Early Trough Levels and Antibodies to Infliximab Predict Safety and Success of Reinitiation of Infliximab Therapy

Filip Baert,[*] David Drobne,[*] Ann Gils,[‡] Niels Vande Casteele,[‡] Scott Hauenstein,[§] Sharat Singh,[§] Steve Lockton,[§] Paul Rutgeerts,[*] and Séverine Vermeire[*]

[*]Department of Gastroenterology, University Hospitals Leuven, Leuven, Belgium; [‡]Department of Pharmaceutical and Pharmacological Sciences, Laboratory for Therapeutic and Diagnostic Antibodies, KU Leuven, Leuven, Belgium; and [§]Prometheus Laboratories, Inc, San Diego, California

BACKGROUND & AIMS: **Few agents are available for the treatment of inflammatory bowel diseases, and patients frequently become unresponsive to biologics. We investigated the feasibility of reinitiating infliximab therapy for patients who previously received only episodic therapy with, lost response to, or had infusion reactions to infliximab. We also aimed to identify factors associated with the success and safety of restarting infliximab, such as antibodies to infliximab and trough levels of the drug.**

METHODS: **From the inflammatory bowel disease biobank, we identified 128 consecutive patients (105 patients with Crohn's disease, 23 patients with ulcerative colitis) who restarted infliximab after a median 15-month discontinuation (range, 6–125 mo; 28 patients for loss of response or infusion reactions, 100 patients for remission or pregnancy). We also analyzed serum samples that had been collected during the first period of infliximab therapy (T-1), when therapy was reinitiated (T0), and at later time points (T+1, T+2) for trough levels and antibodies to infliximab. We investigated correlations among response to treatment, infusion reactions, treatment modalities, trough levels, and antibodies to infliximab.**

RESULTS: **Reinitiation of infliximab therapy produced a response in 84.5% of patients at week 14, 70% of patients at 1 year, and in 61% of patients at more than 4 years. Fifteen patients had acute infusion reactions and 10 patients had delayed infusion reactions. The absence of antibodies to infliximab at T+1 (hazard ratio [HR], 0.14; 95% confidence interval [CI], 0.026–0.74; $P = .021$) and reinitiation with concomitant immunomodulator therapy were associated with short-term responses (HR, 6.0; 95% CI, 1.3–27; $P = .019$). Pregnancy or remission as reason for discontinuation (HR, 2.70; 95% CI, 1.09–6.67; $P = .033$) and higher trough levels at T+1 (HR, 2.94; 95% CI, 1.18–7.69; $P = .021$) were associated with long-term response. Undetectable antibodies to infliximab at T+1 were associated with the safety of reinitiating therapy (HR for infusion reaction with detectable antibodies to infliximab, 7.7; 95% CI, 1.88–31.3; $P = .004$).**

CONCLUSIONS: **Reinitiating infliximab therapy can be safe and effective for patients with Crohn's disease or ulcerative colitis after a median 15-month discontinuation period.**

Keywords: Remicade; Drug Holiday; Antidrug Antibody; Pharmacokinetics.

Current recommendations are to continue anti–tumor necrosis factor (TNF) as a regularly scheduled maintenance therapy when patients have a complete or good partial response upon the initial induction treatment.[1] Despite this standard maintenance therapy, a significant group of patients who initially respond have a loss of response (LOR) over time.[2–5] A large body of evidence has emerged showing that immunogenicity (ie, the generation of antidrug antibodies) at least partially explains this LOR. Trough level (TL) measurements and the detection of antidrug antibodies are new diagnostic tools to asses pharmacokinetics, including immunogenicity, and potentially improve the durable efficacy and safety of anti-TNF therapy.[6]

Abbreviations used in this paper: ATI, antibodies to infliximab; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IBD, inflammatory bowel disease; IFX, infliximab; IMM, immunomodulator; IR, infusion reaction; IV, intravenous; LOR, loss of response; ROC, receiver operating curve; TL, trough level; TNF, tumor necrosis factor.

