ORIGINAL ARTICLE

Ustekinumab Induction and Maintenance Therapy in Refractory Crohn's Disease

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ABSTRACT

BACKGROUND

In patients with Crohn's disease, the efficacy of ustekinumab, a human monoclonal antibody against interleukin-12 and interleukin-23, is unknown.

METHODS

We evaluated ustekinumab in adults with moderate-to-severe Crohn's disease that was resistant to anti–tumor necrosis factor (TNF) treatment. During induction, 526 patients were randomly assigned to receive intravenous ustekinumab (at a dose of 1, 3, or 6 mg per kilogram of body weight) or placebo at week 0. During the maintenance phase, 145 patients who had a response to ustekinumab at 6 weeks underwent a second randomization to receive subcutaneous injections of ustekinumab (90 mg) or placebo at weeks 8 and 16. The primary end point was a clinical response at 6 weeks.

RESULTS

The proportions of patients who reached the primary end point were 36.6%, 34.1%, and 39.7% for 1, 3, and 6 mg of ustekinumab per kilogram, respectively, as compared with 23.5% for placebo ($P=0.005$ for the comparison with the 6-mg group). The rate of clinical remission with the 6-mg dose did not differ significantly from the rate with placebo at 6 weeks. Maintenance therapy with ustekinumab, as compared with placebo, resulted in significantly increased rates of clinical remission (41.7% vs. 27.4%, $P=0.03$) and response (69.4% vs. 42.5%, $P<0.001$) at 22 weeks. Serious infections occurred in 7 patients (6 receiving ustekinumab) during induction and 11 patients (4 receiving ustekinumab) during maintenance. Basal-cell carcinoma developed in 1 patient receiving ustekinumab.

CONCLUSIONS

Patients with moderate-to-severe Crohn's disease that was resistant to TNF antagonists had an increased rate of response to induction with ustekinumab, as compared with placebo. Patients with an initial response to ustekinumab had significantly increased rates of response and remission with ustekinumab as maintenance therapy. (Funded by Janssen Research and Development; CERTIFI ClinicalTrials.gov number, NCT00771667.)

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Crohn's disease is a chronic inflammatory bowel disease.[1] One third of patients do not have a response to initial treatment with tumor necrosis factor (TNF) antagonists (primary nonresponse)[2-6]; another one third have a transient response[2,4,6] and require dose escalation or a switch to another therapy (secondary nonresponse).[7,8] Patients with primary nonresponse are unlikely to benefit from another TNF antagonist. Patients with secondary nonresponse who switch to a second TNF antagonist are less likely to have a response than are patients who have not received a TNF antagonist.[4,6] These represent difficult clinical problems.

Preclinical studies have implicated interleukin-12 and interleukin-23 in the pathophysiology of Crohn's disease.[9-13] In humans, studies showing the overexpression of the interleukin-12 p35 and interleukin-12/23 p40 subunits, studies showing polymorphisms in genes encoding the interleukin-12/23 p40 subunit and interleukin-23 receptor,[9,14] and genomewide association studies[15] have all linked the pathogenesis of Crohn's disease with the interleukin-12/23 inflammation pathway. Ustekinumab, a fully human $IgG_{1\kappa}$ monoclonal antibody, blocks the biologic activity of interleukin-12 and interleukin-23 through their common p40 subunit by inhibiting receptors for these two cytokines on T cells, natural killer cells, and antigen-presenting cells.[16] Monoclonal antibodies directed against interleukin-12/23 p40 have also shown efficacy in murine colitis models.[17-20]

In a previous phase 2a study, ustekinumab was shown to have efficacy in patients with moderate-to-severe Crohn's disease, particularly among patients previously receiving infliximab.[21] Ustekinumab is currently approved for moderate-to-severe plaque psoriasis.

In this 36-week, randomized, double-blind, placebo-controlled phase 2b trial of ustekinumab (comprising 8-week induction and 28-week maintenance phases), we evaluated patients with moderate-to-severe Crohn's disease that was resistant to TNF antagonists.

Methods

Patients

From October 2008 through December 2010, we evaluated patients at 153 centers in 12 countries (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol was approved by the institutional review board at each study center. The study was conducted and reported in accordance with the protocol and statistical analysis plan, available at NEJM.org. All patients provided written informed consent.

Eligibility criteria included an age of at least 18 years and at least a 3-month history of Crohn's disease with a score of 220 to 450 points on the Crohn's Disease Activity Index (CDAI; scores range from approximately 0 to 600, with higher scores indicating worse disease and a 50-point change indicating the minimal clinically important difference).[22,23] All patients met specified criteria for a primary nonresponse, a secondary nonresponse, or unacceptable side effects after receiving a TNF antagonist at an approved dose (Tables S1A through S1D in the Supplementary Appendix).

