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Four-Year Maintenance Treatment With Adalimumab in Patients with Moderately to Severely Active Ulcerative Colitis: Data from ULTRA 1, 2, and 3

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OBJECTIVES: **The safety and efficacy of adalimumab for patients with moderately to severely active ulcerative colitis (UC) has been reported up to week 52 from the placebo-controlled trials ULTRA (Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab) 1 and 2. Up to 4 years of data for adalimumab-treated patients from ULTRA 1, 2, and the open-label extension ULTRA 3 are presented.**

METHODS: **Remission per partial Mayo score, remission per Inflammatory Bowel Disease Questionnaire (IBDQ) score, and mucosal healing rates were assessed in adalimumab-randomized patients from ULTRA 1 and 2 up to week 208. Corticosteroid-free remission was assessed in adalimumab-randomized patients who used corticosteroids at lead-in study baseline. Maintenance of remission per partial Mayo score and mucosal healing was assessed in patients who entered ULTRA 3 in remission per full Mayo score and with mucosal healing, respectively. As observed, last observation carried forward (LOCF) and nonresponder imputation (NRI) were used to report efficacy. Adverse events were reported for any adalimumab-treated patient.**

RESULTS: **A total of 600/1,094 patients enrolled in ULTRA 1 or 2 were randomized to receive adalimumab and included in the intent-to-treat analyses of the studies. Of these, 199 patients remained on adalimumab after 4 years of follow-up. Rates of remission per partial Mayo score, remission per IBDQ score, mucosal healing, and corticosteroid discontinuation at week 208 were 24.7%, 26.3%, 27.7% (NRI), and 59.2% (observed), respectively. Of the patients who were followed up in ULTRA 3 (588/1,094), a total of 360 patients remained on adalimumab 3 years later. Remission per partial Mayo score and mucosal healing after ULTRA 1 or 2 to year 3 of ULTRA 3 were maintained by 63.6% and 59.9% of patients, respectively (NRI). Adverse event rates were stable over time.**

CONCLUSIONS: **Remission, mucosal healing, and improved quality of life were maintained in patients with moderately to severely active UC with long-term adalimumab therapy, for up to 4 years. No new safety signals were reported.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Ulcerative colitis (UC) is a chronic, progressive inflammatory bowel disease characterized by mucosal inflammation of the colon. The clinical features include bloody diarrhea, abdominal pain, fecal incontinence, urgency, and tenesmus (1,2). Although the cause of UC remains unknown, the important role of tumor necrosis factor (TNF) in the pathogenesis has become accepted on the basis of empiric data (3). Current treatment goals for patients with UC include induction of remission and mucosal healing, avoidance of hospitalization and colectomy, and improving quality of life.

Adalimumab, a fully human monoclonal antibody specific for human TNF, is approved worldwide for multiple indications,

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including UC (4,5). The efficacy of adalimumab in inducing and maintaining remission, up to 52 weeks, in patients with moderately to severely active UC was demonstrated in the pivotal ULTRA (*Ul*cerative Colitis *L*ong-*T*erm *R*emission and Maintenance with *A*dalimumab) 1 and 2 clinical trials that evaluated patients whose disease was active despite treatment with conventional therapies (6–9). Adalimumab was also shown to reduce the number of all-cause and UC-related hospitalizations compared with placebo treatment. Colectomy rates were low in the ULTRA 1 and 2 studies and did not differ significantly between adalimumab- and placebo-treated patients (10). The safety of adalimumab has been extensively studied in patients with rheumatoid arthritis, Crohn's disease, and other inflammatory disorders (11); yet, long-term data from patients with UC are lacking. The ongoing, open-label extension study, ULTRA 3, is evaluating the long-term safety and efficacy of adalimumab in patients with UC. In this report we present remission and mucosal healing rates, improvement in health-related quality of life and work productivity, and reduction of hospitalization rates with prolonged adalimumab maintenance treatment, up to 4 years, using data from patients who received adalimumab during ULTRA 1, ULTRA 2, or ULTRA 3. The safety profile of long-term adalimumab therapy is also reported.

METHODS

ULTRA 1 and ULTRA 2 trial designs

Detailed information regarding the designs and patient dispositions of ULTRA 1 and ULTRA 2 has been published previously. (6,7) Briefly, these were phase 3, double-blind, placebo-controlled clinical trials that assessed the efficacy and safety of adalimumab for the treatment of moderately to severely active UC in adult patients with a diagnosis of UC for at least 90 days, Mayo score of 6–12, and endoscopy subscore ≥2, despite concurrent or previous treatment with oral corticosteroids and/or immunosuppressants. Patients who had previously been exposed to anti-TNF therapy were eligible for ULTRA 2. In both studies, corticosteroid tapering was allowed at or after week 8, at the discretion of the investigator, for patients who demonstrated a satisfactory clinical response.

