ORIGINAL ARTICLE

Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease

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ABSTRACT

BACKGROUND

Ustekinumab, a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23, was evaluated as an intravenous induction therapy in two populations with moderately to severely active Crohn's disease. Ustekinumab was also evaluated as subcutaneous maintenance therapy.

METHODS

We randomly assigned patients to receive a single intravenous dose of ustekinumab (either 130 mg or approximately 6 mg per kilogram of body weight) or placebo in two induction trials. The UNITI-1 trial included 741 patients who met the criteria for primary or secondary nonresponse to tumor necrosis factor (TNF) antagonists or had unacceptable side effects. The UNITI-2 trial included 628 patients in whom conventional therapy failed or unacceptable side effects occurred. Patients who completed these induction trials then participated in IM-UNITI, in which the 397 patients who had a response to ustekinumab were randomly assigned to receive subcutaneous maintenance injections of 90 mg of ustekinumab (either every 8 weeks or every 12 weeks) or placebo. The primary end point for the induction trials was a clinical response at week 6 (defined as a decrease from baseline in the Crohn's Disease Activity Index [CDAI] score of ≥100 points or a CDAI score <150). The primary end point for the maintenance trial was remission at week 44 (CDAI score <150).

RESULTS

The rates of response at week 6 among patients receiving intravenous ustekinumab at a dose of either 130 mg or approximately 6 mg per kilogram were significantly higher than the rates among patients receiving placebo (in UNITI-1, 34.3%, 33.7%, and 21.5%, respectively, with $P \leq 0.003$ for both comparisons with placebo; in UNITI-2, 51.7%, 55.5%, and 28.7%, respectively, with $P < 0.001$ for both doses). In the groups receiving maintenance doses of ustekinumab every 8 weeks or every 12 weeks, 53.1% and 48.8%, respectively, were in remission at week 44, as compared with 35.9% of those receiving placebo ($P = 0.005$ and $P = 0.04$, respectively). Within each trial, adverse-event rates were similar among treatment groups.

CONCLUSIONS

Among patients with moderately to severely active Crohn's disease, those receiving intravenous ustekinumab had a significantly higher rate of response than did those receiving placebo. Subcutaneous ustekinumab maintained remission in patients who had a clinical response to induction therapy. (Funded by Janssen Research and Development; ClinicalTrials.gov numbers, NCT01369329, NCT01369342, and NCT01369355.)

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Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract that is treated with glucocorticoids, immunosuppressants, tumor necrosis factor (TNF) antagonists, or integrin inhibitors.[1-3] The drawbacks of these agents include an increased risk of infection[4-7] and cancer[8] and limited efficacy.[9] Ustekinumab is a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23 that has been approved for use in the treatment of psoriasis and psoriatic arthritis.[10] In previous trials involving patients with psoriasis in which ustekinumab was administered subcutaneously for up to 5 years, the drug was not associated with an increased risk of serious adverse events.[11,12]

In a previous phase 2b trial, intravenous ustekinumab induction therapy in patients with Crohn's disease that was refractory to treatment with TNF antagonists showed a significant benefit in terms of clinical response but not remission, and subcutaneously administered maintenance doses of ustekinumab were efficacious during a period of 22 weeks.[2] This phase 3 development program for the treatment of Crohn's disease with ustekinumab consisted of two 8-week induction trials (UNITI-1 and UNITI-2) and one 44-week maintenance trial (IM-UNITI), representing 52 weeks of therapy.

Methods

Study Design and Oversight

UNITI-1 and UNITI-2 were conducted at 178 sites in 23 countries and 175 sites in 23 countries, respectively, and IM-UNITI was conducted at 260 sites in 27 countries. All were double-blind, placebo-controlled trials performed from July 2011 through June 2015. The institutional review board at each participating institution approved the protocols (which are available with the full text of this article at NEJM.org), and all the patients provided written informed consent. All three trials were conducted in accordance with the protocols and statistical analysis plans (available with the protocols).

A steering committee composed of academic investigators and Janssen scientists designed the trials. The steering committee and Janssen personnel analyzed and interpreted data and contributed to the manuscript. The first two authors wrote the initial draft of the manuscript. All the authors approved the decision to submit the manuscript for publication and vouch for the veracity and completeness of the data and analyses and the fidelity of the trials to the protocols. Editorial support was provided by Janssen.

Patients

Patients 18 years of age or older who had had Crohn's disease for at least 3 months and had a score on the Crohn's Disease Activity Index (CDAI) of 220 to 450 out of a possible range of 0 to 600 (with higher scores indicating more severe disease)[13,14] were enrolled in the induction trials. In UNITI-1, patients were required to have received one or more TNF antagonists at approved doses and to have met the criteria for primary nonresponse (the absence of a response) or secondary nonresponse (a response that was not maintained) or to have had unacceptable side effects (for details, see the Supplementary Appendix, available at NEJM.org). In UNITI-2, patients were required to have had treatment failure or unacceptable side effects when treated with immunosuppressants (i.e., azathioprine, mercaptopurine, or methotrexate) or glucocorticoids. Patients in UNITI-2 could have previously received one or more TNF antagonists provided they had not had unacceptable side effects and had not met the criteria for primary or secondary nonresponse to treatment. They were also required to have objective evidence of active Crohn's disease, which was defined as either a serum level of C-reactive protein (CRP) of more than 3.0 mg per liter, a fecal calprotectin level of more than 250 mg per kilogram of body weight, or endoscopic ulcerations in the ileum, the colon, or both. Patients who completed UNITI-1 or UNITI-2 could enroll in the IM-UNITI maintenance trial. The primary (randomized) population in IM-UNITI consisted of patients who had a clinical response to ustekinumab induction therapy.

Stable doses of immunosuppressants, mesalamine, antibiotics, or oral glucocorticoids (≤40 mg of prednisone per day or ≤9 mg of budesonide per day) or a combination thereof were permitted. Patients were required to have no history of treatment with interleukin-12 or interleukin-23 antagonists. Previous treatment with intravenous glucocorticoids, TNF antagonists, or natalizumab was not permitted for specified washout periods (for details, see the UNITI-1, UNITI-2, and IM-UNITI protocols). Patients with gastrointestinal conditions that might require surgery or

might preclude the use of the CDAI to assess the response to treatment and those with infections (including active tuberculosis) or a history of cancer were excluded.

Therapies for Crohn's disease were maintained at stable doses from baseline of induction therapy through week 44 of maintenance therapy. In patients who had a response to treatment after induction and who were receiving glucocorticoids, tapering was initiated at week 0 of IM-UNITI (for details, see the Supplementary Appendix).