Patients were permitted to continue receiving stable doses of drugs for the treatment of Crohn's disease, including oral prednisolone (≤40 mg per day) or budesonide (≤9 mg per day), immunomodulators (e.g., azathioprine, mercaptopurine, or methotrexate), mesalamine, and antibiotics, if they had been taking the drugs for at least the prespecified period before study entry of 3 weeks, 4 weeks, 3 weeks, and 3 weeks, respectively. Patients had not received previous therapies specifically targeting interleukin-12 or interleukin-23. Previous treatment with intravenous glucocorticoids, TNF antagonists, or natalizumab was not permitted for the prespecified washout periods of 3 weeks, 8 weeks, and 12 months, respectively.

Excluded were patients who had undergone bowel resection within 6 months before enrollment and those with the short-bowel syndrome, clinically significant stricture that could require surgery or preclude the use of the CDAI to assess the response to therapy, abscess, active tuberculosis, current infection, or other previous or current opportunistic infection or cancer.

Study Design

During the induction phase (weeks 0 to 8), 526 patients were randomly assigned to receive intravenous ustekinumab (Stelara, Janssen Biotech) in doses of 1, 3, or 6 mg per kilogram of body weight or placebo (Fig. S1 in the Supplementary Appendix). During the maintenance phase (weeks 8 to 36), patients who had a response to ustekinumab as induction therapy and those who did not have a response underwent separate randomization to

receive subcutaneous ustekinumab (90 mg) or placebo at weeks 8 and 16, with efficacy assessed at week 22. Transition from the induction phase to the maintenance phase occurred at the same visit at week 8.

Patients who had a response to placebo induction received subcutaneous placebo at weeks 8 and 16; those who did not have a response to placebo induction received a subcutaneous injection of ustekinumab (270 mg) at 8 weeks, followed by an injection of 90 mg at 16 weeks. Glucocorticoid tapering was mandated in patients with a clinical response, beginning at 8 weeks. Otherwise, concomitant medications remained constant through week 22. Maintenance end points were assessed at 22 weeks. Patients were followed through 36 weeks for the safety analysis.

We selected intravenous administration (rather than subcutaneous injection) of ustekinumab for the induction phase on the basis of improved clinical outcomes in the phase 2a trial.[21] We selected subcutaneous administration for the maintenance phase because a reduced amount of the drug is generally required to maintain efficacy, and subcutaneous administration offers greater convenience for patients.

Adaptive randomization, performed centrally, was used for both phases. In the induction phase, randomization was based on the investigative site and the initial response to a TNF antagonist (i.e., the response to the first TNF antagonist if >1 agent was previously administered). In the maintenance phase, randomization was based on the investigative site and the induction dose; for patients with an initial response to ustekinumab, a third factor was the remission status at 6 weeks.

END POINTS

The primary end point was a clinical response (≥100-point decrease from the baseline CDAI score) at week 6, which was selected on the basis of the phase 2a trial[21] as the optimal timing of separation from placebo for this measure. Patients with a baseline CDAI score of 248 points or less were considered to have a clinical response if the CDAI score was less than 150.[22,23] Major secondary end points were clinical remission (CDAI score, <150 points) at week 6, clinical response at week 4, and clinical remission at week 22 among patients with a response to ustekinumab at week 6. Patients who underwent surgery for Crohn's disease, had protocol-prohibited changes in concomitant medications, or had insufficient data for calculation of CDAI scores were considered not to have had a clinical response or remission at that time point, as were patients who discontinued the study drug because of a lack of efficacy during maintenance.

EFFICACY AND SAFETY EVALUATIONS

Study visits occurred at weeks 0, 4, 6, 8, 12, 16, 20, 22, 28, and 36. At each visit, we evaluated data for CDAI, adverse events, concomitant medications, and levels of serum ustekinumab and C-reactive protein (CRP). At weeks 0, 22, and 36, we evaluated serum samples for antibodies to ustekinumab, using an antigen-bridging enzyme immunoassay.[24] In an endoscopy substudy conducted at selected sites, with separate informed consent obtained from participants, we assessed the degree of mucosal healing at weeks 0, 6, and 22.

STUDY OVERSIGHT

A steering committee comprising academic investigators and representatives of the sponsor (Janssen Research and Development) designed the study, interpreted the data, and contributed to the manuscript. Janssen representatives collected and analyzed the data, and the first author wrote the first draft of the manuscript. All academic authors had full access to the data and vouch for the veracity and completeness of the data and analyses and for the fidelity of this report to the study protocol. All authors made the decision to submit the manuscript for publication. Janssen analyzed and interpreted the pharmacokinetic data. Editorial assistance was provided by employees of the Medical Affairs Publications Group at Janssen Biotech and by another Janssen employee.

