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Adalimumab Therapy Is Associated With Reduced Risk of Hospitalization in Patients With Ulcerative Colitis

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See related article, Roblin X et al, on page 80 in *CGH*.

BACKGROUND & AIMS: Adalimumab is effective for induction and maintenance of remission in patients with moderate to severe ulcerative colitis (UC). We assessed whether adalimumab, in addition to standard UC therapy, reduced the risk for hospitalization (from all causes, from complications of UC, or from complications of UC or the drugs used to treat it) and colectomy in patients with moderate to severe UC compared with placebo. **METHODS:** Data were combined from patients that received induction therapy (a 160-mg dose followed by an 80-mg dose of adalimumab) or placebo in 2 trials (ULTRA 1 and ULTRA 2; n = 963). The risks of hospitalization and colectomy were compared between groups using unadjusted rates during the 8-week induction period, and patient-year–adjusted rates during 52 weeks. Statistical differences between groups were determined using the χ^2 method and *Z* score normal approximations. Numbers of hospitalizations were compared using Poisson regression with time offset. **RESULTS:** Significant reductions in risk of all-cause, UC-related, and UC- or drug-related hospitalizations (by 40%, 50%, and 47%, respectively; $P < .05$ for all comparisons) were observed within the first 8 weeks of adalimumab therapy compared with placebo. Significantly lower incidence rates for all-cause (0.18 vs 0.26; $P = .03$), UC-related (0.12 vs 0.22; $P = .002$), and UC- or drug-related (0.14 vs 0.24; $P = .005$) hospitalizations were observed during 52 weeks of adalimumab therapy compared with placebo. Rates of colectomy did not differ significantly between patients given adalimumab vs placebo. **CONCLUSIONS:** In patients with moderate to severe UC, the addition of adalimumab to standard of care treatment reduced the number of hospitalizations for any cause, as well as for UC-related and UC- or drug-related complications, compared with placebo. ClinicalTrials.gov numbers, NCT00385736 and NCT00408629.

Keywords: Randomized Placebo-Controlled Study; Anti-TNF; Colectomy; Inflammatory Bowel Disease.

Ulcerative colitis (UC) is an idiopathic bowel disease characterized by chronic inflammation of the mucosa and submucosa of the colon.[1–3] Abdominal pain, bloody diarrhea, fecal urgency, and incontinence are common clinical symptoms.[2,3]

During a severe exacerbation of disease, patients might require hospitalization to receive either medical or surgical treatment, or manage complications arising from either therapy or the disease itself. UC imposes a substantial burden on patients and society in terms of reduced quality of life, reduced work productivity, and high direct medical costs.[4,5] Medical therapy for moderate to severe UC includes corticosteroids, immunosuppressives, and in recent years, the tumor necrosis factor (TNF) antagonist infliximab. Despite the treatment advances of the past decade, hospitalization rates have remained unchanged.[6,7] A study of claims data from 2000 to 2010 found that approximately 34% of patients with moderate to severe UC were hospitalized annually, and many of these patients experienced multiple hospitalization events within a year.[8] In 2008, the cost of UC in the United States was estimated to be $8.1 to $14.9 billion, of which a significant portion ($3.4 billion) consisted of direct medical costs related to hospitalizations and operations.[4]

Adalimumab, a fully human TNF antagonist, was recently approved in both Europe and the United States for the treatment of moderately to severely active UC in patients who failed to respond to conventional therapies. However, the efficacy of this agent for reducing hospitalization and surgery has not been assessed.

The objective of this analysis was to evaluate the effect of adalimumab therapy (induction with 160/80 mg at weeks 0 and 2 followed by maintenance with 40 mg every other week) on the risk of all-cause, UC-related, and UC- or drug-related hospitalization and colectomy compared with placebo. The analysis utilized data generated from 2 large, randomized, double-blind, clinical trials (Ulcerative Colitis Long-Term Remission and Maintenance With Adalimumab [ULTRA] ULTRA 1 and ULTRA 2) that were performed in patients with moderately to severely active UC.

Abbreviations used in this paper: **CI, confidence interval; eow, every other week; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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Methods

Study Design

ULTRA 1 (NCT00385736) was an 8-week, double-blind, placebo-controlled induction trial of adalimumab in patients with moderately to severely active UC with an open-label extension for a total of 52 weeks[9,10] (Figure 1*A* and *B*). Initially, patients were randomly assigned to double-blind treatment with either adalimumab or placebo. The adalimumab group received induction therapy consisting of adalimumab 160/80 mg (160 mg at week 0 and 80 mg at week 2) followed by adalimumab 40 mg every other week (eow) starting at week 4. During the trial, the ULTRA 1 protocol was amended to include a second induction group, adalimumab 80/40 mg (80 mg at week 0, 40 mg at weeks 2, 4, and 6). Under the amended protocol, patients in all 3 treatment groups received open-label adalimumab 40 mg eow from week 8 until week 52/early termination. At week 12, patients with an inadequate response to treatment could increase the dose of adalimumab to 40 mg every week. The 80/40-mg induction regimen was not better than placebo for inducing remission,[9] thus only data from patients randomized to placebo or a 160/80-mg induction dose of adalimumab were included in the present analysis.