RANDOMIZATION

At week 0, patients in both induction trials were randomly assigned, in a 1:1:1 ratio, to receive a single intravenous infusion of 130 mg of ustekinumab, a weight-range–based dose that approximated 6 mg of ustekinumab per kilogram of body weight, or placebo. (The administration of 6 mg of ustekinumab per kilogram meant that patients weighing ≤55 kg received 260 mg, those weighing >55 kg and ≤85 kg received 390 mg, and those weighing >85 kg received 520 mg.)

In the maintenance trial, patients who had a response to ustekinumab induction therapy at week 8 were randomly assigned, in a 1:1:1 ratio, to receive subcutaneous injections of 90 mg of ustekinumab every 8 weeks, 90 mg of ustekinumab every 12 weeks, or placebo through week 40. Patients in the maintenance trial who met loss-of-response criteria (defined as a CDAI score ≥220 and an increase from their baseline CDAI score of ≥100 points) between weeks 8 and 32 underwent dose adjustment from receiving placebo to receiving ustekinumab every 8 weeks or from receiving ustekinumab every 12 weeks to receiving ustekinumab every 8 weeks; patients receiving ustekinumab every 8 weeks continued to receive that regimen after loss of response. Other patient populations entered IM-UNITI but did not undergo randomization (for details, see the IM-UNITI protocol).

Randomization was performed centrally with the use of permuted blocks in all trials. Trial region and CDAI score (≤300 or >300) were used as the stratification variables in both induction trials, and the initial response to TNF antagonist therapy (yes or no) was used in UNITI-1; the dose of ustekinumab during the induction trial and remission at week 0 of the maintenance trial were the stratification variables in IM-UNITI.

END POINTS

In both induction trials, the primary end point was clinical response at week 6, which was defined as a decrease from baseline in CDAI score of at least 100 points or a total CDAI score less than 150.[13,14] Major secondary end points were clinical remission at week 8 (CDAI score <150), clinical response at week 8, and a decrease from baseline in CDAI score of at least 70 points at weeks 3 and 6. Results are presented here for the following other prespecified secondary end points: clinical response at week 3; clinical remission at weeks 3 and 6; decrease from baseline in CDAI score of at least 70 points at week 8; change in CDAI score, change in CRP level, and normalization of CRP level (<3.0 mg per liter) at weeks 3, 6, and 8; and change in fecal calprotectin level and normalization of fecal calprotectin level (≤250 or ≤100 mg per kilogram) at week 6.

In the maintenance trial, the primary end point was clinical remission at week 44 (CDAI score <150). Major secondary end points at week 44 were clinical response (decrease in CDAI score of ≥100 points from week 0 of induction or clinical remission), maintenance of remission among patients in remission at week 0 of the maintenance trial, glucocorticoid-free remission, and remission in patients who met the criteria for primary or secondary nonresponse or who had unacceptable side effects when treated with a TNF antagonist (UNITI-1 population). Results are presented here for the following other prespecified secondary end points: clinical remission at week 44 in the subgroup of patients in whom conventional therapy failed (UNITI-2 population), change in CDAI score through week 44, change in CRP level through week 44, and change in fecal calprotectin level at week 44.

For the induction and maintenance trials, patients with treatment failure (i.e., those who had a surgery related to Crohn's disease, had prohibited changes in concomitant medications for Crohn's disease, or had begun receiving a prohibited concomitant medication) or who had data that were insufficient to calculate CDAI scores (i.e., data on fewer than four of the eight CDAI components) were not considered to have a response or to be in remission. Patients who had a loss of response or discontinued the trial agent owing to lack of therapeutic effect or an adverse event of worsening of disease were also

considered to have treatment failure in the maintenance trial.

EVALUATION OF EFFICACY AND SAFETY

At weeks 0, 3, 6, and 8 during induction and at 4-week intervals during maintenance, CDAI scores, adverse events, concomitant medications, and CRP levels were evaluated. Fecal calprotectin levels were evaluated at weeks 0 and 6 during induction and at weeks 8, 24, and 44 during maintenance. Quality-of-life measures (i.e., the Inflammatory Bowel Disease Questionnaire and the Short-Form 36 Health Questionnaire), health economic outcomes, and outcomes for endoscopy (performed in a subtrial) were examined but are not reported here. The statistical analysis section details the prespecified analyses that are presented in this report; a comprehensive list of all prespecified analyses can be found in the statistical analysis plans for each trial (see the protocols).

In UNITI-1 and UNITI-2, follow-up for patient safety occurred either through week 8 in patients who entered the maintenance trial or 20 weeks after the induction dose in patients who did not enter the maintenance trial. In IM-UNITI, patients were followed through week 44. To maintain blinding in IM-UNITI, all the patients received either ustekinumab or placebo every 4 weeks from week 8 through week 40.

PHARMACOKINETICS AND IMMUNOGENICITY

Serum ustekinumab levels were evaluated at weeks 0, 3, 6, and 8 during induction and every 4 weeks during maintenance. Antidrug antibodies were evaluated by means of a drug-tolerant electrochemiluminescence assay at weeks 0 and 6 during induction and at weeks 12, 24, 36, and 44 during maintenance.

STATISTICAL ANALYSIS

For both induction trials and for the maintenance trial, we compared primary and major secondary end points for each ustekinumab group and the placebo group using a two-sided, Cochran–Mantel–Haenszel chi-square test with adjustment for the stratification variables. In the maintenance trial, induction trial (UNITI-1 or UNITI-2) was added as a stratification variable. The type I error rate in each of the three trials was controlled at an alpha level of 0.05 for the primary and major secondary end points with the use of a hierarchical testing procedure (for details, see the Supplementary Appendix).

The analyses of secondary end points (i.e., all end points except for the primary and major secondary end points) were to proceed regardless of the outcomes for the primary and major secondary end points. These secondary end points were not adjusted for multiplicity. Statements of significance for these secondary end points are based on nominal P values and should be interpreted cautiously.

Continuous end points were analyzed by means of analysis of covariance on van der Waerden normal scores. Dichotomous end points were analyzed by means of a Cochran–Mantel–Haenszel chi-square test. Rules for treatment failure and missing data were also applied for secondary end points. For continuous end points, baseline values (from week 0 of induction) were assigned from the time of treatment failure, and the last available observation was carried forward for missing data. For dichotomous end points, the rules for treatment failure and missing data that were specified for the primary end point were applied.

To evaluate the consistency of the treatment effect, we conducted prespecified subgroup analyses. The results of the subgroup analyses of the primary end point for each trial and for the first major secondary end point of remission at week 8 of UNITI-1 and UNITI-2 can be found in Figures S1 and S2 in the Supplementary Appendix.