STATISTICAL ANALYSIS

We based all sample-size and power calculations on a dose of 6 mg of ustekinumab per kilogram as compared with placebo. We calculated that 496 patients (124 per group) would provide 90% power to detect a 20% difference in clinical response, assuming a response rate of 50% for 6 mg of ustekinumab per kilogram and 30% for placebo.

We analyzed the end points of clinical response at week 6, remission at week 6, and clinical response at week 4 using a two-sided Cochran–Mantel–Haenszel chi-square test at an alpha level of 0.05, with stratification according to the initial response to a TNF antagonist. For patients who

had a response to ustekinumab at week 6, we analyzed the proportion of patients in remission at week 22 using the Cochran–Mantel–Haenszel chi-square test, stratified according to the intravenous induction dose and clinical-remission status at week 6. To control for type I error for the primary end point, a prespecified, fixed-sequence-testing procedure was used, beginning with the highest dose. The study was considered to be positive if there was a significant difference in the clinical response at week 6 between the group receiving 6 mg of ustekinumab per kilogram and the group receiving placebo. Testing for clinical remission at week 22 was performed if the comparison between 6 mg of ustekinumab per kilogram and placebo was positive for the primary end point. Analyses of the other secondary end points were not adjusted for multiple comparisons; statements of statistical significance for these end points are based on nominal P values.

To evaluate the consistency of the treatment effect for the clinical response at week 6, we performed 23 prespecified subgroup analyses (Fig. S3 in the Supplementary Appendix). We calculated odds ratios and 95% confidence intervals for the proportions of patients who had a response at week 6 in the group receiving 6 mg of ustekinumab per kilogram and the group receiving placebo.

We used analysis of covariance to evaluate other secondary continuous end points (i.e., change from baseline in the CDAI score and CRP level). Secondary categorical end points (i.e., 70-point response [a decrease from the baseline CDAI score of ≥70 points], sustained 100-point clinical response [a sustained 100-point decrease in the CDAI score], and sustained remission at week 22 among patients who had a response at week 6) were analyzed with the use of a Cochran–Mantel–Haenszel chi-square test. These analyses were not adjusted for multiple comparisons.

Treatment-failure rules were applied to all efficacy end points: baseline (week 0) values were assigned from the time of treatment failure for continuous end points, and dichotomous end points were considered not to have been achieved. If data were missing, dichotomous end points were considered not to have been achieved; the last observation was carried forward for continuous end points. All efficacy analyses were based on the intention-to-treat principle, with data for all patients who underwent randomization included in analyses of induction end points and data for all patients who had a response to ustekinumab at week 6 included in analyses of maintenance end points. Safety analyses were based on actual treatment received.

RESULTS

PATIENTS

Overall, 526 patients were randomly assigned to a treatment study group in the induction phase (Fig. S2 in the Supplementary Appendix). Demographic and baseline disease characteristics were similar across all groups (Table 1). However, median CDAI scores for the group receiving placebo and the group receiving 1 mg of ustekinumab per kilogram were somewhat lower (302.5 and 306, respectively) than those for the groups receiving higher doses of ustekinumab (3 mg per kilogram, 327; 6 mg per kilogram, 333). In addition, the median CRP value in the placebo group (9.3 mg per liter) was slightly lower than those in the ustekinumab groups (11.8 mg per liter, 13.0 mg per liter, and 12.6 mg per liter for the groups receiving 1 mg, 3 mg, and 6 mg per kilogram, respectively). In approximately 50% of patients, treatment regimens with at least two TNF antagonists had failed.

Among patients receiving intravenous placebo or ustekinumab in the induction phase, 113 and 364 proceeded to the maintenance phase, respectively. Patients who had a response to ustekinumab as induction therapy (145) and those who did not have a response (219) underwent a second randomization separately at week 8 to receive either subcutaneous placebo or 90 mg of ustekinumab as maintenance therapy at weeks 8 and 16. The demographic and baseline disease characteristics of these populations are summarized in Table S2B in the Supplementary Appendix.

Overall, 336 of 526 patients (63.9%) completed the study through week 36 (Fig. S2 in the Supplementary Appendix). Thirty patients (5.7%) discontinued therapy but completed the follow-up for the safety analysis, and 160 (30.4%) discontinued therapy without completing the safety follow-up. Reasons for discontinuation during the two treatment phases are shown in Tables S3A and S3B in the Supplementary Appendix.

