Adalimumab in the Treatment of Moderate-to-Severe Ulcerative Colitis: ULTRA 2 Trial Results

Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142:257-265.e13.

Moderately to severely active ulcerative colitis (UC) is typically managed with conventional therapy consisting of corticosteroids and/or immunosuppressive agents such as azathioprine and 6-mercaptopurine. Despite long-term, high-dose therapy, many patients fail to respond to treatment or achieve disease remission. Infliximab (Remicade, Janssen Biotech), an intravenously administered monoclonal antibody directed against tumor necrosis factor alpha (TNF-α), is approved by the US Food and Drug Administration (FDA) for management of UC in patients who have had an inadequate response to conventional therapy. The ACT 1 and ACT 2 trials demonstrated the efficacy and safety of infliximab for this indication; significantly higher proportions of patients receiving infliximab achieved a clinical response compared with patients receiving placebo.[1]

Since infliximab was FDA-approved for the management of UC in 2006, no other TNF-α–targeted agent has been approved except for adalimumab (Humira, Abbott), which received FDA approval in September 2012. Adalimumab is a subcutaneously administered anti–TNF-α monoclonal antibody that is also FDA-approved for the treatment of Crohn's disease. Adalimumab was shown to be active in several small open-label studies and case reports of patients with UC. The results of these studies and case reports led to the ULTRA 1 study, an 8-week, multicenter, randomized, double-blind, placebo-controlled trial that evaluated the ability of adalimumab to induce clinical remission in patients with moderate-to-severe UC.[2]

The rate of clinical remission at Week 8 among 186 patients who were naïve to anti–TNF-α therapy was significantly higher in those treated with adalimumab compared with those receiving placebo (19% vs 9%; *P*=.031). To further investigate the efficacy and safety of adalimumab in patients with moderate-to-severe UC and to gather long-term (1 year) data, the ULTRA 2 study was conducted.[3]

Study Description

ULTRA 2 was an international, multicenter, randomized, double-blind, placebo-controlled, phase III, clinical trial conducted between November 2006 and March 2010. A total of 518 adult patients were enrolled in the study, and 24 patients were excluded from analysis due to site noncompliance. All patients had confirmed moderate-to-severe UC that had been active for at least the 3 months before enrollment despite concurrent treatment with corticosteroids and/or immunomodulators (azathioprine or 6-mercaptopurine). Concurrent treatment with corticosteroids or immunomodulators was not an enrollment requirement for those patients who had failed to respond to or could not tolerate treatment. Concurrent therapy with 5-aminosalicylates was allowed but not required. Active disease was measured as a Mayo score of 6–12 points, with an endoscopy subscore of 2 or greater. Prior treatment with infliximab was permitted if it had been discontinued because of loss of response or drug intolerance for more than 8 weeks. Complete study inclusion and exclusion criteria are listed in Table 1.

Patients were first stratified by prior exposure to anti–TNF-α drugs and then randomly selected in a 1:1 fashion to receive subcutaneous injections of either adalimumab or placebo. Adalimumab was administered at doses of 160 mg and 80 mg at Week 0 and Week 2, respectively, and then 40 mg at Week 4 and every other week thereafter. If concurrent corticosteroid therapy was used, a stable dosage (prednisone ≥20 mg/day for at least 2 weeks or <20 mg/day for at least 40 days) was required before baseline. In patients with a satisfactory clinical response, the corticosteroid could be tapered after Week 8 at the investigator's discretion. Stable dosages for the 3 months prior to baseline also were required in patients receiving immunomodulators (≥1.5 mg/kg/day or the highest tolerated dosage of azathioprine or ≥1 mg/kg/day or the highest tolerated dosage of 6-mercaptopurine, with

Table 1. Inclusion and Exclusion Criteria for Enrollment: The ULTRA 2 Trial

Inclusion criteria
Diagnosis of moderate-to-severe ulcerative colitis confirmed by either a biopsy or flexible sigmoidoscopy
Active disease for 3 or more months prior to study enrollment despite concurrent treatment with corticosteroids, azathioprine, or 6-mercaptopurine*

Exclusion criteria

History of or planned surgical resection
  – Subtotal colectomy with ileorectostomy
  – Colectomy with ileoanal pouch
  – Koch pouch
  – Ileostomy