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Apart from LOR and despite the current recommendations patients sometimes will discontinue therapy for various reasons including durable remission, pregnancy, safety, or financial concerns. When symptoms reappear, restarting anti-TNF can be indicated. Very little is known, however, about restarting the same anti-TNF agent after a drug holiday. Physicians often preemptively will switch from one anti-TNF agent to another when considering that patients might have developed antidrug antibodies during the previous course or will develop them after restarting treatment. Moreover, restarting an anti-TNF agent that was discontinued because of persistent LOR or the occurrence of an infusion reaction (IR) is considered not very useful and/or a major risk for an IR.

In this cohort we studied patients who restarted infliximab (IFX) for various reasons including LOR and IR. In addition, a proportion of patients was treated episodically during their first IFX course. Restarting IFX in these patients carries a high risk for developing antidrug antibodies and hence IRs and no response or secondary LOR.[7]

The aim of this study was to examine the safety and success of restarting IFX after a long drug holiday. Co-primary end points were to identify the role of IFX TLs and antibodies to IFX (ATI) and to find predictors of success and safety upon restarting IFX.

Materials and Methods

Study Design

This was a retrospective single-center study of a consecutive series of inflammatory bowel disease (IBD) patients followed up at the University Hospitals Leuven in Belgium.

Study Population

Through a systematic search of the IBD biobank we identified 132 patients (109 patients with Crohn's disease, 23 patients with ulcerative colitis) who had received IFX treatment in the past and who were restarted on IFX maintenance therapy after a minimum drug holiday of 6 months. Four patients were excluded from the series because of insufficient clinical data. Complete clinical information on treatment modalities and short-term and long-term treatment success and serial serum samples were available for 128 of 132 patients (97%). All but 1 patient had a minimum follow-up period of 1 year at the time of the last data analysis. All patients were retreated with IFX using maintenance therapy. However, the treatment modality of the first IFX course varied: 70 patients were treated episodically only during the first course, 16 patients were treated episodically initially and received maintenance treatment later, and 72 patients received maintenance treatment from the beginning. All patients were treated according to the Belgian reimbursement criteria for IFX. This means that all patients were allergic or refractory to steroids and/or immunomodulators (IMMs) (ie, azathioprine, 6 mercaptopurine, or methotrexate) for a minimum of 3 months before IFX was started. Only 5-mg/kg infusions were used. The treating physicians were not aware of TL and ATI measurements at the time of treatment decisions.

Data Collection

Clinical information on treatment modalities was collected retrospectively from the electronic patient charts. In addition to simple demographic data, the following data were collected in detail: for the first treatment period the start date of IFX, for episodic treatment the numbers of infusions, and for maintenance treatment the duration of IFX treatment. Treatment modalities were as follows: premedication with 250 mg intravenous (IV) hydrocortisone and 10 mg of levocetirizine orally at (re)start of IFX, a 3-dose (weeks 0, 2, and 6) induction regimen or not, the use of concomitant IMM co-treatment at the start of IFX, the reason for stopping the first IFX course (remission/pregnancy vs LOR despite dose intensification and/or shortening of the interval [LOR] and/or serious IR), and, finally, the duration of the drug holiday in months.

For the second treatment period the following data were collected: the start date and the duration of IFX maintenance treatment. Treatment modalities were as follows: IV steroid prophylaxis at initiation of IFX, single vs 3-dose (weeks 0, 2, and 6) induction dose, and the use of concomitant IMM at restart of IFX.

The co-primary end points were response to IFX retreatment and safety after restarting IFX.

The initial response to IFX was assessed by experienced clinicians (and retrospectively reconfirmed by the first author [F.B.]) at weeks 10 to 14. Patients who became completely symptom free were considered full responders to the IFX treatment. Patients who had distinct clinical improvement with an obvious decrease of disease activity (assessed by a standard clinical evaluation using clinical criteria, as included in the Harvey Bradshaw index) but who still had symptoms were considered partial responders. Patients who had no benefit after a median of 2 infusions discontinued treatment and were considered primary nonresponders. Biological activity also was assessed in all the patients using C-reactive protein (CRP) levels at baseline, at week 4 in the case of a single infusion, and at week 10 in the case of induction treatment. A decrease in CRP levels of 50% between baseline and assessment time and/or normalization of CRP levels (<3 mg/L) was classified as a biological response.

Treatment response was evaluated in all patients at 3 different time points: short term (ie, at weeks 10–14 or