In the induction trials, calculations for sample size and power were based on comparisons of the group receiving 6 mg of ustekinumab per kilogram and the placebo group. We calculated that 675 patients (225 patients per treatment) in UNITI-1 and 600 patients (200 patients per treatment) in UNITI-2 would provide a power of more than 90% at a two-sided significance level of 0.05 to detect the following: a between-group difference of 15 percentage points in UNITI-1, assuming a response rate of 25% for placebo and 40% for 6 mg of ustekinumab per kilogram at week 6 (on the basis of data from the phase 2b trial[2]), and a between-group difference of 17 percentage points in UNITI-2, assuming a response rate of 33% for placebo and 50% for 6 mg of ustekinumab per kilogram at week 6 (on the basis of data from the phase 2a trial[15]). For the main-

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	UNITI-1			UNITI-2			IM-UNITI		
	Placebo	Ustekinumab		Placebo	Ustekinumab		Placebo	Ustekinumab	
	(N=247)	130 mg (N=245)	6 mg/kg† (N=249)	(N=210)	130 mg (N=209)	6 mg/kg† (N=209)	(N=133)	90 mg/12 wk (N=132)	90 mg/8 wk (N=132)
Male sex — no. (%)	118 (47.8)	98 (40.0)	101 (40.6)	99 (47.1)	104 (49.8)	90 (43.1)	59 (44.4)	56 (42.4)	58 (43.9)
Age — yr	37.3±11.8	37.4±11.8	37.3±12.5	40.2±13.1	39.1±13.8	38.4±13.1	39.5±12.7	37.9±13.2	38.6±13.7
Weight — kg	71.5±17.7	68.4±17.4	69.5±19.5	74.0±19.9	74.4±21.3	71.9±18.8	72.3±17.3	70.6±16.9	70.0±19.6
Duration of disease — yr‡	12.1±8.4	11.8±8.3	12.7±9.2	10.4±9.8	8.7±8.5	8.7±8.4	10.6±9.5	10.3±8.7	9.5±8.7
CDAI§	319.0±59.7	321.0±64.7	327.6±62.0	302.2±61.7	304.1±57.0	302.2±58.9	319.1±60.8	320.4±66.7	313.1±58.0
Median C-reactive protein — mg/liter	8.5	10.4	9.9	8.5	7.4	7.8	9.6	8.8	9.1
Median fecal calprotectin — mg/kg	515.8	399.9	530.2	415.5	519.6	523.2	587.4	536.5	567.5
GI areas involved — no. (%)									
Total	246	245	249	210	208	209	133	132	132
Ileum only	28 (11.4)	38 (15.5)	37 (14.9)	44 (21.0)	53 (25.5)	49 (23.4)	19 (14.3)	26 (19.7)	19 (14.4)
Colon only	48 (19.5)	36 (14.7)	40 (16.1)	37 (17.6)	44 (21.2)	43 (20.6)	28 (21.1)	23 (17.4)	29 (22.0)
Ileum and colon	166 (67.5)	171 (69.8)	171 (68.7)	129 (61.4)	109 (52.4)	117 (56.0)	86 (64.7)	83 (62.9)	84 (63.6)
Proximal GI tract	45 (18.3)	57 (23.3)	54 (21.7)	32 (15.2)	34 (16.3)	29 (13.9)	28 (21.1)	18 (13.6)	19 (14.4)
Perianal GI tract	107 (43.5)	107 (43.7)	107 (43.0)	57 (27.1)	60 (28.8)	61 (29.2)	43 (32.3)	39 (29.5)	46 (34.8)
Medications for Crohn's disease taken at baseline — no. (%)									
One or more medications	185 (74.9)	178 (72.7)	174 (69.9)	158 (75.2)	161 (77.0)	170 (81.3)	101 (75.9)	106 (80.3)	108 (81.8)
Immunosuppressant¶	81 (32.8)	74 (30.2)	78 (31.3)	73 (34.8)	74 (35.4)	72 (34.4)	47 (35.3)	52 (39.4)	44 (33.3)
Aminosalicylate	54 (21.9)	50 (20.4)	50 (20.1)	89 (42.4)	89 (42.6)	93 (44.5)	46 (34.6)	47 (35.6)	49 (37.1)
Glucocorticoid‖	111 (44.9)	121 (49.4)	108 (43.4)	75 (35.7)	80 (38.3)	92 (44.0)	59 (44.4)	58 (43.9)	64 (48.5)
History of disease refractory to treatment with TNF antagonist — no. (%)	246 (99.6)	243 (99.2)	246 (98.8)	NA	NA	NA	61 (45.9)	59 (44.7)	58 (43.9)
No history of TNF antagonist treatment — no. (%)	NA	NA	NA	131 (62.4)	152 (72.7)	144 (68.9)	52 (39.1)	53 (40.2)	52 (39.4)
History of TNF antagonist treatment failure — no. (%)**									
Patients who received 1 drug	112 (45.3)	124 (50.6)	120 (48.2)	NA	NA	NA	NA	NA	NA
Patients who received 2 or 3 drugs	134 (54.3)	119 (48.6)	126 (50.6)	NA	NA	NA	NA	NA	NA

Primary nonresponse	74 (30.0)	70 (28.6)	72 (28.9)	NA	NA	NA	NA	NA	NA
Secondary nonresponse	170 (68.8)	173 (70.6)	171 (68.7)	NA	NA	NA	NA	NA	NA
Unacceptable side effects	87 (35.2)	78 (31.8)	105 (42.2)	NA	NA	NA	NA	NA	NA

* Plus–minus values are means ±SD. There were no significant differences among the treatment groups in the three trials. GI denotes gastrointestinal, NA not applicable, and TNF tumor necrosis factor.

† Weight-range–based doses of ustekinumab approximate 6 mg per kilogram of body weight (with 260 mg prescribed for patients weighing ≤55 kg, 390 mg for patients weighing >55 kg and ≤85 kg, and 520 mg prescribed for patients weighing >85 kg).

‡ In UNITI-1, data on duration of disease were available for 246 patients in the placebo group.

§ The Crohn's Disease Activity Index (CDAI) consists of eight factors, with each factor totaled after adjustment with a weighting factor ranging from 1 to 30. CDAI scores range from approximately 0 to 600, with higher scores indicating more severe disease activity.

¶ The immunosuppressants included azathioprine, mercaptopurine, and methotrexate.

‖ The glucocorticoids 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.

tenance trial, calculations of sample size and power were performed with assumed remission rates at week 44 of 15% for the placebo group and 35% for the group receiving 90 mg of ustekinumab every 8 weeks, with 100 patients per treatment group yielding 90% power, and with a two-sided significance level of 0.05.

Efficacy analyses were conducted in accordance with the intention-to-treat principle. Safety analyses were performed for all patients who received at least one dose of a trial agent, and pharmacokinetics analyses were performed for those receiving ustekinumab.