Prior therapies
  – Adalimumab
  – Intravenous corticosteroids, therapeutic enemas, suppositories, or oral antimicrobial therapy in the 2 weeks prior to study screening
  – Cyclosporine, tacrolimus, mycophenolate mofetil, or intravenous antimicrobial therapy in the 1 month prior to enrollment
  – Any investigational agent in the month (or 5 half-lives) prior to study baseline

Other current diagnosis
  – Fulminant colitis
  – Toxic megacolon
  – Ulcerative proctitis
  – Indeterminate colitis
  – Crohn's disease

Disease history
  – Listeriosis
  – Histoplasmosis
  – Chronic or active hepatitis B infection
  – HIV infection
  – Immunodeficiency syndrome
  – Untreated tuberculosis
  – CNS demyelinating disease
  – Malignancy (other than successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma, or localized carcinoma in situ of the cervix)

Current total parenteral nutrition
Positive *Clostridium difficile* stool assay
History of primary nonresponse to infliximab
Evidence of dysplasia or malignancy in the screening colonoscopy/sigmoidoscopy

*Concurrent therapy was not required for patients who did not respond or were intolerant to treatment.

CNS=central nervous system.

stable dosage for ≥1 month prior to baseline). Concurrent immunomodulator dosages remained constant during study treatment.

Baseline patient characteristics were similar between the adalimumab and placebo treatment arms. Slightly more than half of the study population was male (60%); the mean patient age was 40.4 years, and the mean weight was 76.2 kg. Most patients had a diagnosis of either pancolitis (49%) or disease located in the descending colon (39%). The mean duration of disease prior to study enrollment was 8.3±7.23 years, and the mean Mayo score was 8.9±1.63. Most patients were receiving concomitant therapy at baseline, including corticosteroids (59%), immunomodulators (azathioprine or 6-mercaptopurine; 35%), or both (19%). A total of 40% of the study population had prior exposure to infliximab.

Table 2. Secondary Efficacy Endpoints Met: The ULTRA 2 Trial

Efficacy endpoint	Adalimumab (n=248), %	Placebo (n=246), %	*P*-value
Sustained endpoints (Weeks 8 and 52)			
– Clinical remission	8.5	4.1	.047
– Clinical response	23.8	12.2	<.001
– Mucosal healing	18.5	10.6	.013
Mayo subscores ≤1 at Week 8			
– Physician Global Assessment	46.0	37.4	.058
– Stool frequency	37.9	28.5	.028
– Rectal bleeding	70.2	58.1	.006
Corticosteroid discontinuation*			
– Discontinued before Week 52 and achieved remission at Week 52	13.3	5.7	.035
– Discontinued for ≥90 days before Week 52 and achieved remission at Week 52	13.3	5.7	.035
– Discontinued and achieved sustained remission at Weeks 32 and 52	10.0	1.4	.002
Rate of IBDQ response			
– Week 8	26.2	16.3	.007
– Week 52	58.1	45.5	.006

*Analysis restricted to patients receiving corticosteroid therapy at baseline.

IBDQ=Inflammatory Bowel Disease Questionnaire.

Overall patient assessments were made at each clinic visit from baseline through Week 52 and included physical examination, vital signs, prior and current medications, and general laboratory tests. Adverse events were recorded at each clinic visit. Efficacy evaluations were conducted at Weeks 0, 2, 4, 8, 12, 16, and 20 and then every 6 weeks thereafter through Week 52. Assessments included disease activity (assessed by a full Mayo score at Weeks 0, 8, 32, and 52 and a partial Mayo score without endoscopy at all other weeks) and health-related quality of life, assessed with the Inflammatory Bowel Disease Questionnaire (IBDQ).

Clinical response, clinical remission, and mucosal healing were assessed at Weeks 8, 32, and 52. Clinical response was defined as a decrease of 3 points or more and 30% or more from baseline in the total Mayo score plus either a concomitant decrease in the rectal bleeding subscore of 1 or more points or an absolute rectal bleeding subscore of either 0 or 1. Clinical remission was defined as achieving a total Mayo score of 2 points or less with no individual subscore greater than 1 point. Mucosal healing was defined as an endoscopy subscore of 0 or 1. Responses and remissions were considered sustained if they persisted to Week 52.

The primary efficacy endpoint was the rate of clinical remission at Weeks 8 and 52. Secondary endpoints included the rates of clinical response and mucosal healing at Weeks 8 and 52; the rates of sustained clinical response, clinical remission, and mucosal healing; the rates of corticosteroid-free remission at Weeks 32 and 52; Mayo subscores; and the rate of IBDQ response (defined as an increase of ≥16 points).