ULTRA 2 (NCT00408629) was a 52-week, double-blind, placebo-controlled induction (160/80 mg at weeks 0/2) and maintenance (40 mg eow) trial of adalimumab in patients with moderately to severely active UC[11] (Figure 1*C*). Approximately 40% of the ULTRA 2 study participants had previously received a TNF antagonist. At or after week 10, patients who met criteria for inadequate response could be switched to open-label adalimumab 40 mg eow beginning at week 12. Patients who demonstrated an inadequate response at 2 consecutive visits at least 14 days apart while on open-label administration of 40 mg eow could increase their dose of adalimumab to 40 mg every week.

On completion of the ULTRA 1 and 2 studies, patients had the option to enroll into the open-label adalimumab extension trial M10-223 (NCT00573794).

Patients

The ULTRA 1 and 2 trials were approved by the Institutional Review Board of each center and all patients who participated in the trials gave informed consent. Patients in ULTRA 1 were TNF-antagonist–naïve with moderately to severely active UC, defined as a Mayo score $\geq$6 points and endoscopic subscore $\geq$2 points, despite concurrent and stable therapy with corticosteroids and/or immunosuppressive agents. ULTRA 2 enrolled TNF-antagonist–naïve (60%) and TNF-antagonist–experienced (40%) patients, despite concurrent and stable therapy with corticosteroids and/or immunosuppressive agents with the same requirements for Mayo score, and concomitant therapy. A complete medical history, including comorbidities, was collected during a screening period. The presence of UC was confirmed endoscopically; patients with disease limited to the rectum were excluded. Additional details of the inclusion/exclusion criteria for these studies have been published elsewhere.[9,11] Patients who completed ULTRA 1 and 2 could enroll into the open-label extension study M10-223.

Outcomes

The outcomes examined in this analysis were all-cause, UC-related, UC- or drug-related hospitalizations, and colectomy. Events of hospitalization and colectomy were identified by a review of reports of serious adverse events. Two experienced gastroenterologists (Brian G. Feagan and William J. Sandborn) who were unaware of the treatment assignment performed the review. Disagreement at the initial assessment was resolved through additional review by the same 2 reviewers. All-cause hospitalizations were defined as serious adverse events resulting in admission to the hospital for any reason. UC-related hospitalizations were defined as hospital admissions due to adverse events or complications that were related to UC and included the following categories: UC-related surgery; hospitalizations for nonsurgical UC-related events, such as UC-related flares; and hospitalizations related to the complications/extra-intestinal manifestations of UC. Drug-related hospitalizations were defined as hospital admissions potentially due to adverse events related to any medications used to treat UC as judged by the reviewers.

Data Analysis

Patient sample and follow-up. Data from the ULTRA 1 and 2 studies were combined for this analysis using methods described previously by the authors.[12,13] All authors had access to the study data and reviewed and approved the final manuscript. The patient sample included all patients in the 160/80-mg and placebo groups who received at least one injection of randomized study drug (adalimumab or placebo).

For adalimumab-treated patients, the follow-up period included the combined double-blind and open-label periods, and was either 70 days (5 times the half-life of adalimumab) after the last dosing date of ULTRA 1 and 2 if they did not enroll into extension trial M10-223 or the last date of the study (ULTRA 1 and 2) if they enrolled into M10-223. For those patients who withdrew from the studies, the follow-up period was 70 days after the last dosing date.

For placebo patients who chose not to enroll into the extension trial or who prematurely discontinued the study (ULTRA 1 and 2), the last day of the follow-up period was 70 days after the last dosing date (if the patient remained on placebo) or 70 days after the switch to open-label (if the patient switched to open-label adalimumab). For those placebo-randomized patients who enrolled into M10-223, the last day of follow-up was either the last study day (ULTRA 1 and 2) or 70 days after the last dosing date/switch to open-label adalimumab (depending on whether the patient remained on placebo or switched to open-label active treatment), whichever came first.

Statistical Analysis

Primary analysis. *8-Week induction period analysis.* The risks of hospitalization (all-cause, UC-related, and UC- or drug-related) and colectomy during the first 8 weeks of therapy (induction period) were calculated by dividing the number of patients who experienced each respective event during the first 8 weeks by the total number of patients in each group. Differences in the risk of hospitalization and colectomy in the induction period between the 2 treatment groups were compared using χ^2 tests.