INTRODUCTION

Infliximab, a chimeric antibody to tumor necrosis factor alpha, has been a major advance in the treatment of both luminal and fistulizing Crohn’s disease since its introduction into clinical practice in 1998. Infliximab has been effective as both an induction (1) and a maintenance therapy (2–5) for Crohn’s disease. In this article we will review the approach to patients with Crohn’s disease who have lost response to infliximab therapy at standard initial dosing (5 mg/kg every eight weeks for maintenance).

INFLIXIMAB FOR CROHN’S DISEASE

Infliximab is effective for the induction and maintenance of remission in inflammatory and fistulizing Crohn’s disease. Clinical trials have shown the efficacy and safety of infliximab over the first year of therapy. However, most patients with Crohn’s disease who have a...
clinical response to infliximab are continued on therapy beyond one year. The timing and need for dose intensification of infliximab in these patients has been studied.

Currently, infliximab is administered at 5 mg/kg body weight with induction at weeks 0, 2, and 6 followed by maintenance infusion every eight weeks. As time passes, patients receiving infliximab for maintenance therapy may lose all or some of their initial therapeutic response. In rheumatoid arthritis patients treated with infliximab, 50%–62% lose response to their initial dose and interval (6–8) and require dose intensification. For patients with a decrease in response to therapy, dose intensification may be considered to regain therapeutic response. Dose intensification may be achieved by two means; the dose may be increased to 10 mg/kg or the frequency of infusion may be decreased to as often as every four to six weeks.

**DOSE INTENSIFICATION OF INFlixIMAB**

A retrospective study evaluated the proportion of patients that require infliximab dose intensification and factors that may predict the need for dose intensification over a thirty month study interval (9). This study evaluated patients who were primary responders to infliximab. Dose intensification was defined as decreasing the dosing interval to less than eight weeks or by increasing the dose to 10 mg/kg. Over the thirty month study period, 54.3% of patients had a change in their dosing or interval of infliximab (Figure 1). The
The rate of dose intensification at thirty months did not differ between patients with and without lapses in infliximab therapy, between those who were naïve to infliximab or had been on infliximab in the past, between those on concomitant immunomodulators or infliximab monotherapy, and between smokers and non-smokers (Figure 2).

The rate of dose intensification increases over time. The majority (85%) of patients maintained the same dose and interval for infliximab at six months. At one year, 63.8% of patients were on the same infliximab dose and schedule and only 54.3% of patients were receiving the same dose and interval at two years after initiating therapy. The majority of patients (75.9%) who required dose intensification remained on infliximab at the conclusion of the study which suggests that (continued on page 13)
the majority of patients who lost response to infliximab were able to regain response with an increased dose or decreased dosing interval.

**ANTI-TNF ANTIBODIES AND INFlixIMAB CONCENTRATION**

Treatment with infliximab can result in the formation of antibodies to infliximab. In a 10 month study of patients receiving infliximab therapy for Crohn’s disease, 61% of patients had detectable levels of antibodies to infliximab (10). Patients with antibodies to infliximab at a certain threshold (8.0 mcg/mL or greater) before an infusion had a shorter duration of response to infliximab and a higher risk of infusion reactions. Another study displayed that an induction regimen of infliximab with scheduled infusions resulted in reduced antibody formation and greater clinical benefit compared to a single dose of therapy followed by episodic therapy with infliximab (11). Concomitant immunosuppressive therapy was predictive of lower titers of antibodies to infliximab.

Serum infliximab concentration is another variable to consider when evaluating response to therapy. Serum infliximab concentrations can be measured with ELISA (enzyme-linked immunosorbent assay) (12). In a clinical trial of infliximab for the maintenance of Crohn’s disease, a detectable trough level of infliximab was associated with a higher rate of endoscopic improvement and a lower C-reactive protein (13). The rate of clinical remission was higher in patients with a detectable infliximab trough regardless of the presence of antibodies to infliximab. Another study displayed that infliximab concentrations were significantly lower in patients with an infusion reaction compared to patients who had never experienced an infusion reaction (10). Concomitant immunosuppressive therapy was predictive of high concentrations of infliximab four weeks after infusion.

## WHEN DOSE INTENSIFICATION IS INEFFECTIVE

When a patient fails to respond to infliximab dose intensification or is intolerant of infliximab, other medical options are available. Two other anti-TNF agents (adalimumab and certolizumab) are currently available for the treatment of Crohn’s disease. Adalimumab is a fully human TNF antagonist. In a placebo controlled trial, adalimumab improved remission at four weeks compared to placebo in this subset of Crohn’s patients who had responded to infliximab but lost response or became intolerant of infliximab (14). The long term effect of adalimumab in these patients has not yet been studied. Certolizumab is a pegylated humanized antibody fragment to TNF and has been shown to have efficacy as an induction and maintenance therapy for Crohn’s disease. In patients with Crohn’s disease who

---

**Figure 3. Algorithm for infliximab loss of response.**

- **Patient on maintenance infliximab with symptoms of Crohn’s Disease**
  - Perform colonoscopy and small bowel imaging
  - **Active Crohn’s disease**
    - ↑ Dose to 10 mg/kg
    - ↓ Interval up to every 6 weeks
  - No response
  - ↓ Interval of infliximab to 6 weeks
  - ↑ Dose of infliximab to 10 mg/kg
  - Discontinue infliximab and consider an alternative biologic agent

---
had previously received infliximab with no response, lost response or intolerance certolizumab achieved response in 62% and remission in 39% of patients at six weeks (15). This appears to indicate that certolizumab is a viable option for therapy in Crohn’s disease patients with prior exposure to infliximab. However, long-term data has not yet been obtained.

**RECOMMENDATIONS**

Anti-TNF therapy has greatly changed the way that Crohn’s disease is treated. There are now three anti-TNF agents available for therapy in Crohn’s disease. Although formal guidelines for dose intensification of infliximab do not exist, we suggest the following (Figure 3).

- Infliximab is generally started at 5 mg/kg body weight with induction infusions at 0, 2, and 6 weeks followed by maintenance therapy every eight weeks.
- If a patient begins to have active Crohn’s disease symptoms (by CRP or endoscopy or imaging) on 5 mg/kg every eight weeks, we would either increase dose to 10 mg/kg or decrease interval or both.
- In our experience, maximal therapy consists of 10 mg/kg body weight every six weeks. If the patient is still having symptoms with or without low infliximab trough concentration, then it is reasonable to switch to adalimumab or certolizumab.

**References**