The efficacy analysis was performed in the intent-to-treat population, and the safety analysis was performed in all patients who had received at least 1 dose of the study drug. Patients with an inadequate response to treatment by Week 12 were permitted to switch to open-label adalimumab (40 mg every other week). Dosage escalation to 40 mg weekly was allowed in patients treated with open-label adalimumab who continued to demonstrate an inadequate response.

Efficacy Results

Patients treated with adalimumab achieved a significantly higher rate of clinical remission than patients receiving placebo both at Week 8 (17% vs 9%; *P*=.019) and at Week 52 (17% vs 9%; *P*=.004). The benefit in clinical remission associated with adalimumab was observed across several baseline patient characteristics, including sex, median age, race, weight, prior use of anti–TNF-α therapy, corticosteroid or immunomodulator therapy, C-reactive protein level, Mayo score, endoscopy score, duration of disease, and site of disease. A significant improvement in the rate of clinical response also was observed with adalimumab compared with placebo at Week 8 (50% vs 35%; *P*<.001) and Week 52 (30% vs 18%; *P*=.002). More patients in the adalimumab arm achieved mucosal healing than in the placebo arm (Week 8: 41% vs 32%; *P*=.032 and Week 52:

25% vs 15%; *P*=.009). Other secondary efficacy endpoints are listed in Table 2. A benefit was shown with adalimumab for each of these endpoints compared with placebo, with most endpoints achieving statistical significance.

Prior exposure to infliximab appeared to influence response to adalimumab; the rate of clinical remission in infliximab-naïve patients treated with adalimumab was more than double that of patients who had prior exposure (Week 8: 21% vs 9% and Week 52: 22% vs 10%).

At Week 8, the difference in clinical remission rates between the adalimumab and placebo arms was significant among patients who had never been exposed to infliximab (21% vs 11%; *P*=.017). In contrast, the difference in clinical remission rates between the adalimumab and placebo arms at Week 8 in patients who had been exposed to infliximab did not reach statistical significance (9% vs 7%; *P*=.559). At Week 52, differences in clinical remission between the active treatment and placebo arms reached statistical significance in relation to both infliximab-naïve patients (22% vs 12%; *P*=.029) and infliximab-experienced patients (10% vs 3%; *P*=.039).

In both treatment arms, the proportion of patients in whom corticosteroid therapy was successfully tapered markedly increased between Week 8 and Week 20 and then remained steady. The proportion was significantly higher in the adalimumab arm than the placebo arm for most of the weeks of follow-up.

Safety Results

The overall safety profile of adalimumab was similar to that of placebo. The majority of treatment-emergent adverse events were nonserious and mild or moderate in severity. The incidence rate of any adverse event considered to be possibly related to the study drug was 33% in the adalimumab arm and 39% in the placebo arm. The rate of severe adverse events was comparable in the adalimumab and placebo groups (16% vs 14%), as was the rate of serious adverse events (12% in both groups). Slightly more patients in the placebo arm than the adalimumab arm discontinued the study due to an adverse event (13% vs 9%).

Significantly more patients receiving adalimumab than those receiving placebo had an adverse event related to an injection site reaction (12% vs 4%; *P*<.001) or a hematologic adverse event (2% vs 0%; *P*=.003). The most common hematologic event was leukopenia, and all leukopenias occurred in patients who were receiving concomitant immunosuppressant drugs at baseline. Differences in the incidence rates of other reported adverse events—including any infection, malignancy, lupus-like syndrome, and events related to congestive heart failure—between the adalimumab and placebo groups did

not reach statistical significance. No cases of demyelinating disease or lymphoma were reported, and no deaths occurred during the study.

Antibodies to adalimumab in sera collected throughout the study period were detected in 3% of patients in the adalimumab arm. Among patients treated with adalimumab, those who were in remission at Week 52 had higher median serum trough adalimumab concentrations over the course of the study period than those who were not in remission. The median serum trough levels for Week 52 remitters versus nonremitters were 11.4 µg/mL versus 8.49 µg/mL, respectively, at Week 8, 10.6 µg/mL versus 6.95 µg/mL at Week 32, and 10.8 µg/mL versus 6.18 µg/mL at Week 52.