RESULTS

PATIENTS

In UNITI-1 and UNITI-2, 741 and 628 patients, respectively, underwent randomization. The percentages of patients who discontinued the trial prematurely were low in both trials (Fig. S3 in the Supplementary Appendix). Overall, 1281 patients were enrolled in IM-UNITI, with 397 patients in the primary population and 884 patients in the population that did not undergo randomization. Few patients who underwent randomization discontinued the trial agent before week 44 (Fig. S4 in the Supplementary Appendix).

In both induction trials and in the maintenance trial, baseline and disease characteristics were similar among the groups (Table 1, and Table S1 in the Supplementary Appendix). In UNITI-1, approximately 50% of the patients who had been treated with two or more TNF antagonists met the criteria for primary or secondary nonresponse or had unacceptable side effects; 29.1% fulfilled the criteria for primary nonresponse, 69.4% fulfilled the criteria for secondary nonresponse, and 36.4% had unacceptable side effects. In UNITI-2, 68.6% of patients had not received TNF antagonists (data not shown).

INDUCTION THERAPY

In UNITI-1, the percentages of patients who had a response at week 6 were significantly higher in the groups that received ustekinumab at a dose of either 130 mg or 6 mg per kilogram (34.3% and 33.7%, respectively) than in the placebo group (21.5%), with an absolute difference between 130 mg of ustekinumab and placebo of 12.8 percentage points (95% confidence interval [CI], 5.0 to 20.7; P=0.002) and between 6 mg of

ustekinumab per kilogram and placebo of 12.3 percentage points (95% CI, 4.5 to 20.1; P=0.003) (Fig. 1, and Table S2 in the Supplementary Appendix). In UNITI-2, the percentages of patients who had a response at week 6 were also significantly higher in the groups that received ustekinumab at a dose of either 130 mg or 6 mg per kilogram (51.7% and 55.5%, respectively) than in the placebo group (28.7%), with an absolute difference between 130 mg of ustekinumab and placebo of 23.0 percentage points (95% CI, 13.8 to 32.1) and between 6 mg of ustekinumab per kilogram and placebo of 26.8 percentage points (95% CI, 17.7 to 35.9) (P<0.001 for both comparisons) (Fig. 1, and Table S2 in the Supplementary Appendix). In both trials, the efficacy of ustekinumab was generally consistent in the two treatment groups across prespecified subgroups (Figs. S1 and S2 in the Supplementary Appendix).

The rates at which patients met the criteria for all major secondary efficacy end points that were included in the hierarchical testing plan (i.e., remission at week 8, response at week 8, and decrease from baseline in CDAI score of ≤70 points at weeks 3 and 6) were significantly higher in the two ustekinumab groups than in the placebo group (Fig. 1A and 1B, and Fig. S5 in the Supplementary Appendix). The differences between the two ustekinumab groups and the placebo group in the rates of response and remission at the remaining trial visits (i.e., response at week 3, remission at weeks 3 and 6, decrease from baseline in CDAI score of ≤70 points at week 8, and change in CDAI score) were nominally significant, except with regard to remission at week 3 for the group in both trials that received 130 mg of ustekinumab (Fig. 1A and 1B, and Fig. S6 in the Supplementary Appendix).

In the induction trials, both doses of ustekinumab were associated with greater reductions in and normalization of serum CRP levels than was placebo. The differences between ustekinumab and placebo were nominally significant and were observed as early as week 3 and persisted through week 8. Similar effects were observed for fecal calprotectin levels at week 6 (Fig. 2A and 2B, and Table S3 in the Supplementary Appendix).

MAINTENANCE THERAPY

In IM-UNITI, the percentage of patients who were in remission at week 44 was significantly higher in the groups that received 90 mg of ustekinumab every 8 weeks or every 12 weeks (53.1% and 48.8%, respectively) than in the placebo group (35.9%), with an absolute difference between treatment every 8 weeks and placebo of 17.2 percentage points (95% CI, 5.3 to 29.2; P=0.005) and between treatment every 12 weeks and placebo of 13.0 percentage points (95% CI, 1.1 to 24.9; P=0.04) (Fig. 3, and Table S4 in the Supplementary Appendix). The efficacy of ustekinumab was generally consistent in the two treatment groups across prespecified subgroups (Fig. S7 in the Supplementary Appendix).

The percentage of patients who continued to have a response at week 44 was significantly higher in the groups that received treatment every 8 weeks or every 12 weeks than in the placebo group (P=0.02 and P=0.03, respectively) (Fig. 3A). The rate of remission at week 44 was significantly higher among patients who entered maintenance in remission and who received treatment every 8 weeks — but not those who received treatment every 12 weeks — than among those who received placebo (Fig. 3A). The rate of glucocorticoid-free remission at week 44 was significantly higher in the group that received treatment every 8 weeks — but only nominally higher in the group that received treatment every 12 weeks (owing to the hierarchical testing procedure) — than in the placebo group. The absolute between-group differences for the subgroup of patients who had met the criteria for primary or secondary nonresponse to TNF antagonists or who had unacceptable side effects (44.8% of the primary population enrolled from UNITI-1) were similar to those observed for the population included in the analysis of the primary end point (i.e., patients from both UNITI-1 and UNITI-2) but were not significant (Fig. 3B).

Analyses of the prespecified secondary end points showed that in the subgroup of patients in whom conventional therapy failed (55.2% of the primary population enrolled from UNITI-2), the percentage of patients who were in remission at week 44 was higher in the group that received treatment every 8 weeks than in the placebo group, and the difference was nominally significant; however, the percentage was only numerically higher in the group that received treatment every 12 weeks than in the placebo group (Fig. 3B). The percentages of patients who were in sustained clinical remission (i.e., remission at