The original protocol for ULTRA 1 had a 12-week double-blind phase in which anti-TNF-naive patients were randomized to receive placebo for 8 weeks or adalimumab 160/80 mg at weeks 0/2, followed by 40 mg at weeks 4/6. At weeks 8/10, patients randomized to placebo received adalimumab 160/80 mg, and patients randomized to adalimumab continued to receive adalimumab 40 mg every other week. After the study began, at the request of the European regulatory authorities, the protocol was amended to add a second adalimumab induction group of 80/40 mg at weeks 0/2, followed by 40 mg at weeks 4/6. Under the amended protocol, the double-blind period was reduced to 8 weeks. ULTRA 1 included a subset of patients who were enrolled under both the original protocol and the amended protocol. Patients who completed the double-blind phase of the trial (8 or 12 weeks) could enter an open-label phase during which all patients received adalimumab 40 mg every other week. ULTRA 1 concluded at week 52. During the open-label phase, patients who experienced an inadequate response could escalate to 40 mg weekly. Inadequate response was defined as partial Mayo score (PMS, Mayo score without endoscopy subscore) ≥baseline score on two consecutive visits at least 14 days apart, for patients with baseline PMS 4–7. For patients with a baseline PMS 8–9, inadequate response was defined as PMS ≥7 on two consecutive visits at least 14 days apart.

In ULTRA 2, patients were randomized to receive placebo or adalimumab (160/80 mg at weeks 0/2, followed by 40 mg every other week). The last study visit occurred at week 52. Patients with an inadequate response (same definition as above) could move to open-label adalimumab 40 mg every other week beginning at week 12 and subsequently to 40 mg weekly for continued inadequate response.

ULTRA 3

All patients who completed ULTRA 1 or ULTRA 2 could enter the open-label extension, ULTRA 3. Patients who completed ULTRA 2 on blinded therapy (either adalimumab or placebo) received open-label adalimumab 40 mg every other week in ULTRA 3. Patients who completed the lead-in study (ULTRA 1 or ULTRA 2) on open-label adalimumab 40 mg every other week or weekly continued their same dosing regimens in ULTRA 3. For patients who entered ULTRA 3 from a blinded cohort or on open-label every other week dosing, escalation to 40 mg weekly dosing was allowed after week 12 of ULTRA 3 for inadequate response (same definition as in ULTRA 1 and 2) or disease flare (defined as a PMS difference ≥3 compared with the baseline PMS of ULTRA 3 on two consecutive visits at least 14 days apart). Increase to 40 mg weekly was allowed at week 2 of ULTRA 3 or thereafter for patients who entered ULTRA 3 with an inadequate response on open-label every other week dosing. Corticosteroid tapering was allowed after week 12 of ULTRA 3 for patients with a clinical response, but if corticosteroid tapering was begun in the lead-in study (ULTRA 1 or ULTRA 2), patients could continue their corticosteroid taper upon entry into ULTRA 3.

Data analysis

The long-term efficacy of adalimumab up to 4 years of treatment was assessed in all patients randomized to adalimumab in ULTRA 1 and ULTRA 2 who received at least one dose of adalimumab (ADA), excluding 10 patients from GCP (Good Clinical Practice)-noncompliant sites (ADA Randomized Set, N=600). Efficacy in the ADA Randomized Set was assessed through week 208. Some of the patients in this analysis set (i.e., patients who discontinued prematurely from ULTRA 1, 2, or 3 and patients who did not enroll into ULTRA 3) did not have 208 weeks of adalimumab exposure. Of the 600 patients in the ADA Randomized Set, 199 remained on adalimumab at week 208. Patients who entered ULTRA 3 from either ULTRA 1 or ULTRA 2 (including patients who were randomized to placebo at lead-in study baseline), with the exception of four patients from GCP-noncompliant sites (ADA Extension Set, N=588), were analyzed to evaluate the maintenance efficacy of adalimumab from week 0 to week 156 of ULTRA 3, which corresponds to week 208 from lead-in study baseline. Of the 588 patients enrolled in ULTRA 3, a total of 360

remained on adalimumab at the ULTRA 3 week 156 study visit. Subgroup analyses by previous anti-TNF use were also performed.

Efficacy end points assessed in the ADA Randomized Set were remission per PMS (PMS ≤2 with no subscore >1), remission per Inflammatory Bowel Disease Questionnaire (IBDQ) score (IBDQ score ≥170), (12) and mucosal healing (endoscopy subscore ≤1). Discontinuation of corticosteroids and corticosteroid-free remission (full Mayo score ≤2 with no individual subscore >1 and discontinued corticosteroid use) were assessed in patients from the ADA Randomized Set who received corticosteroids at lead-in study baseline (*N*=356). Maintenance of remission (per PMS) and maintenance of mucosal healing through year 3 of ULTRA 3 was assessed in patients from the ADA Extension Set who entered ULTRA 3 in remission per full Mayo score (*N*=242) or with mucosal healing (*N*=409), respectively. Because of the timing of endoscopies in ULTRA 3, rates of mucosal healing and remission per full Mayo score (reported as part of corticosteroid-free remission) are reported up to week 196 from lead-in study baseline. Maintenance of mucosal healing is reported up to week 144 of ULTRA 3, which corresponds to week 196 from lead-in study baseline.