INDUCTION PHASE

Primary End Point

The proportion of patients who had a clinical response was significantly greater among patients

Table 1. Baseline Characteristics of the Patients in the Induction Phase.*

Characteristic	Placebo (N=132)	Ustekinumab				Total (N=526)
		1 mg/kg (N=131)	3 mg/kg (N=132)	6 mg/kg (N=131)	Combined (N=394)	
Male sex — no. (%)	64 (48.5)	48 (36.6)	57 (43.2)	48 (36.6)	153 (38.8)	217 (41.3)
Age — yr	39.5±13.1	38.8±12.0	38.2±12.6	39.4±13.2	38.8±12.6	39.0±12.7
Weight — kg	74.4±20.5	72.4±18.7	72.4±19.5	74.1±21.4	73.0±19.9	73.3±20.0
Duration of disease — yr	12.4±9.1	12.2±7.4	12.0±9.1	12.7±8.9	12.3±8.5	12.3±8.6
Crohn's Disease Activity Index score†	312.4±64.2	318.5±62.4	326.8±63.1	338.0±67.3	327.7±64.6	323.9±64.8
Median CRP — mg/liter‡	9.3	11.8	13.0	12.6	12.6	10.8
Crohn's disease drugs at baseline — no. (%)						
≥1 medication	101 (76.5)	91 (69.5)	96 (72.7)	92 (70.2)	279 (70.8)	380 (72.2)
Immunomodulatory drug§	30 (22.7)	33 (25.2)	28 (21.2)	35 (26.7)	96 (24.4)	126 (24.0)
Aminosalicylate drug	24 (18.2)	20 (15.3)	22 (16.7)	25 (19.1)	67 (17.0)	91 (17.3)
Glucocorticoid¶	73 (55.3)	59 (45.0)	71 (53.8)	59 (45.0)	189 (48.0)	262 (49.8)
Failure of previous treatment — no. (%)						
Any immunomodulatory drug§	113 (85.6)	116 (88.5)	119 (90.2)	119 (90.8)	354 (89.8)	467 (88.8)
Contraindication to drug developed	101 (89.4)	105 (90.5)	98 (82.4)	97 (81.5)	300 (84.7)	401 (85.9)
TNF antagonist						
1 drug	71 (53.8)	64 (48.9)	66 (50.0)	66 (50.4)	196 (49.7)	267 (50.8)
2 or 3 drugs	60 (45.5)	67 (51.1)	66 (50.0)	64 (48.9)	197 (50.0)	257 (48.9)
Failure criteria met‖						
Primary nonresponse	44 (33.3)	39 (29.8)	41 (31.1)	36 (27.5)	116 (29.4)	160 (30.4)
Secondary nonresponse	91 (68.9)	96 (73.3)	98 (74.2)	95 (72.5)	289 (73.4)	380 (72.2)
Unacceptable side effects	41 (31.1)	48 (36.6)	40 (30.3)	47 (35.9)	135 (34.3)	176 (33.5)

* Plus–minus values are means ±SD. There were no significant differences among groups except for the mean baseline Crohn's Disease Activity Index (CDAI) score ($P<0.05$ by analysis of variance). TNF denotes tumor necrosis factor.

† This index consists of eight factors, with each factor totaled after adjustment with a weighting factor ranging from 1 to 30. CDAI scores can range from approximately 0 to 600, with higher scores indicating more severe disease activity and a 50-point change indicating the minimal clinically important difference.

‡ C-reactive protein (CRP) values were available for 127 patients in the placebo group; among patients receiving ustekinumab, values were available for 123 patients receiving 1 mg per kilogram, 124 patients receiving 3 mg per kilogram, and 127 patients receiving 6 mg per kilogram.

§ Listed are all patients who received a full course of an immunomodulatory drug. Immunomodulatory drugs included azathioprine, mercaptopurine, and methotrexate.

¶ Glucocorticoid formulations included budesonide.

‖ Patients may have reported more than one reason for treatment failure. Primary nonresponse refers to the absence of an initial response. Secondary nonresponse refers to an initial response that was not maintained.

receiving 6 mg of ustekinumab per kilogram than among those receiving placebo (39.7% vs. 23.5%; absolute difference, 16.2 percentage points; 95% confidence interval [CI], 5.1 to 27.3; $P=0.005$) (Fig. 1A). According to the prespecified analysis plan, the nonsignificant finding for the dose of 3 mg of ustekinumab per kilogram (34.1%, $P=0.06$) prevented the declaration of significance for the 1-mg dose (36.6%, $P=0.02$).