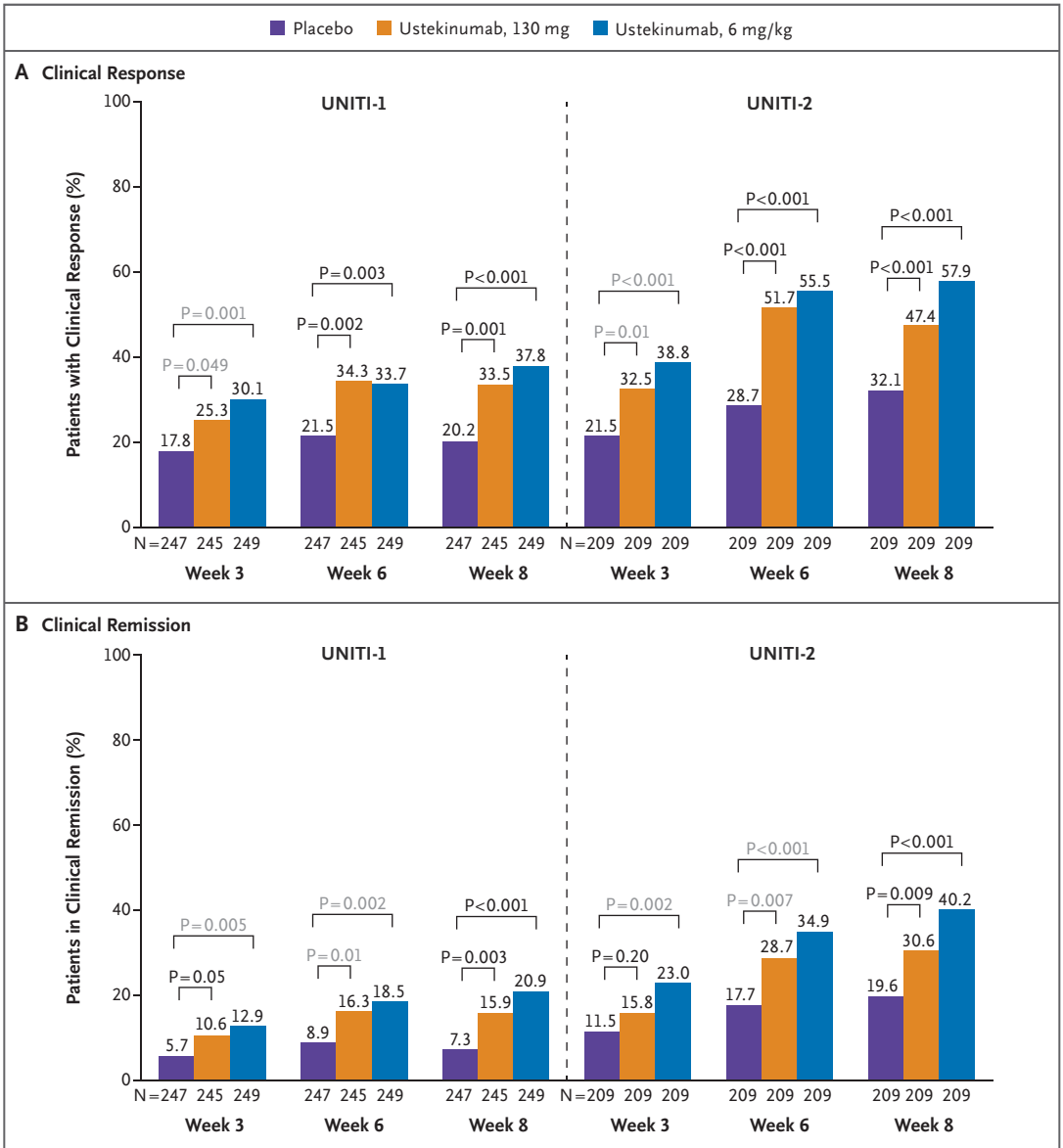

Figure 1. Patients with a Clinical Response or Clinical Remission during Induction.

Panel A shows the rates of clinical response (i.e., a decrease from baseline in Crohn's Disease Activity Index [CDAI] score of ≥100 points or a CDAI score <150) and Panel B shows the rates of clinical remission (CDAI score <150) at weeks 3, 6, and 8 of the induction trials in the groups receiving ustekinumab at a dose of either 130 mg or 6 mg per kilogram and in the placebo groups. For all the P values in gray, P<0.05 is only nominally significant, since the end point is not among the type I error–controlled end points, and should therefore be interpreted with caution. Weight-range–based doses of ustekinumab approximating 6 mg per kilogram of body weight are as follows: 260 mg (weight, ≤55 kg), 390 mg (weight, >55 kg and ≤85 kg), and 520 mg (weight, >85 kg). Patients who had a surgery related to Crohn's disease, had prohibited changes in concomitant medications for Crohn's disease, or had begun receiving a prohibited concomitant medication were considered to have treatment failure (treated as if they did not have a clinical response or clinical remission) from that time point onward, regardless of their CDAI score. Patients for whom there were insufficient data to calculate the CDAI score at a given time point were treated as if they did not have a clinical response or clinical remission at that time point.

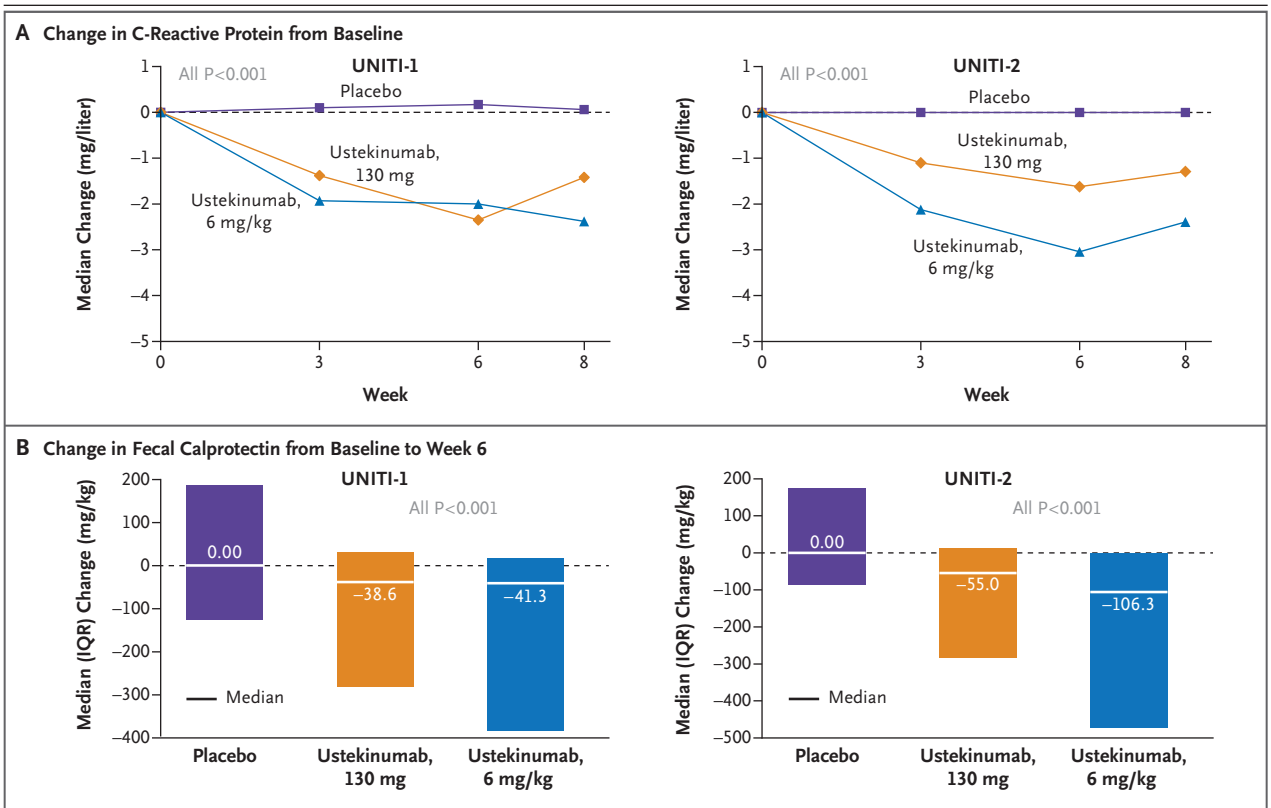

Figure 2. Change from Baseline in C-Reactive Protein and Fecal Calprotectin Levels during Induction.