Work Productivity and Activity Impairment (WPAI) was assessed using the WPAI questionnaire (13) in patients randomized to adalimumab from ULTRA 2 (*N*=248). WPAI questionnaires were not completed in ULTRA 1. The WPAI score consists of four components: an assessment of activity impairment in all patients and assessments of work time missed, impairment while working, and overall work impairment in employed individuals. Each score ranges from 0% (no impairment) to 100% (total loss of work productivity or activity). A decrease in scores indicates improvement, and lower scores signify little impact of disease on work and activity.

Exposure-adjusted incidence rates of all-cause hospitalization (hospitalization for any reason), UC-related hospitalization (hospitalization due to adverse events or complications related to UC, including those occurring because of UC-related surgery, UC-related flares, and extraintestinal manifestations of UC), and colectomy were assessed during ULTRA 3 in the ADA Extension Set, including four patients from GCP-noncompliant sites (*N*=592). Patient-based incidence rates (number of patients with hospitalizations or colectomy per patient-years at risk) and event-based incidence rates (number of hospitalizations per total patient-years of follow-up time), given that patients could be hospitalized more than once, were calculated from the first dose in ULTRA 3 until 15 April 2013 or until 70 days after the last dose, whichever came first.

Clinical assessment

PMS and WPAI questionnaires (ULTRA 2 only) were assessed at every study visit. PMS was determined using the worst patient-reported stool frequency and rectal bleeding subscores from 3 days before the study visit. Endoscopies were performed at baseline and at weeks 8, 32 (in ULTRA 2 only), and 52 in ULTRA 1 and 2, and every 48 weeks in ULTRA 3. The IBDQ questionnaire was completed at baseline, at weeks 4, 8 (20, 32 in ULTRA 2 only), and 52 in ULTRA 1 and 2, and at every study visit during ULTRA 3. Adverse events were analyzed through 70 days after the last adalimumab dose for any patient who received at least one dose of adalimumab in ULTRA 1, 2, or 3 (*N*=1,010), including patients from GCP-noncompliant sites. In this analysis, the data cutoff date for efficacy end points and safety is 15 April 2013. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

Statistical methods

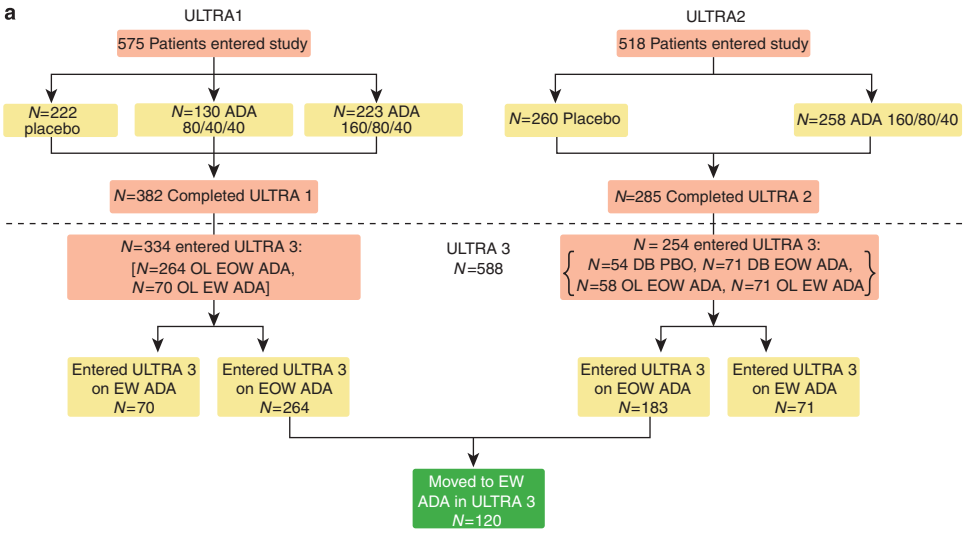
Mean WPAI scores, corticosteroid-free remission, and complete discontinuation of corticosteroids were reported over time as observed values. Long-term remission rates over time (per PMS and per IBDQ score) and mucosal healing rates over time were analyzed using nonresponder imputation (NRI), whereby patients with missing data were assumed not to have achieved the end point. A modified NRI was used to analyze remission per PMS in patients who remained on every other week dosing, whereby NRI was used for patients with missing data and at the point of moving to weekly dosing. Maintenance of remission per PMS and mucosal healing (for patients in the ADA Extension Set who entered ULTRA 3 in remission per full Mayo score or with mucosal healing, respectively) were analyzed using NRI and last observation carried forward (LOCF). For LOCF, the last nonmissing value was carried forward.