The efficacy of 6 mg of ustekinumab per kilogram was generally consistent across demographic and baseline disease characteristics in the prespecified subgroup analyses (Fig. S3 in the Supplementary Appendix). In subgroups of patients who did not have a primary or secondary response to a TNF antagonist and patients in whom treatment with at least two TNF antagonists had failed, ustekinumab was consistently effective.

Rates of response at week 6 according to serum ustekinumab levels are shown in Table S4

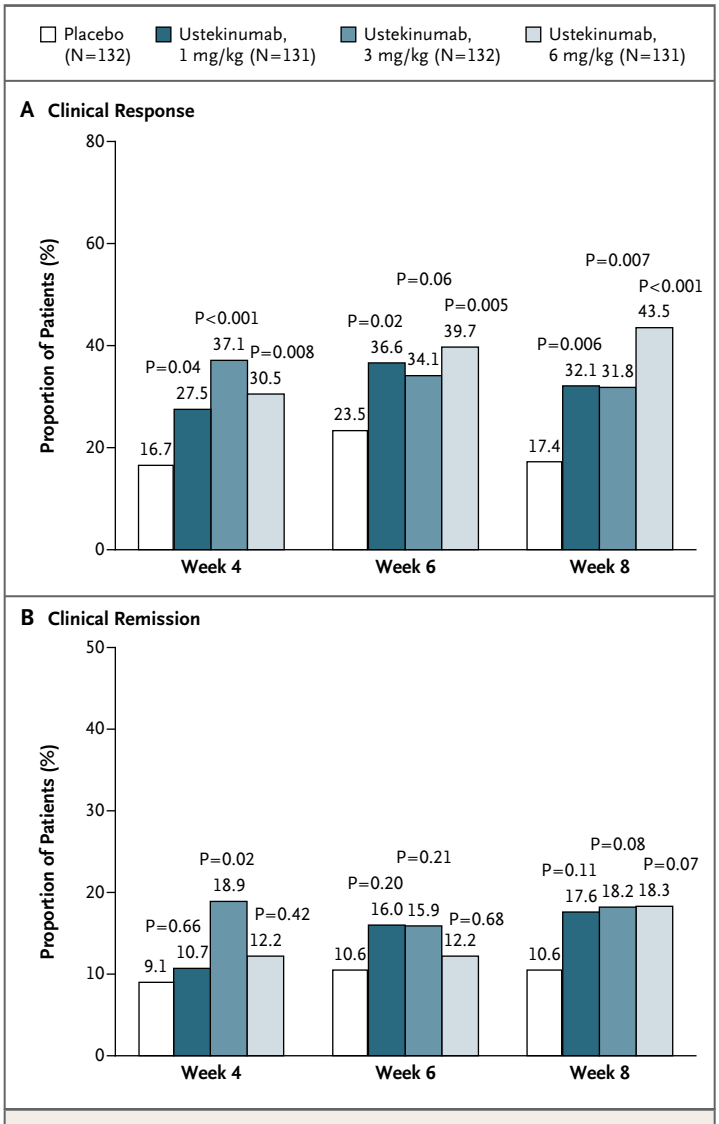

Figure 1. Efficacy of Ustekinumab in the Induction Phase.

Shown are the proportions of patients who had a clinical response (Panel A) or clinical remission (Panel B). Patients who underwent surgery for Crohn's disease or had prohibited changes in the use of concomitant medications were not considered to have had a clinical response or remission, regardless of their score on the Crohn's Disease Activity Index (CDAI). Patients who had insufficient data for calculation of the CDAI score were not considered to have had a clinical response or remission.

in the Supplementary Appendix. The proportion of patients who had a response was modestly higher among patients with a serum ustekinumab level of 1.5 μg per milliliter or greater.

Secondary End Points

Rates of clinical remission at weeks 6 and 8 did not differ significantly between patients receiving ustekinumab and those receiving placebo (Fig. 1B, and Table S5 in the Supplementary Appendix). At all visits, the proportion of patients who had a 70-point response was significantly higher in the group of patients receiving 6 mg of ustekinumab per kilogram than in the placebo group (Table S5 in the Supplementary Appendix). At all visits, mean reductions in the CDAI score were significantly greater in the group receiving 6 mg of ustekinumab per kilogram than in the placebo group (Fig. S4 in the Supplementary Appendix). At all visits, reductions in mean CRP levels were significantly greater among patients receiving 6 mg of ustekinumab per kilogram than among those receiving placebo (Fig. S5 and Table S4 in the Supplementary Appendix). Results for these secondary end points among patients receiving ustekinumab at a dose of 1 mg or 3 mg per kilogram were similar to those among patients receiving 6 mg of ustekinumab per kilogram.

