A Panel to Predict Long-term Outcome of Infliximab Therapy for Patients With Ulcerative Colitis

Maria Theresa Arias,[*] Niels Vande Casteele,[‡] Séverine Vermeire,[*] Anthony de Buck van Overstraeten,[§] Thomas Billiet,[*] Filip Baert,[*] Albert Wolthuis,[§] Gert Van Assche,[*] Maja Noman,[*] Ilse Hoffman,[‖] Andre D'Hoore,[§] Ann Gils,[‡] Paul Rutgeerts,[*] and Marc Ferrante[*]

[*]Department of Gastroenterology, University Hospitals Leuven, [‡]Department of Pharmaceutical and Pharmacological Sciences, Laboratory for Therapeutic and Diagnostic Antibodies, [§]Department of Abdominal Surgery, [‖]Department of Pediatrics, KU Leuven–University of Leuven, Leuven, Belgium

BACKGROUND & AIMS: **Infliximab is effective for patients with refractory ulcerative colitis (UC), but few factors have been identified that predict long-term outcome of therapy. We aimed to identify a panel of markers associated with outcome of infliximab therapy to help physicians make personalized treatment decisions.**

METHODS: **We collected data from the first 285 patients with refractory UC (41% female; median age, 39 y) treated with infliximab before July 2012 at University Hospitals Leuven, in Belgium. We performed a Cox regression analysis to identify independent factors that predicted relapse-free and colectomy-free survival, and used these factors to create a panel of markers (risk panel).**

RESULTS: **During a median follow-up period of 5 years, 61% of patients relapsed and 20% required colectomy. Independent predictors of relapse-free survival included short-term complete clinical response (odds ratio [OR], 3.75; 95% confidence interval [CI], 2.35–5.97; $P < .001$), mucosal healing (OR, 1.87; 95% CI, 1.17–2.98; $P = .009$), and absence of atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA) (OR, 1.96; 95% CI, 1.23–3.12; $P = .005$). Independent predictors of colectomy-free survival included short-term clinical response (OR, 7.74; 95% CI, 2.76–21.68; $P < .001$), mucosal healing (OR, 4.02; 95% CI, 1.16–13.97; $P = .028$), baseline level of C-reactive protein (CRP) of 5 mg/L or less (OR, 2.95; 95% CI, 1.26–6.89; $P = .012$), and baseline level of albumin of 35 g/L or greater (OR, 3.03; 95% CI, 1.12–8.22; $P = .029$). Based on serologic analysis of a subgroup of 112 patients, levels of infliximab greater than 2.5 μg/mL at week 14 of treatment predicted relapse-free survival ($P < .001$) and colectomy-free survival ($P = .034$). A risk panel that included levels of pANCA, CRP, albumin, clinical response, and mucosal healing identified patients at risk for UC relapse or colectomy (both $P < .001$).**

CONCLUSIONS: **Clinical response and mucosal healing were confirmed as independent predictors of long-term outcome from infliximab therapy in patients with UC. We identified additional factors (levels of pANCA, CRP, and albumin) to create a risk panel that predicts long-term outcomes of therapy. Serum levels of infliximab at week 14 of treatment also were associated with patient outcomes. Our risk panel and short-term serum levels of infliximab therefore might be used to guide therapy.**

Keywords: Drug; Response To Therapy; Prognostic Factor; Biomarker.

In 2005, the landmark Active Ulcerative Colitis Trials (ACT1 and ACT2) showed a significant benefit for the use of infliximab (IFX) in patients with moderate-to-severe ulcerative colitis (UC).[1] In these double-blind, placebo-controlled trials, patients randomized to IFX not only experienced higher clinical response and remission rates, but also higher mucosal healing rates, lower hospitalization rates, and lower colectomy rates during up to 1 year of follow-up evaluation.[1,2] In parallel, a Scandinavian placebo-controlled

Abbreviations used in this paper: **ACT, Active Ulcerative Colitis Trials; ASCA, anti-Saccharomyces cerevisiae antibodies; ASUC, acute severe ulcerative colitis; CI, confidence interval; CRP, C-reactive protein level; CS, corticosteroids; IFX, infliximab; IMM, immunomodulatory agents; IQR, interquartile range; OR, odds ratio; pANCA, atypical perinuclear antineutrophil cytoplasmic antibodies; UC, ulcerative colitis.**

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trial provided evidence for the use of IFX in patients with acute severe ulcerative colitis (ASUC) refractory to intravenous corticosteroids (CS).[3,4] Most recently, the Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif group showed that IFX was at least as efficacious as cyclosporine for this indication.[5]