Cox proportional hazards regression analysis was used to identify predictors of loss of remission in patients from the ADA Extension Set by fitting one model per potential prognostic factor. Crude hazard ratios with 95% confidence intervals and *P*-values were calculated. Baseline variables of lead-in study (ULTRA 1 or 2) assessed were age, sex, weight, disease duration, site of UC, Mayo score, C-reactive protein (CRP), immunomodulator (IMM) use, corticosteroid use, aminosalicylate use, tobacco use, albumin concentration, and previous anti-TNF use. Variables assessed at the time of enrollment into ULTRA 3 were IMM use, corticosteroid use, CRP, and albumin concentration. Time-dependent variables (from time of enrollment into ULTRA 3 until loss of remission or last observation in ULTRA 3) assessed during ULTRA 3 were CRP levels and albumin concentration, and change in CRP and albumin concentration over time. The time to loss of remission (defined as PMS >2 for at least two consecutive visits) was measured for patients in the ADA Extension Set who were in remission per PMS at the time of enrollment into ULTRA 3 (*N*=307).

RESULTS

Patient disposition and baseline characteristics

Detailed patient demographics from ULTRA 1 and ULTRA 2 were reported previously (6,7). The disposition of patients in ULTRA 3 is shown in **Figure 1a**. More than half of the patients who enrolled in the lead-in studies enrolled in ULTRA 3 (588/1,094, 53.7%). Fifty-four patients did not receive any adalimumab before enrolling in ULTRA 3. Of the 588 patients analyzed in the ADA Extension Set, 56.8% (334/588) enrolled from ULTRA 1 and 43.2% (254/588) enrolled from ULTRA 2 (**Figure 1a**). The number of patients at each study visit in the ADA Randomized Set and ADA Extension Set is shown in **Figure 1b**.



b Number of patients by visit

Week from lead-in study baseline	ADA Randomized set (N)	ADA Extension set (N)
0	600	N/A
52	389	588
100	292	517
160	225	418
208	199	360

Figure 1. Patient enrollment in the ULTRA studies. (**a**) Patient flow into ULTRA 3. ADA, adalimumab; EOW, every other week; EW, weekly; OL, open label; ULTRA, *U*lcerative Colitis *L*ong-*T*erm *R*emission and Maintenance with *A*dalimumab. One patient in ULTRA 2 was randomized to adalimumab but did not receive the study drug. (**b**) The number of patients by study visit in the ADA Randomized Set and the ADA Extension Set. DB, double blind; PBO, placebo.

Baseline characteristics (from lead-in study) for the ADA Randomized and ADA Extension Sets are shown in **Supplementary Table S1** online. A majority of patients were white males, and median disease duration was ~6 years. The mean Mayo score was ~9, about half of the patients had pancolitis, and over half of the patients were using oral corticosteroids at lead-in study baseline. The rate of previous anti-TNF use was 16.2% in the ADA Randomized Set and 13.9% in the ADA Extension Set. Baseline demographics and characteristics were similar between anti-TNF-naive and anti-TNF-experienced patients in the ADA Randomized Set (**Supplementary Table S1**).

Long-term efficacy outcomes

Remission and mucosal healing rates were achieved early (data shown from week 8) and maintained through 4 years of treatment (**Figure 2a–d**). At 1 year of maintenance therapy, 32.2% (193/600 (NRI)) of patients randomized to adalimumab at lead-in study baseline were in remission per PMS and 42.3% (254/600 (NRI)) of adalimumab-randomized patients had mucosal healing (**Figure 2a,b**). Rates at year 4 were 24.7% (148/600 (NRI)) and 27.7% (166/600 (NRI)) for remission per PMS and mucosal healing, respectively. When patients from this analysis set who escalated to weekly dosing were imputed as nonresponders (modified NRI), the rate of remission per PMS was 27.3% at week 52 and 18.2% at week 208 (**Figure 2a**). Of the 242 patients who entered ULTRA 3 in remission per full Mayo score, 78.5% (LOCF) and 63.6% (NRI) remained in remission per PMS 3 years later (**Figure 2c**). Of the 409 patients who entered ULTRA 3 with mucosal healing, 81.7% (LOCF) and 59.9% (NRI) maintained mucosal healing through week 144 of ULTRA 3 (**Figure 2d**). Over time, remission and mucosal healing rates were generally greater in anti-TNF-naive compared with anti-TNF-experienced patients (**Supplementary Figure S1a,b**). During the first 3 years of ULTRA 3, a total of 120/588 (20.4%) patients in the ADA Extension Set escalated to weekly dosing. Mean PMS improved in this subgroup of patients from 6.0 (last PMS before moving to weekly dosing) to 3.0 (last weekly value).

Predictors of loss of remission

None of the variables analyzed at baseline of lead-in study or at the time of enrollment into ULTRA 3 was a significant predictor of loss of remission (**Supplementary Table S2**). In contrast, the time-dependent covariates CRP and albumin were significantly associated with loss of remission. Patients with increasing CRP concentrations and decreasing serum albumin concentrations during ULTRA 3 were significantly more likely to lose remission. The median time to loss of remission was not estimable for patients in the ADA Extension Set who entered ULTRA 3 in remission per