Mucosal healing was observed in 1 of 9 patients (11.1%) who were evaluated in the placebo group and in 8 of 41 patients (19.5%) in the combined ustekinumab group, but the difference was not significant (P=1.00) and comparisons were limited by the small sample (Table S5 in the Supplementary Appendix).

MAINTENANCE PHASE

Patients with Induction Response

The proportion of patients who had a clinical response at week 22 was significantly greater in the ustekinumab group than in the placebo group (69.4% vs. 42.5%; absolute difference, 26.9 percentage points; 95% CI, 11.5 to 42.5; P<0.001) (Fig. 2A, and Table S6 in the Supplementary Appendix). Among patients with a response to ustekinumab in the induction phase, 41.7% of patients receiving 90 mg of ustekinumab in the maintenance phase were in clinical remission at week 22, as compared with 27.4% of patients receiving placebo (absolute difference, 14.3 percentage points; 95% CI, 2.0 to 27.1; P=0.03) (Fig. 2B, and Table S6 in the Supplementary Appendix). The efficacy of 90 mg of ustekinumab was generally consistent among demographic and baseline disease characteristics evaluated in ad hoc subgroup analyses (Fig. S6 in the Supplementary Appendix).

At week 22, the proportion of patients with a sustained clinical response (i.e., a clinical response at every visit during the maintenance

phase) was greater in the ustekinumab group than in the placebo group (55.6% vs. 32.9%, P=0.005) (Fig. S7 in the Supplementary Appendix). Among patients in remission at week 6, remission was maintained at week 22 in 78.6% of patients receiving ustekinumab, as compared with 53.3% of those receiving placebo (P=0.06) (Fig. S8 in the Supplementary Appendix). More patients in the ustekinumab group than in the placebo group were in glucocorticoid-free remission at week 22, regardless of whether glucocorticoids had been used at baseline (30.6% vs. 17.8%, P=0.048) (Fig. S9 in the Supplementary Appendix). Among patients with an induction response, reductions in mean CDAI scores and CRP levels were sustained in those who continued to receive ustekinumab maintenance therapy but were not sustained in those receiving placebo (Fig. S10 and Table S6 in the Supplementary Appendix).

Patients without Induction Response

Among patients who did not have a response to ustekinumab as induction therapy, the rates of clinical response at week 22 were similar in the group receiving maintenance therapy with 90 mg of ustekinumab and the placebo group (20.2% and 18.2%, respectively; P=0.71). Of 85 patients who did not have a response to placebo induction and who crossed over to receive a subcutaneous injection of 270 mg of ustekinumab at week 8, 35.3% had a clinical response at week 16.

SAFETY

Induction Phase

The duration of follow-up (approximately 8 weeks) and proportions of patients with at least one adverse event were similar among the four study groups in the induction phase. Overall rates of infection were also similar. Serious infections were reported in five patients receiving 6 mg of ustekinumab per kilogram (*Clostridium difficile* infection, viral gastroenteritis, urinary tract infection, anal abscess, and vaginal abscess), in one patient receiving 1 mg of ustekinumab per kilogram (staphylococcal infection in a central catheter), and in one patient receiving placebo (anal abscess). Serious adverse events were uncommon through week 8, and except for events of Crohn's disease, no serious adverse event was reported in more than one patient receiving ustekinumab. Infusion reactions were uncommon, were not serious, and occurred at similar rates in the combined ustekinumab group and the placebo group (4.3% and 4.5%, respectively) (Table 2, and Table S8 in the Supplementary Appendix).