In the past decade, several real-life, open-label cohort studies have provided more data on the efficacy and safety of IFX in patients with refractory UC.[6–9] Short-term clinical response, short-term normalization of C-reactive protein level (CRP), and short-term mucosal healing were among the predictors of colectomy-free survival.[7,8,10,11] In contrast, an increased baseline CRP level, a shorter disease duration before IFX, and previous treatment with intravenous cyclosporine have been associated with a higher colectomy risk.[7,9] In a Canadian trial, detectable IFX serum levels were associated with higher clinical remission rates, higher endoscopic improvement rates, and lower colectomy rates, but no firm conclusions could be drawn on their predictive value.[12]

In 2008, we presented the outcome of the first 121 outpatients with refractory UC treated with IFX in our center.[6] With the current study we aimed to explore the extended long-term outcome of a larger cohort of patients with refractory UC treated with IFX in our tertiary referral center. Furthermore, we defined predictors of long-term, relapse-free and colectomy-free survival, and specifically evaluated the predictive value of IFX serum levels. Based on the provided risk factors, we developed a risk panel to predict long-term outcome to IFX. This risk panel may guide personalized therapy in patients starting IFX for refractory UC.

Methods

Patient Population

All patients with refractory UC who received a first infusion of IFX before July 2012 were included in this study, allowing a follow-up period of at least 6 months. Eligible patients did not respond to CS alone, immunomodulatory agents (IMM) alone, or a combination of both, were intolerant to any of these drugs, or were unable to taper CS. We identified 285 patients (41% female), with a median age at first IFX of 39.1 years (interquartile range [IQR], 28.8–50.6 y). Among these 285 patients, 39 received IFX for ASUC refractory to intravenous CS. Before IFX initiation, latent tuberculosis, cytomegalovirus, and *Clostridium difficile* infection were excluded. All individuals provided written informed consent for this study, which was approved by the local ethics committee of the Catholic University of Leuven. Patients' characteristics are listed in Table 1.

Serologic and Genetic Markers

Data on levels of CRP, hemoglobin, thrombocytes, and albumin were collected prospectively as part of a standardized follow-up evaluation of all patients treated with IFX. The presence of anti–*Saccharomyces cerevisiae* antibodies (ASCA) and atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA) were evaluated through an enzyme-linked immunosorbent assay. Serum samples were collected at baseline and at week 14 immediately before the fourth IFX administration (trough level). Serum IFX levels were measured using an in-house–developed enzyme-linked immunosorbent assay.

Based on a previously reported association with the need for colectomy,[13] we assessed the multidrug resistance gene 1 C3435T genotype by TaqMan genotyping assay (Applied Biosystems Inc, Carlsbad, CA).

Definitions

The extent of disease was categorized using the Montreal classification.[14] Endoscopic severity of disease before IFX was determined according to the Mayo endoscopic subscore in 265 patients.[15] Short-term response to IFX was assessed after 10 to 14 weeks and was defined as complete if there was an absence of diarrhea and blood, and partial if there was marked clinical improvement (less diarrhea, less abdominal pain) but still persistent rectal blood loss.[16] To assess short-term mucosal healing, endoscopy was performed in 200 patients both before and 10 to 14 weeks after the first IFX infusion. Mucosal healing was defined as a Mayo endoscopic subscore of 0 or 1, and was assessed only in patients with a Mayo endoscopic subscore of 2 or 3 at inclusion (n = 200).[16] Normalization of CRP level was analyzed in patients with an increased baseline CRP level (>5 mg/L) if a second CRP level was available 10 to 14 weeks after first IFX infusion (n = 149).

Long-term outcome was evaluated at last follow-up evaluation. Relapse-free survival was defined as the absence of clinical relapse requiring IFX dose optimization, medical rescue therapy, or colectomy, and was evaluated only in patients who initially responded to the therapy and received maintenance IFX therapy. Colectomy-free survival was evaluated in all patients and was defined as the absence of colectomy throughout follow-up evaluation, regardless of clinical findings and the need for medical interventions. Of note, patients who underwent colectomy for neoplastic lesions (n = 5) also were included in the analysis for colectomy-free survival.

Administration of Infliximab and Concomitant Therapy

At study start, patients received either a single dose of 5 or 10 mg IFX per kilogram of body weight, or an induction scheme with IFX at weeks 0, 2, and 6. Six patients received 1 (n = 5) or 2 (n = 1) extra infusions of IFX before week 14. Fifteen patients from the 214 patients showing clinical response discontinued IFX after