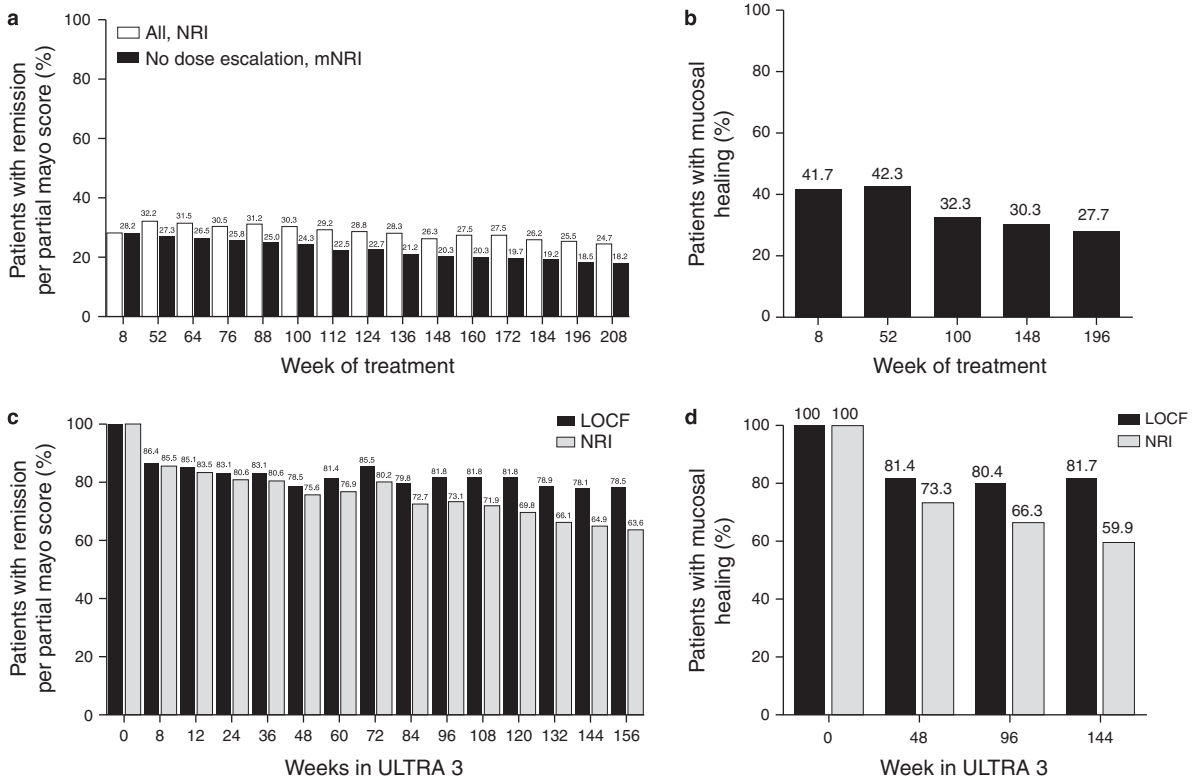


Figure 2. Long-term remission and mucosal healing rates with adalimumab treatment. (**a**) Proportion of patients with remission per partial Mayo score over time in the ADA Randomized Set (*N*=600). Gray bars indicate all patients randomized to adalimumab at lead-in study baseline (All, NRI); black bars indicate patients randomized to every other week adalimumab dosing imputing no remission for patients who escalated to weekly dosing (no dose escalation, mNRI). (**b**) Proportion of patients with mucosal healing over time in the ADA Randomized Set (*N*=600), NRI analysis. (**c**) Maintenance of remission per partial Mayo score in patients who entered ULTRA 3 in remission per full Mayo score from the ADA Extension Set (*N*=242). Black bars indicate LOCF and gray bars indicate NRI analysis. (**d**) Maintenance of mucosal healing in patients who entered ULTRA 3 with mucosal healing from the ADA Extension Set (*N*=409). Black bars indicate LOCF and gray bars indicate NRI analysis. ADA, adalimumab; LOCF, last observation carried forward; mNRI, modified nonresponder imputation; NRI, nonresponder imputation; ULTRA, *U*lcerative Colitis *L*ong-*T*erm *R*emission and Maintenance with *A*dalimumab.

PMS, as more than half of the patients maintained remission during the follow-up period (**Supplementary Figure S2**).

Maintenance of corticosteroid-free remission

The corticosteroid-free remission rates for patients in the ADA Randomized Set who received corticosteroids at lead-in study baseline increased from week 52 (27.4%, 65/237) to week 196 (39.7%, 48/121, observed analysis) of adalimumab treatment. The proportion of patients who discontinued corticosteroids increased over time from week 16 to week 208 of adalimumab treatment (**Figure 3**).

Health-related quality of life

At 1 year of adalimumab maintenance therapy, 40.3% (242/600 (NRI)) of patients in the ADA Randomized Set achieved remission per IBDQ score (IBDQ score ≥170). Remission rates per IBDQ score averaged between 26% and 36% throughout ULTRA 3 (**Figure 4**). Anti-TNF-naive patients had numerically higher rates of remission per IBDQ score relative to anti-TNF-experienced patients throughout the entire duration of follow-up (**Supplementary Figure S1c**).

