Follow-up with standard dose of IFX, months (IQR)</td>
<td>12 (13.5)</td>
</tr>
<tr>
<td>Follow-up with escalated dose of IFX, months (IQR)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>17 (51)</td>
</tr>
<tr>
<td>Location of disease, n (%)</td>
<td>Terminal ileum 5 (15)</td>
</tr>
<tr>
<td>Behavior, n (%)</td>
<td>Inflammatory 14 (42)</td>
</tr>
<tr>
<td>Perianal disease, n (%)</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Premedication with corticosteroids, n (%)</td>
<td>23 (69)</td>
</tr>
<tr>
<td>Concurrent immunomodulators, n (%)</td>
<td>25 (76)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>12 (37)</td>
</tr>
<tr>
<td>Previous surgery, n (%)</td>
<td>19 (58)</td>
</tr>
</tbody>
</table>

SD, standard deviation; IQR, interquartile range; IFX, infliximab.
patients who lost response after achieving remission, three had no-response and four had partial response at the end of follow-up. Among these patients, three discontinued infliximab – two were switched to adalimumab and one to certolizumab –, the treatment was going to be intensified again (10 mg/kg each four weeks) in two patients and two patients were maintained with the same regimen of infliximab (one received steroids and the other patient was on infliximab due to perianal disease and was maintained with mild drainage through the fistula).

From the six patients who had partial response to the intensified regimen, two had partial response and four had no-response at the end of follow-up. Two patients received adalimumab and one patient received tacrolimus after the discontinuation of infliximab, two patients underwent surgery and one patient was lost of follow-up.

3.4. Management of patients who did not respond to the escalated therapy

There were seven patients in our cohort who did not respond to the escalated therapy (four of them had increased the dose from 5 mg/kg to 10 mg/kg and two of them shortened the interval between infusions). From these patients, infliximab was switched to adalimumab in three, to tacrolimus in one and to certolizumab in one patient. One patient underwent surgery due to lack of response to the escalated regimen. Finally, a patient was lost of follow-up, so we have not information regarding the subsequent treatment.

3.5. Safety of the escalated dosage

One patient who initially experienced infusion reactions with the standard dose suffered an infusion reaction after 36 doses of intensified treatment, although this subsided when the infusion rate was reduced. One patient developed a herpes zoster infection with the escalated dose, although this did not lead to interruption of treatment.

4. Discussion

As a new option for treatment, infliximab has proven to be efficacious in both luminal and fistulizing CD. In the short term, up to 80% of patients experience rapid improvement in their symptoms, and up to 50% of patients achieve remission. This response can be maintained with scheduled repeated dosing, and maintenance infusions at 8-week intervals are now recommended. However, even with the scheduled maintenance treatment, the long-term efficacy of infliximab is limited by a loss of response over time. When patients who are on maintenance with infliximab lose the response, the dose can be escalated to regain therapeutic benefit.

In our study, 79% of patients regained their response after the first escalated dose. This high initial efficacy is consistent with the results of previous reports. In the ACCENT I study, an increase to 10 mg/kg in patients with luminal CD restored response in 90% of patients who lost response to 5 mg/kg. Furthermore, approximately 80% of patients who had lost response while on the 10-mg/kg schedule regained their response after the dose was increased to 15 mg/kg. In the ACCENT II trial, 57% of patients with fistulizing CD who had lost their response on the 5-mg/kg dose, subsequently responded to 10 mg/kg.

Regueiro et al. found that 54% of patients whose dose was escalated regained their response. In a cohort of initial responders, Schnitzler et al. reported that the dose had to be adjusted to keep the disease under control in approximately half of their patients, and therapy was successful in most cases (only 22% had to stop infliximab because of loss of response despite interventions). Hyams et al. performed a study in a pediatric population with CD and found that 75% of patients who had lost response regained efficacy when the dose was escalated. In summary, most patients who lose their response to infliximab are able to regain it, at least transiently, after escalation, but it is unknown whether the beneficial effect of this intensification is prolonged or transient.

To the best of our knowledge, there are no published data on the durability of the initial response to intensification of the infliximab dose over time. In the ACCENT I trial, 59% of patients whose dose was escalated from 5 mg/kg to 10 mg/kg were still taking the drug at the end of the study period (54 weeks). However, over half of these patients received an intensified regimen for less than 6 months before the study period ended. In the study by Regueiro et al., all patients with an initial response to the intensified regimen were still on infliximab at the end of the study period, although the authors did not provide the duration of follow-up.

Our study is the first to provide information on the long-term efficacy of an escalated dosage. We found that the annual risk for loss of response was 43% per patient-year of follow-up. This risk is much higher than the 13% loss of efficacy per patient-year of follow-up with the standard dose of infliximab estimated by Gisbert and Panes in a recent review.

High trough serum concentrations of infliximab have been associated with higher rates of clinical remission and endoscopic improvement, and longer duration of response. Low trough serum concentrations may be caused by both immunogenicity mechanisms and factors not related to immunogenicity. As an exogenous protein, infliximab can
lead to the development of anti-infliximab antibodies in 8%–61% of patients. \(^{6,12,21}\) In the ACCENT I trial, the early development of antibodies seemed to lower serum infliximab concentrations, and this finding has been confirmed in other studies. \(^{12}\) However, variable rates of loss of response to infliximab have been reported irrespective of the presence of antibodies. This finding suggests that loss of efficacy may be explained not only by immunogenicity mechanisms, but also by other factors such as rapid clearance of the drug, independently of the formation of anti-infliximab antibodies or increased levels of other pro-inflammatory molecules. \(^{2}\)

Dosage escalation may lead to higher trough serum concentrations of infliximab. \(^{11}\) This could explain the high rate of initial response to the intensified therapy that we found in our study, which is consistent with that reported by other authors. \(^{5,6}\)

Five percent of the patients from the ACCENT I trial who received maintenance treatment was antibody-positive when their treatment was intensified. \(^{12}\) After dose escalation, 16% of these patients were antibody-positive. \(^{12}\) The frequent and rapid increase in antibody titers after escalation might explain the high risk of loss of response with intensified treatment, which was >40% per patient-year of follow-up in our study.

We did not find predictive factors of loss of response to the escalated dosage. The role of concurrent immunomodulators in optimizing response is controversial. All our patients were on scheduled infliximab treatment, and the impact of immunomodulators on the development of anti-infliximab antibodies has been shown to be minimal. \(^{11}\)

Only one patient presented an infusion reaction and another patient developed a herpes zoster infection that did not lead to interruption of treatment. This suggests that dose escalation is a safe option in patients who have previously tolerated the standard dose.

One limitation of our study is its retrospective design, although we were able to calculate the HBI using data from medical reports. Another obvious limitation is the sample size, which could be responsible for the lack of statistical significance with some variables. However, the reduced sample size alone should not invalidate our observations of the high efficacy of dose escalation and the high risk of loss of initial response.

In conclusion, most patients who lose response to infliximab are able to benefit from an increase in the dose or a decrease in the interval, suggesting that dosage escalation is an effective and safe option for these patients. However, efficacy is often transient, as nearly half of the patients lose response after a year of follow-up.

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References