Panel A shows the median change in C-reactive protein levels during the induction trials and Panel B shows the median change in the fecal calprotectin levels at week 6 of the induction trials (the prespecified time at which the primary end point was assessed) in the groups receiving ustekinumab at a dose of either 130 mg or 6 mg per kilogram and in the placebo groups. In Panel B, the white line indicates the median, and the top and bottom bars the interquartile range (IQR). For all the P values in gray, P<0.05 is only nominally significant, since the end point is not among the type I error–controlled end points, and should therefore be interpreted with caution.

weeks 36, 40, and 44) were significantly higher in the groups that received treatment every 8 weeks or every 12 weeks than in the placebo group (46.1% and 40.3%, respectively, vs. 26.0%; P<0.001 and P=0.02 [both nominal]). Median CDAI scores worsened in the placebo group and remained generally unchanged in both treatment groups, with the group that received treatment every 8 weeks having consistently better scores than the placebo group from week 24 onward and the group that received treatment every 12 weeks having better scores than the placebo group from week 32 onward (Fig. 3C).

More than half the patients who did not have a response to a single dose of intravenous ustekinumab at induction and received an additional 90-mg dose of subcutaneous ustekinumab at the initiation of maintenance therapy had a clinical response 8 weeks after receiving the 90-mg dose. Of those patients, 68.1% continued to have a response and 50.2% were in remission at week 44, after receiving 90 mg of ustekinumab every 8 weeks (for details, see the Supplementary Appendix). The efficacy results for patients in the primary population whose dose was escalated at the time of loss of response are included in the Supplementary Appendix.

Median CRP levels for patients in both ustekinumab groups remained generally unchanged at week 44, whereas the levels for patients in the placebo group increased over time, with clear separation from the ustekinumab groups beginning at week 12 (Fig. 3D). The percentages of patients in whom the fecal calprotectin level remained at 250 mg per kilogram or lower were also significantly higher in both ustekinumab

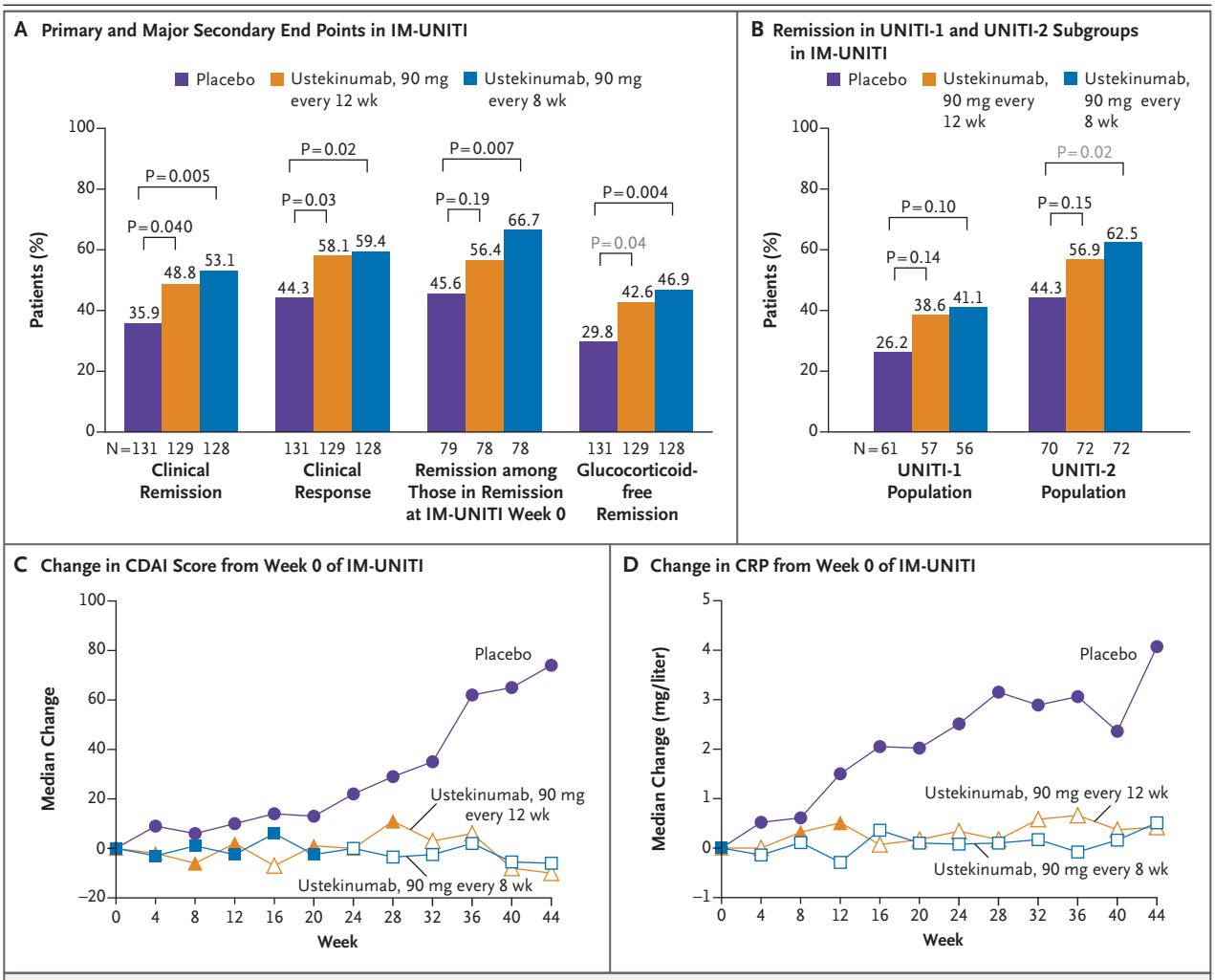

Figure 3. Patient Responses to Maintenance Therapy.