WPAI scores over time in adalimumab-randomized patients from ULTRA 2 are shown in **Supplementary Figure S3**. Mean percent scores for each WPAI component (work time missed, impairment while working, overall work impairment, and activity impairment) decreased from ULTRA 2 baseline through week 208, indicating an improvement in work productivity and degree of activity impairment.

Hospitalization and colectomy

Incidence rates of hospitalizations and colectomy for patients during ULTRA 3 were lower than those observed during the double-blind treatment period of ULTRA 1 and 2 for patients receiving adalimumab dosing of 160/80/40 mg (**Table 1**). This was observed for UC-related as well as for all-cause hospitalizations.

Safety

A total of 1,010 patients received at least one dose of adalimumab in ULTRA 1, 2, or 3, representing 2,338.0 patient-years of exposure. An overview of treatment-emergent adverse events is shown in **Table 2**. Exposure-adjusted rates of adverse events in all adalimumab-treated patients during the entire treatment period were

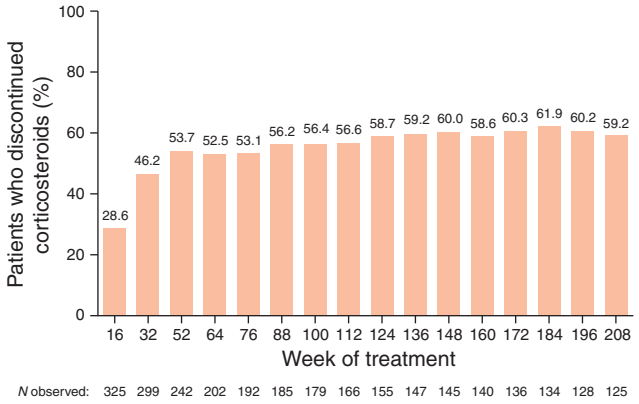


Figure 3. Discontinuation of corticosteroids over time in patients who used corticosteroids at lead-in study baseline from the adalimumab (ADA) Randomized Set (*N*=356). As-observed analysis.

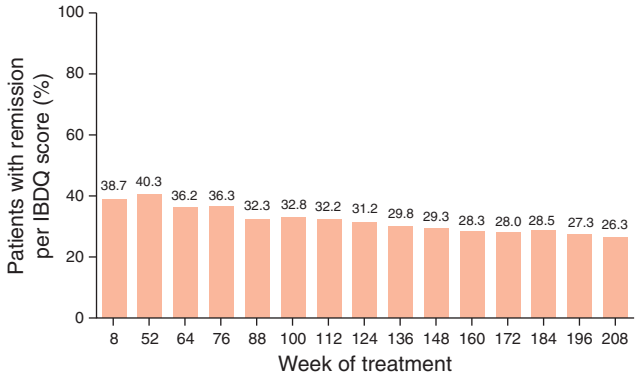


Figure 4. Proportion of patients with remission per IBDQ score (IBDQ ≥170) over time in the ADA Randomized Set (*N*=600). NRI analysis. ADA, adalimumab; IBDQ, Inflammatory Bowel Disease Questionnaire; NRI, nonresponder imputation.

similar to or lower than those observed during the double-blind treatment period for patients receiving placebo or 160/80/40 mg adalimumab. The most frequently reported serious adverse event was worsening or flare of UC. Two serious events of cytomegalovirus colitis were reported. After the double-blind study period, one serious infection of tuberculosis and two treatment-emergent fatal adverse events were reported. A fatal cardiorespiratory arrest occurred in a 35-year-old male who had previous exposure to mercaptopurine and corticosteroids and for 3 days before his death suffered from nonserious flu syndrome, cephalgia, and myalgia. Right ventricular failure occurred in a 47-year-old female with a history of asthma, diabetes mellitus, hypertension, steatosis, and smoking. Three events of B-cell lymphoma occurred during ULTRA 3. All three patients had a history of smoking and either previous or concomitant azathioprine use. Of the patients randomized to adalimumab who were receiving concomitant corticosteroids and/or IMMs at lead-in study baseline, serious infection rates were similar to those observed for patients receiving adalimumab monotherapy (3.7 events/100 patient-years (E/100PY) adalimumab monotherapy, 3.0 E/100PY adalimumab with corticosteroids and without IMM, 3.6 E/100PY adalimumab with IMM and without corticosteroids, and 2.8 E/100PY adalimumab with corticosteroids and IMM).

DISCUSSION

Adalimumab is approved worldwide for the treatment of adult patients with moderately to severely active UC. Previously reported data demonstrating efficacy and safety in this patient population are limited to clinical trial data of up to 1 year (6–9). This report presents a conservative estimate of the long-term efficacy and safety of adalimumab therapy with up to 4 years of follow-up in patients with moderately to severely active disease. At year 4 of treatment, remission and mucosal healing were achieved by 24.7% and 27.7% (NRI), respectively, of patients initially randomized to adalimumab at lead-in study baseline. Approximately 60% of patients who entered ULTRA 3 and had achieved remission and mucosal healing at year 1 maintained these end points at year 4, when assessed using a conservative NRI methodology for missing data. No new safety concerns were observed, and the incidence of adverse events declined or remained stable over time.