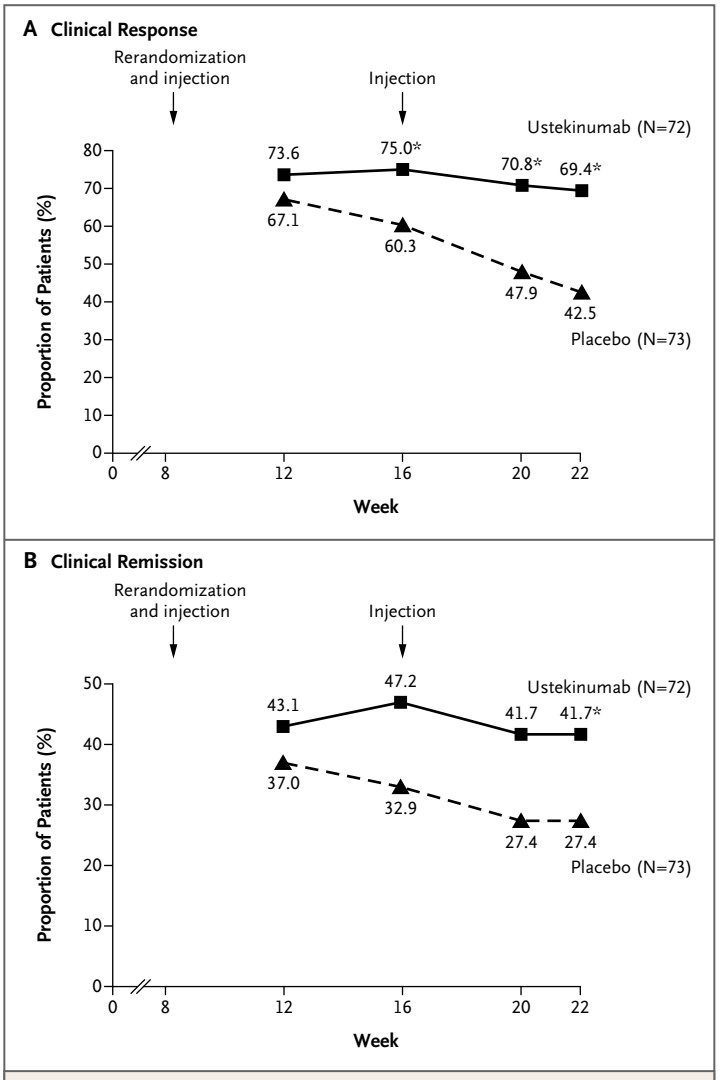

Figure 2. Efficacy of Ustekinumab in the Maintenance Phase.

Shown are the proportions of patients with a response to induction therapy who had a clinical response (Panel A) or clinical remission (Panel B) from week 12 to week 22 during maintenance therapy. Patients who discontinued the assigned study agent because of a lack of efficacy, underwent surgery for Crohn's disease, or had prohibited changes in the use of concomitant medications after week 8 were not considered to have had a clinical response or remission, regardless of their CDAI score. Patients who had insufficient data for calculation of the CDAI score were not considered to have had a clinical response or remission. Asterisks indicate P<0.05 for the comparison with placebo.

Maintenance Phase

Among patients with a response to ustekinumab as induction therapy, rates of adverse events and

Table 2. Adverse Events during the Induction Phase (Week 0 to Week 8).

Adverse Event	Placebo (N=132)	Ustekinumab			
		1 mg/kg (N=130)	3 mg/kg (N=133)	6 mg/kg (N=131)	Combined (N=394)
		number of patients (percent)			
Any adverse event	94 (71.2)	89 (68.5)	88 (66.2)	80 (61.1)	257 (65.2)
Common adverse events*					
Nasopharyngitis	6 (4.5)	7 (5.4)	7 (5.3)	8 (6.1)	22 (5.6)
Abdominal pain	9 (6.8)	5 (3.8)	8 (6.0)	7 (5.3)	20 (5.1)
Nausea	11 (8.3)	9 (6.9)	1 (0.8)	8 (6.1)	18 (4.6)
Crohn's disease event	13 (9.8)	7 (5.4)	5 (3.8)	5 (3.8)	17 (4.3)
Arthralgia	5 (3.8)	8 (6.2)	8 (6.0)	6 (4.6)	22 (5.6)
Headache	8 (6.1)	8 (6.2)	9 (6.8)	13 (9.9)	30 (7.6)
Infection					
Any	32 (24.2)	33 (25.4)	30 (22.6)	29 (22.1)	92 (23.4)
Serious	1 (0.8)	1 (0.8)	0	5 (3.8)	6 (1.5)
Serious adverse event†	11 (8.3)	6 (4.6)	8 (6.0)	9 (6.9)	23 (5.8)
Infusion reaction	6 (4.5)	5 (3.8)	5 (3.8)	7 (5.3)	17 (4.3)

* Common adverse events were defined as events occurring in at least 5% of patients in any study group.
† Serious adverse events that were reported during the induction phase are summarized in Table S8 in the Supplementary Appendix.

serious adverse events and the duration of follow-up (approximately 25 weeks) were similar in the ustekinumab group and the placebo group (Table 3, and Tables S7 and S9 in the Supplementary Appendix). There were no deaths, major adverse cardiovascular events, tuberculosis, or other serious opportunistic infections. One basal-cell carcinoma was reported in a patient who received 1 mg of ustekinumab per kilogram, followed by 90 mg at weeks 8 and 16.

Of 427 ustekinumab-treated patients with appropriate samples for analysis, 3 (0.7%) had positive results for antibodies to ustekinumab through week 36. Because most patients (81%) had undetectable serum ustekinumab levels at week 36, circulating levels of ustekinumab did not have a marked effect on the incidence of antibodies.