Panel A shows the rates at week 44 of the maintenance trial (after a total of 52 weeks of treatment) of clinical remission, clinical response, clinical remission among patients in clinical remission at week 0 of the maintenance trial, and glucocorticoid-free remission. Panel B shows the rates of clinical remission at week 44 in the subgroup of patients who met the criteria for primary or secondary nonresponse or had unacceptable side effects when treated with tumor necrosis factor (TNF) antagonists (UNITI-1 population) and in the subgroup of patients who did not have a response or had unacceptable side effects when treated with previous conventional therapy (UNITI-2 population). Panel C shows the median change in the CDAI score from week 0 of the maintenance trial, and Panel D shows the median change in C-reactive protein levels from week 0 of the maintenance trial. In Panels A and B, for the P values in gray, $P<0.05$ is only nominally significant according to the hierarchical testing procedure and should therefore be interpreted with caution. In Panels C and D, the white data points indicate that $P<0.05$ for the comparison with placebo, but these values are only nominally significant since the end point is not among the type I error–controlled end points and should therefore be interpreted with caution.

groups than in the placebo group at week 44, although the significance was nominal (Fig. S8 in the Supplementary Appendix).

SAFETY

In UNITI-1, the rates of adverse events in the groups receiving 130 mg of ustekinumab, 6 mg of ustekinumab per kilogram, and placebo were 64.6%, 65.9%, and 64.9%, respectively. The percentages of patients in these groups with a serious adverse event were 4.9%, 7.2%, and 6.1%, respectively (Table 2). In UNITI-2, the corresponding rates of adverse events were 50.0%, 55.6%, and 54.3%, and the corresponding rates of serious

Table 2. Adverse Events through Week 8 in UNITI-1 and UNITI-2 and through Week 44 in IM-UNITI.

Event	UNITI-1			UNITI-2			IM-UNITI		
	Placebo	Ustekinumab		Placebo	Ustekinumab		Placebo	Ustekinumab	
	(N=245)	130 mg (N=246)	6 mg/kg (N=249)	(N=208)	130 mg (N=212)	6 mg/kg (N=207)	(N=133)	90 mg/12 wk (N=132)	90 mg/8 wk (N=131)
	number (percent)								
Any adverse event	159 (64.9)	159 (64.6)	164 (65.9)	113 (54.3)	106 (50.0)	115 (55.6)	111 (83.5)	106 (80.3)	107 (81.7)
Common adverse events*									
Arthralgia	18 (7.3)	26 (10.6)	15 (6.0)	4 (1.9)	8 (3.8)	9 (4.3)	19 (14.3)	22 (16.7)	18 (13.7)
Headache	22 (9.0)	20 (8.1)	20 (8.0)	14 (6.7)	20 (9.4)	10 (4.8)	15 (11.3)	15 (11.4)	16 (12.2)
Nausea	18 (7.3)	20 (8.1)	13 (5.2)	5 (2.4)	7 (3.3)	11 (5.3)	9 (6.8)	10 (7.6)	4 (3.1)
Pyrexia	15 (6.1)	14 (5.7)	15 (6.0)	10 (4.8)	6 (2.8)	11 (5.3)	10 (7.5)	11 (8.3)	8 (6.1)
Nasopharyngitis	13 (5.3)	12 (4.9)	11 (4.4)	10 (4.8)	10 (4.7)	14 (6.8)	10 (7.5)	17 (12.9)	14 (10.7)
Abdominal pain	13 (5.3)	9 (3.7)	13 (5.2)	7 (3.4)	5 (2.4)	10 (4.8)	16 (12.0)	13 (9.8)	11 (8.4)
Crohn's disease event	24 (9.8)	13 (5.3)	6 (2.4)	10 (4.8)	8 (3.8)	7 (3.4)	19 (14.3)	16 (12.1)	16 (12.2)
Fatigue	13 (5.3)	6 (2.4)	9 (3.6)	4 (1.9)	3 (1.4)	4 (1.9)	6 (4.5)	8 (6.1)	6 (4.6)
Infections†									
Any	58 (23.7)	57 (23.2)	64 (25.7)	48 (23.1)	31 (14.6)	45 (21.7)	66 (49.6)	61 (46.2)	63 (48.1)
Serious	3 (1.2)	3 (1.2)	7 (2.8)	3 (1.4)	3 (1.4)	1 (0.5)	3 (2.3)	7 (5.3)	3 (2.3)
Serious adverse events	15 (6.1)	12 (4.9)	18 (7.2)	12 (5.8)	10 (4.7)	6 (2.9)	20 (15.0)	16 (12.1)	13 (9.9)
Adverse events associated with infusion or injection-site reactions‡	5 (2.0)	11 (4.5)	9 (3.6)	6 (2.9)	5 (2.4)	3 (1.4)	1 (0.8)	3 (2.3)	9 (6.9)

* The listed adverse events were reported by at least 5% of the patients in any group.
† Infections were assessed by the investigator.
‡ Adverse events associated with infusions in UNITI-1 and UNITI-2 refer to events that occurred within 1 hour after infusion. Adverse events summarized for IM-UNITI refer to injection-site reactions.

adverse events were 4.7%, 2.9%, and 5.8%. Rates of adverse events occurring within 1 hour after an ustekinumab infusion were similar across the groups receiving both doses in UNITI-1 and UNITI-2. At week 44 of IM-UNITI, the percentages of patients in the primary population with at least one adverse event in the groups receiving 90 mg of ustekinumab every 8 weeks, 90 mg of ustekinumab every 12 weeks, and placebo were 81.7%, 80.3%, and 83.5%, respectively. The percentages of patients with a serious adverse event were 9.9%, 12.1%, and 15.0%, respectively. Serious infection developed in 13 patients across all three study groups, occurring at rates of 2.3% in the group receiving ustekinumab every 8 weeks, 5.3% in the group receiving ustekinumab every 12 weeks, and 2.3% in the placebo group.

One patient, in the group receiving 6 mg of ustekinumab per kilogram in UNITI-1, had a preexisting monoclonal gammopathy and did not continue to the maintenance trial. The patient received a diagnosis of multiple myeloma after the 20-week safety follow-up period. In UNITI-2, basal-cell carcinoma developed in one patient receiving placebo.