The safety profile of up to 4 years of adalimumab therapy was consistent with adverse event rates reported from Crohn's disease clinical trials and with the overall safety profile of adalimumab across multiple indications (11,14). The overall exposure-adjusted rate of adverse events observed during the 4-year follow-up period was lower than that observed during the double-blind period, and rates of infection and malignancy were stable over time. Of the three patients with B-cell lymphomas reported during ULTRA 3, all had previous or concomitant azathioprine use, a known risk factor for lymphoma in patients with IBD (15,16).

Current treatment guidelines for patients with UC identify both control of symptoms and avoidance of colectomy and corticosteroid therapy as important treatment goals. Our results demonstrated the favorable efficacy of long-term adalimumab treatment for patients with UC. Patients responded well to long-term therapy, with stable remission and mucosal healing rates observed over 4 years. Although the ADA Extension Set is a "selected" population in that patients who completed the lead-in studies chose to continue therapy past 1 year, we show that prolonged adalimumab treatment is associated with maintenance of remission and mucosal healing in patients for an additional 3 years of follow-up. Furthermore, ongoing adalimumab treatment in these patients was associated with low rates of hospitalization and colectomy over time in patients with moderately to severely active UC. As an increase in colectomy and hospitalization incidence rates was not observed at later time points, our data support the idea that long-term adalimumab therapy is beneficial for patients in avoiding these events and is not associated with a cumulative safety risk over time. The favorable effect of long-term adalimumab therapy is further demonstrated by the observation that with ongoing therapy for 4 years, ~60% of patients receiving corticosteroids at the first adalimumab dose discontinued corticosteroids and 40% were in corticosteroid-free remission.

Table 1. Hospitalization and colectomy incidence rates for adalimumab-treated patients during double-blind and ULTRA 3 studies

Outcome	Weeks 0–52,[a] ADA 160/80/40 mg, *N*=480, *n*/PY at risk (IR)	ULTRA 3, *N*=592, *n*/PY at risk (IR)
A. Exposure-adjusted patient-based analysis of hospitalizations and colectomy (n/PY (IR))		
All-cause hospitalization	69/387.5 (0.18)	135/1,455.0 (0.09)
UC-related hospitalization	47/398.1 (0.12)	59/1,658.6 (0.04)
Colectomy	15/408.1 (0.04)	16/1,709.3 (0.01)
B. Exposure-adjusted event-based analysis of hospitalizations (n/PY (IR))		
All-cause hospitalization	85/410.2 (0.21)	204/1,711.5 (0.12)
UC-related hospitalization	56/410.2 (0.14)	86/1,711.5 (0.05)

ADA, adalimumab; IR, incidence rate; PY, patient-years; UC, ulcerative colitis; ULTRA 3, *U*lcerative Colitis *L*ong-*T*erm *R*emission and Maintenance with *A*dalimumab 3.
In (A), *n* is the number of patients with event, and in (B) *n* is the number of events.
[a]Week 52 data reported in Feagan *et al.* (10).

Table 2. Treatment-emergent adverse event rates

	DB exposure up to week 52		Exposure as of 15 April 2013
	PBO, *N*=483, PY=152.9, E (E/100 PY)	ADA (160/80/40 mg),[a] *N*=480, PY=179.0,E (E/100 PY)	All ADA,*N*=1,010, PY=2338.0, E (E/100 PY)
Any AE	1,318 (862.2)	1,412 (789.0)	8,057 (344.6)
Serious AE	69 (45.1)	55 (30.7)	414 (17.7)
AE leading to discontinuation	63 (41.2)	39 (21.8)	249 (10.7)
Serious infection	10 (6.5)	4 (2.2)	79 (3.4)
Opportunistic infection (excluding TB)	1 (0.7)	2 (1.1)	6 (0.3)
Active tuberculosis	0	0	1 (<0.1)
Injection site reaction	25 (16.4)	84 (46.9)	246 (10.5)
Any malignancy incl. lymphoma	2 (1.3)	2 (1.1)	23 (1.0)[b]
Lymphoma	0	0	3 (0.1)
Congestive heart failure	0	1 (0.6)	4 (0.2)
Demyelinating disease	0	0	3 (0.1)
Hepatic event	0	0	12 (0.5)
UC worsening/flare	106 (69.4)	82 (45.8)	588 (25.2)
Death[c]	0	0	2 (0.1)

ADA, adalimumab; AE, adverse event; DB, double-blind; E/100PY, events/100 patient-years; incl., including; PBO, placebo; PY, patient-years; TB, tuberculosis; UC, ulcerative colitis.
[a]ADA 80/40/40 mg treatment group not shown.
[b]One malignant event was reported twice in the same patient.
[c]Only treatment-emergent deaths are shown.

The societal costs of ulcerative colitis, which include loss of employment, decreased work productivity, and loss of social function, are considerable. However, very few studies have demonstrated the potential benefit of anti-TNF therapy on such indirect costs. We observed important increases in work productivity that paralleled improved health-related quality of life. Approximately 40% of patients randomized to adalimumab at lead-in study baseline had IBDQ-defined remission after 1 year of maintenance therapy. IBDQ remission rates were sustained with ongoing therapy through the following 3 years. Work time missed remained low over time (between 4% and 7%) after 1 year of adalimumab treatment. Taken together, these results have important implications in assessing the cost effectiveness of adalimumab therapy that will be evaluated in a separate analysis.

