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ORIGINAL ARTICLE

Therapeutic drug monitoring is predictive of loss of response after de-escalation of infliximab therapy in patients with inflammatory bowel disease in clinical remission

Aurélien Amiot[a,b,c,*], **Anne Hulin**[b,d,e], **Mehdi Belhassan**[a,b], **Chantal Andre**[b,e,f], **Charlotte Gagniere**[a,b], **Yann Le baleur**[a,b], **Jean-Pierre Farcet**[b,e,f], **Jean-Charles Delchier**[a,b], **Sophie Hüe**[b,e,f]

[a] *Department of Gastroenterology, Henri-Mondor Hospital, DHU VIC, AP—HP, 94000 Créteil, France*
[b] *University of Paris Est Creteil, 94000 Créteil, France*
[c] *LIC, Laboratoire d'Investigation Clinique EA 4393, 94000 Créteil, France*
[d] *Laboratory of Pharmacology-Toxicology, Henri-Mondor Hospital, DHU VIC, AP—HP, 94000 Créteil, France*
[e] *Laboratory of Biological Immunology, Henri-Mondor Hospital, DHU VIC, AP—HP, 94000 Créteil, France*
[f] *INSERM, Unit U-955, IMRB, 94000 Créteil, France*

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Summary
Background: There is no evidence that therapeutic drug monitoring is helpful in patients with inflammatory bowel disease patients in clinical remission with infliximab therapy.
Methods: Eighty consecutive inflammatory bowel disease patients in clinical remission on infliximab maintenance therapy were included and followed-up for at least one year. Infliximab trough level and antibody to infliximab concentration were measured prior to enrollment. At the time of enrollment, physicians in charge were free to alleviate infliximab therapy. Discrepancies between blind and therapeutic drug monitoring-based adjustments were assessed at the end of the follow-up period. Relapse-free survival was analyzed using univariate and multivariate analyses.

Abbreviations: CD, Crohn's disease; CRP, C-reactive protein; IBD, inflammatory bowel disease; TNF, tumor necrosis factor; UC, ulcerative colitis.

* Corresponding author at: Department of Gastroenterology, Henri-Mondor Hospital, DHU VIC, AP—HP, 51, avenue du Marechal-de-Lattre-de-Tassigny, 94010 Creteil, France. Tel.: +33 1 49 81 43 58/33 1 49 81 23 62; fax: +33 1 49 81 23 52.
E-mail address: aurelien.amiot@hmn.aphp.fr (A. Amiot).

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Results: The mean infliximab trough level was 3.1 μg/mL. Antibody to infliximab was found in 15 (19%) patients. At the end of the follow-up period, 18 (22.5%) patients experienced a relapse. The 3, 6, 9 and 12-month relapse-free rates were 98%, 87%, 86% and 80%, respectively. In our multivariate analysis, relapse-free survival was negatively associated with discrepancies between therapeutic drug monitoring-based and blind adjustments of infliximab therapy, absence of concomitant immunomodulator, the absence of mucosal healing, prior use of infliximab, infliximab therapy duration > 2 years and C-reactive protein levels > 5 mg/L at the time of enrollment.

Conclusion: In patients with inflammatory bowel disease in clinical remission on infliximab therapy, de-escalation of infliximab therapy should be considered based on therapeutic drug monitoring rather than according to symptoms and CRP.

Introduction

Infliximab, a monoclonal chimeric IgG1 antibody, can induce and maintain clinical remission, reduce hospitalizations and surgeries and improve quality of life, in both Crohn's disease and ulcerative colitis [1,2]. However, up to 10% of patients per year will experience loss of response over time [3]. Therefore, assessing risk factors for loss of response and developing strategies to prevent loss of response to infliximab are important for the improvement of long-term patient outcomes.

The mechanisms of loss of response to infliximab could involve the pharmacology of infliximab, patient and disease characteristics and the development of alternative inflammatory pathways [3,4]. Loss of response to infliximab could be caused by a drop in infliximab trough levels (ITL) and/or the formation of antibodies to infliximab (ATI). Low ITL and increased ATI formation are significantly associated with loss of response and occurrence of hypersensitivity reactions [5].

However, whether ITL and ATI monitoring should impact infliximab therapy adjustments in patients in clinical remission is still questionable. Indeed, two ongoing randomized controlled trials are evaluating the value of individualized infliximab therapy adjustments based on therapeutic drug monitoring (TDM), called TDM-based adjustments, compared with infliximab therapy adjustments based on symptoms and CRP levels [6,7].

Thus, the aim of this study was to evaluate the clinical value of TDM to guide infliximab adjustments in IBD patients in clinical remission. We prospectively studied 80 patients in clinical remission on infliximab maintenance therapy and compared the two infliximab therapy adjustment strategies, with and without TDM.

Patients and methods

Patients

Between January and May 2012, we prospectively included all consecutive adult IBD patients in clinical remission who were treated with infliximab and followed-up at the Henri-Mondor Hospital. Eligible patients were at least 17 years old and originally received infliximab for active IBD. Exclusion criteria included extra-intestinal manifestation without significant IBD activity as the initial indication for infliximab, persistence of active luminal and/or fistulizing disease, an ostomy and pregnancy or lactation. All patients were in clinical remission according to HBI (< 4) for CD patients and partial UCDAI (≤ 3 with a combined stool frequency and rectal bleeding subscore of ≤ 1), for UC and unclassified colitis. The protocol was approved by the appropriate ethics committee.

Clinical and demographic data were collected including age at diagnosis, gender, smoking habits, CD phenotype according to the Montreal classification, and history of medical and surgical treatment of CD [8]. Biological data, including CRP (mg/L), hemoglobin (g/dL), leukocyte (per mm^3) and platelet (per mm^3) counts, were collected. In a subgroup of patients, an ileocolonoscopy was performed in the 6 months preceding infliximab withdrawal. Mucosal healing was defined as the absence of ulcers [9].

All the patients were prospectively enrolled and the data were analyzed after one year of follow-up. All patients were subjected to a standardized follow-up protocol at each infusion. HBI and/or partial UCDAI scores were calculated at every visit for Crohn's disease, ulcerative colitis and unclassified colitis. A relapse was defined by a Harvey-Bradshaw index score above 4 points or the need to introduce any specific CD treatment [10]. Partial UCDAI score was calculated in case of relapse in UC and unclassified colitis patients. A relapse was defined by a partial UCDAI score (UCDAI score without endoscopy subscore) above 2 points and/or a combined stool frequency and rectal bleeding subscores above 0 [2,11]. Additional assessment included physical examination, CRP (mg/L), hemoglobin (g/dL), leukocyte (per mm^3) and platelet (per mm^3) counts.

Infliximab therapy

At the time of enrollment, patients received infusions of infliximab at a dose of 5 to 10 mg/kg every 6 to 10 weeks according to symptoms and CRP, without previous TDM. All patients were treated with intravenous hydrocortisone premedication (200 mg) before each infliximab infusion. All