There were two patients with basal-cell carcinomas in the IM-UNITI primary (randomized) population, one in the placebo group and one in the group receiving 90 mg of ustekinumab every 8 weeks. Among patients who were not in the primary population, six nonmelanoma skin cancers occurred: basal-cell carcinoma in one patient assigned to receive ustekinumab every 8 weeks, two squamous-cell carcinomas in one patient receiving 90 mg of ustekinumab subcutaneously at week 0 of the maintenance trial (treatment was discontinued before the next dose), and two basal-cell carcinomas and one squamous-cell carcinoma in a patient who did not receive ustekinumab. (The patient had had a response to intravenous placebo and in IM-UNITI was assigned to maintenance with placebo.) Of the five patients with nonmelanoma skin cancer who were assigned to receive ustekinumab or placebo, three were currently using or had previously used immunosuppressants. In one patient assigned to receive ustekinumab every 12 weeks, a metastatic adenocarcinoma developed in the small bowel and a carcinoid tumor was found incidentally in the resected bowel.

During 1 year of therapy, there were no deaths or instances of the reversible posterior leukoencephalopathy syndrome. Three opportunistic infections occurred, including one case of listeria meningitis in a patient in the group receiving 6 mg of ustekinumab per kilogram who was taking 30 mg of prednisone per day (in UNITI-1) and two nonserious cases of esophageal candidiasis — one in a patient receiving placebo who was taking 40 mg of prednisone per day and methotrexate (in UNITI-2) and one in a patient who was not in the primary IM-UNITI population and was receiving 90 mg of ustekinumab subcutaneously every 8 weeks. Pantoprazole and infliximab were prescribed within 2 weeks before the diagnosis of candidiasis.

One case of active pulmonary tuberculosis occurred approximately 10 months after the administration of a single intravenous induction dose of 130 mg of ustekinumab in a patient assigned to receive placebo during maintenance therapy. A nonfatal stroke that resulted from a ruptured cerebral aneurysm was reported in a patient who had received a single dose of 90 mg of ustekinumab subcutaneously at week 0 of the maintenance trial.

PHARMACOKINETICS AND IMMUNOGENICITY

At week 8 of UNITI-1, the respective median serum levels of ustekinumab in the groups receiving 130 mg of ustekinumab and 6 mg per kilogram were 2.1 μg per milliliter (interquartile range, 1.0 to 3.4) and 6.4 μg per milliliter (interquartile range, 3.3 to 9.6), respectively. At week 8 of UNITI-2, the respective levels were 2.0 μg per milliliter (interquartile range, 1.2 to 3.5) and 6.3 μg per milliliter (interquartile range, 3.9 to 9.6). At weeks 24 and 44 of IM-UNITI, the median serum levels of ustekinumab in the group receiving 90 mg every 8 weeks were approximately three times as high as the levels in the group receiving 90 mg every 12 weeks (Table S5 in the Supplementary Appendix). In all three trials, an association was observed between serum ustekinumab level and remission (Tables S6 and S7 in the Supplementary Appendix).

After testing was conducted with an assay that can detect antidrug antibodies in the presence of ustekinumab, two patients who had received 130 mg of intravenous ustekinumab were positive for antidrug antibodies, and both had neutralizing antibodies. In IM-UNITI, the incidence of antidrug antibodies at week 44 was low (27 of 1154 patients [2.3%]). Given the small number

of patients with antidrug antibodies, no definite conclusions can be drawn about their effect, although their presence did not preclude efficacy.

DISCUSSION

Both ustekinumab induction regimens showed consistent benefit over placebo, irrespective of previous treatment or response to a TNF antagonist. At week 6 of the induction trials, response rates for both intravenous ustekinumab doses were significantly higher than those for placebo. At week 44 of the maintenance trial, among those who had a response to ustekinumab during induction, both subcutaneous ustekinumab doses showed significantly higher efficacy than placebo.

Ustekinumab was significantly better than placebo with respect to the primary and all major secondary end points for induction at both doses, with the highest rates of response and remission observed with the dose of 6 mg per kilogram. In UNITI-1, patients had relatively severe Crohn's disease of long duration and had met the criteria for primary or secondary nonresponse or had unacceptable adverse effects associated with at least one TNF antagonist. In UNITI-2, the majority of patients had not received a TNF antagonist, and the median baseline CDAI score was similar to those reported in previous induction trials in populations in whom conventional therapy failed or unacceptable side effects occurred.[16,17] Remission was induced at week 8 in 20.9% of patients receiving the regimen of 6 mg of ustekinumab per kilogram in UNITI-1. Higher rates of absolute response and remission were observed in UNITI-2, presumably because disease was less refractory and of relatively shorter duration in patients in whom only conventional therapy had been unsuccessful.

The benefits of ustekinumab in inducing a response were observed as early as week 3. This prompt onset of clinical efficacy, paralleled by decreases in CRP levels, is desirable in such highly symptomatic patients. Improvements in (and greater normalization of) CRP and fecal calprotectin levels after treatment with ustekinumab suggest that objective reduction of inflammation was occurring in tandem with clinical improvements. Although statistical testing was not planned or performed, there appears to be a numerical difference favoring the dose of 6 mg per kilogram over the dose of 130 mg for most efficacy variables; the former was also associated with higher blood levels of ustekinumab.

In IM-UNITI, superiority over placebo was shown for both the primary outcome and the majority of the secondary end points. In both of the groups receiving maintenance doses of subcutaneous ustekinumab, patients had significantly lower CRP and fecal calprotectin levels at week 44 than those who received placebo. Although both the regimen administered every 8 weeks and the regimen administered every 12 weeks were superior to placebo, the totality of the efficacy and exposure–response data appear to favor administration every 8 weeks. The favorable data for this regimen were most apparent for a number of remission-based outcomes. Notably, a high percentage of the patients with a response to ustekinumab at induction were in clinical remission during maintenance with placebo, despite having received only a single intravenous induction dose of ustekinumab. This finding could indicate that ustekinumab has a long duration of action, a likelihood that may become better understood in future trials.

The induction trials presented here evaluated a single intravenous dose of either 130 mg or 6 mg per kilogram (i.e., up to a dose of 520 mg). There were no deaths, and rates of overall adverse events, serious adverse events, and adverse events within 1 hour after infusion occurred at similar rates across groups. The rates of adverse events were similar for subcutaneous maintenance therapy with ustekinumab and placebo, and there was no apparent relationship between dose and safety. The adverse events observed in these trials are consistent with 5 years of cumulative data acquired for patients with psoriasis (who received subcutaneous doses of ≤90 mg)[11,18] and 2 years of safety data for patients with psoriatic arthritis.[19] The rates of antidrug antibodies were low, as measured with the use of a drug-tolerant assay.

In conclusion, intravenous ustekinumab induces response and remission in patients with moderately to severely active Crohn's disease that is refractory to either TNF antagonists or conventional therapy. Among patients who had a response to intravenous induction, subcutaneous ustekinumab administered at a dose of 90 mg every 8 weeks or every 12 weeks was more effective than placebo for maintaining remission.

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APPENDIX

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