Maintaining remission for patients with chronic disease is an important goal for physicians, and identifying factors that may predict loss of remission is of great interest. None of the baseline patient characteristics analyzed in this study was shown to be predictive of loss of remission. Instead, increasing CRP levels and decreasing albumin concentrations during treatment were identified as significant factors associated with a subsequent loss of remission. This finding is not unexpected as both CRP and albumin concentrations indicate the presence of inflammation and may be early indicators of increasing disease activity, that subsequently results in a recurrence of symptoms.

The use of a second anti-TNF agent in patients who have lost response to or become intolerant to treatment with a previous anti-TNF agent has generally been associated with lower efficacy, based on evidence from patients with Crohn's disease (17). This observation may relate to alterations in the underlying mechanism of inflammation of the disease, alterations in pharmacokinetics of the biologic agents being administered, or the presence of functional symptoms or symptoms related to alterations in bowel anatomy and physiology that are not amenable to anti-inflammatory treatment. The adalimumab ULTRA 2 study allowed patients who had failed previous treatment with another anti-TNF agent to be enrolled. Data from this analysis indicated that patients with previous anti-TNF exposure tended to have lower rates of efficacy, although patients exhibiting a clinical response by week 8 have meaningful rates of longer-term efficacy, similar to anti-TNF-naive patients (7,9). During ULTRA 3, patients with previous anti-TNF exposure tended to have lower rates of remission (per PMS and per IBDQ score) and mucosal healing than patients who were anti-TNF naive, although some of these differences diminished at later time points. These data suggest that patients with a history of failure to previous anti-TNF treatment can be considered candidates for treatment with a subsequent anti-TNF agent, although it is possible that it may take longer for these patients to achieve a full response than patients who are anti-TNF naive.

Although the results presented here indicate that long-term adalimumab therapy is beneficial for inducing and maintaining remission in patients with UC, our study has several limitations. First, in the overall study population, the timing of the first adalimumab dose was not the same for each patient because of the protocol design. To overcome this, for the longitudinal efficacy analyses (from lead-in study baseline to week 208), we limited our assessments to a subset of all patients enrolled in ULTRA 1, 2, and 3 (those randomized to adalimumab at lead-in study baseline, 600/1,094) in order to report efficacy for the same treatment duration for all patients. As endoscopy-based outcomes, including mucosal healing and remission per full Mayo score, could not be measured up to week 208 from first adalimumab dose because most patients were not scheduled for endoscopy at this time, data could only be reported up to week 196 of treatment. Second, any long-term clinical study is hampered by loss of patient data over time due to premature discontinuation from the study for any reason (including, but not limited to, lack of efficacy or adverse events). In our analysis, we chose a very conservative estimate of 4 years of adalimumab treatment, imputing nonefficacy for patients who discontinued study participation for any reason. Next, this analysis assessed symptom-based efficacy based on the worse rectal bleeding and stool frequency Mayo subscores of 3 days before the study visit. This "worst rank" method may negatively influence these subscores (and the Physician's Global Assessment subscore, as investigators were also instructed to consider the patient's rectal bleeding subscore and stool frequency subscore when assigning the Physician's Global Assessment subscore) and may underestimate the benefits realized in clinical practice. Last, the data assessments from ULTRA 3 reflect clinical trial patients who completed the 1-year lead-in studies and may not fully reflect real-world patients with moderate-to-severe UC. In addition, the rates of the clinical outcomes observed during ULTRA 3 may be influenced by the open-label design of the study. On the other hand, our study includes many positive features, including prespecified and consistent follow-up conducted under the rigor of a GCP clinical study, and the variety of end points assessed allows characterization of the impact of treatment on different facets of the patient experience.

In conclusion, this comprehensive report, which is based on data from multiple studies, demonstrates that prolonged adalimumab treatment for up to 4 years is well tolerated and is beneficial for patients with moderately to severely active UC in maintaining remission and mucosal healing. The improvement in quality of life, work productivity, and low hospitalization and colectomy rates support the benefit of long-term adalimumab therapy in a patient population who failed conventional therapy and/or previous anti-TNF therapy.

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CONFLICT OF INTEREST

Guarantor of the article: Jean-Frederic Colombel, MD.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Adalimumab was more effective than placebo in inducing and maintaining remission in ulcerative colitis clinical trials.
- ✓ The long-term safety and efficacy of adalimumab, beyond 1 year, for ulcerative colitis has not been reported.

WHAT IS NEW HERE

- ✓ Remission and mucosal healing rates were maintained with up to 4 years of adalimumab therapy.
- ✓ Low colectomy and hospitalization rates and improvement in quality of life were observed with long-term adalimumab treatment.
- ✓ No new safety risks were observed with prolonged adalimumab treatment.

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