Conclusions

The results of ULTRA 2 demonstrated that adalimumab was more effective than placebo in inducing and maintaining clinical remission in patients with moderate-to-severe UC that was not responsive to conventional therapy. Significant improvements in rates of clinical remission, clinical response, and mucosal healing were observed as early as Week 8 and were sustained through Week 52. Adalimumab was generally well tolerated, with the majority of adverse events being mild or moderate in severity and consistent with its use in prior studies.

The study investigators noted that the magnitude of the absolute difference in remission rates between the adalimumab and placebo arms was less than that previously observed with infliximab in similarly designed trials. However, important differences exist between the infliximab and adalimumab clinical trials in UC. ACT 1 and ACT 2 were conducted approximately 8–10 years before ULTRA 2, when patients who failed conventional therapy had no other approved pharmacologic treatment option. Furthermore, unlike the ULTRA 2 study, the infliximab clinical trials did not allow rescue therapy.[1] Importantly, all of the patients in the infliximab studies were naïve to anti–TNF-α therapy; in contrast, approximately 40% of the patients enrolled in ULTRA 2 had prior exposure to an anti–TNF-α agent.

References

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Commentary

Adalimumab: Another Treatment Option for Moderate-to-Severe UC

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The ULTRA 2 results are relevant because they demonstrate the efficacy of adalimumab (Humira, Abbott) for treatment of moderate-to-severe ulcerative colitis (UC). Adalimumab is an injectable tumor necrosis factor alpha (TNF-α) inhibitor, and, as of September 2012, it is the first subcutaneous anti–TNF-α agent indicated for UC.

The ULTRA 2 findings illustrate that drug levels are important predictors of who may respond to adalimumab; patients who had a clinical response or remission at Weeks 8, 32, or 52 had higher serum trough levels of adalimumab than patients who did not achieve remission of UC. This is consistent with what has been seen with the use of infliximab (Remicade, Janssen Biotech).[1] Several differences exist between the pivotal trials of infliximab in UC and the ULTRA 1 and ULTRA 2 trials for adalimumab, preventing direct comparisons between trials. Rescue medication was not available during the infliximab trials, and an open-label protocol was included in the ULTRA 2 trial that may have shaped results regarding treatment response in the placebo arm of that trial. Slight differences in the way the Mayo score was calculated between the current adalimumab trials and the infliximab trials also prevent direct comparisons.

Not surprisingly, the ULTRA 2 trial results showed that patients who were naïve to infliximab had better outcomes than patients who were previously exposed. In fact, the rate of clinical remission and improvement in clinical response and mucosal healing between patients receiving adalimumab and those receiving placebo did not reach statistical significance among those patients who had previously failed infliximab therapy. However, ULTRA 2 was not powered to show a benefit of adalimumab versus placebo in patients who had lost response during previous therapy with infliximab. Also of importance is that the study did not allow inclusion of patients who were primary nonresponders to infliximab but, rather, those who either initially had responded but lost response or were intolerant to the agent.

Seventy-five percent of patients in the ULTRA 2 trial were receiving concurrent prednisone or azathioprine therapy, indicating that UC in these patients was relatively treatment-refractory. No new adverse events were seen in relation to previous placebo-controlled studies[2,3] of adalimumab, although a treatment-emergent risk of an injection site reaction was recorded in the ULTRA 2 trial.

Given that UC in patients with lower serum adalimumab trough levels was less likely to remit and respond in the ULTRA 2 trial, it might be useful to design trials in which patients are given higher doses of adalimumab either for induction or maintenance therapy. Such studies may help determine the most effective dose of adalimumab for treatment of UC. A study examining outcomes in patients receiving open-label adalimumab for more than 52 weeks may also be valuable to learn how long patients remain in remission in relation to whether they received 40 mg of adalimumab every week or every other week. This type of trial, the aim of which is to demonstrate long-term efficacy, has been applied to adalimumab in Crohn's disease and has shown that an impressive sustained benefit can be achieved in patients whose response lasts up to 2 years.[4] The most important studies going forward, however, will probably be those that look into treatment optimization using higher doses of adalimumab and perhaps dose-ranging studies to identify the target serum adalimumab drug level that maximizes outcomes.

In summary, the results of this study show that adalimumab is effective in inducing remission of UC by Week 8 in relation to induction therapy and by Week 52 in relation to maintenance therapy, specifically in patients who have not previously been exposed to infliximab. The findings confirm that subcutaneous adalimumab is an effective management option for the treatment of patients with moderate-to-severe UC.

References

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