DISCUSSION

A sizable proportion of patients with moderate-to-severe Crohn's disease do not have a response to treatment with TNF antagonists, and among patients who do have a response, it is often not sustained or side effects require discontinuation of therapy.[2-6] For such patients, the benefit of additional anti-TNF agents may be limited.[4,6] In our study, after induction therapy, patients with moderate-to-severe Crohn's disease in whom treatment with one or more TNF antagonists had failed were more likely to have a clinical response to 6 mg of ustekinumab per kilogram than to placebo. Induction with ustekinumab did not significantly increase the remission rate. For all other secondary outcomes, the efficacy of 6 mg of ustekinumab per kilogram was superior to that of placebo. Lower induction doses of ustekinumab generally had a numerical benefit, as compared with placebo, although the differences were not significant.

Among patients with a response to ustekinumab in the induction phase, the rate of clinical response at week 22 was greater among those who received maintenance therapy with 90 mg of ustekinumab than among those receiving placebo. Patients who did not have a response to ustekinumab in the induction phase did not benefit from additional ustekinumab therapy in the maintenance phase.

Our inability to identify significant differ-

Table 3. Adverse Events during the Maintenance Phase (Week 8 to Week 36).

Adverse Event	Patients with Response to Ustekinumab at Week 6		Patients with No Response to Ustekinumab at Week 6		All Patients	
	Placebo (N=73)	Ustekinumab (N=72)	Placebo (N=110)	Ustekinumab (N=109)	Placebo (N=183)	Ustekinumab (N=181)
	number of patients (percent)					
Any adverse event	62 (84.9)	54 (75.0)	89 (80.9)	86 (78.9)	151 (82.5)	140 (77.3)
Common adverse events*						
Crohn's disease event	22 (30.1)	11 (15.3)	25 (22.7)	17 (15.6)	47 (25.7)	28 (15.5)
Abdominal pain	8 (11.0)	3 (4.2)	11 (10.0)	10 (9.2)	19 (10.4)	13 (7.2)
Nausea	5 (6.8)	7 (9.7)	8 (7.3)	4 (3.7)	13 (7.1)	11 (6.1)
Nasopharyngitis	6 (8.2)	5 (6.9)	0	6 (5.5)	6 (3.3)	11 (6.1)
Arthralgia	3 (4.1)	5 (6.9)	12 (10.9)	5 (4.6)	15 (8.2)	10 (5.5)
Cough	4 (5.5)	1 (1.4)	3 (2.7)	4 (3.7)	7 (3.8)	5 (2.8)
Infection						
Any	29 (39.7)	23 (31.9)	44 (40.0)	48 (44.0)	73 (39.9)	71 (39.2)
Serious	3 (4.1)	2 (2.8)	4 (3.6)	2 (1.8)	7 (3.8)	4 (2.2)
Serious adverse event†						
Any	12 (16.4)	9 (12.5)	21 (19.1)	22 (20.2)	33 (18.0)	31 (17.1)
Malignant neoplasm	0	1 (1.4)‡	0	0	0	1 (0.6)

* Common adverse events were defined as events occurring in at least 10% of patients in any study group.
† Serious adverse events that were reported during the maintenance phase are summarized in Table S9 in the Supplementary Appendix.
‡ One patient reported having a fully resected basal-cell carcinoma of the skin.

ences in the induction of remission warrants further discussion. The patients in our study had relatively high baseline CDAI scores, a long disease duration, and a history of failed therapies. Among patients receiving 6 mg of ustekinumab per kilogram, the median baseline CDAI score was 333, indicating that for most of these patients to be classified as having a remission, a decrease of more than 180 CDAI points was required.

With respect to safety, a basal-cell carcinoma was reported in one patient receiving ustekinumab. No deaths, serious opportunistic infections, tuberculosis, or major adverse cardiovascular events were reported, but large studies of longer duration are needed to assess uncommon adverse events. These results are somewhat limited by the relatively small sample and short duration of the maintenance phase. Additional efficacy data are needed for the assessment of ustekinumab as maintenance therapy in patients with Crohn's disease. Whether our findings in patients with disease that was resistant to TNF antagonists can be extrapolated to the broader Crohn's disease population is unclear.

In conclusion, patients with moderate-to-severe Crohn's disease that was resistant to TNF antagonists were more likely to have a response to ustekinumab as induction therapy than to placebo, but they were not more likely to have a remission. Patients who had a response to ustekinumab as induction therapy had significantly increased rates of response and remission when ustekinumab was administered as maintenance therapy.

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