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ORIGINAL ARTICLE

Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis

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ABSTRACT

BACKGROUND

In a phase 2 study, the inhibition of the interleukin-17A receptor improved signs and symptoms of psoriatic arthritis. We sought to evaluate the efficacy and safety of secukinumab, an anti–interleukin-17A monoclonal antibody, in such patients.

METHODS

In this double-blind, phase 3 study, 606 patients with psoriatic arthritis were randomly assigned in a 1:1:1 ratio to receive intravenous secukinumab (at a dose of 10 mg per kilogram) at weeks 0, 2, and 4, followed by subcutaneous secukinumab at a dose of either 150 mg or 75 mg every 4 weeks, or placebo. Patients in the placebo group were switched to subcutaneous secukinumab at a dose of 150 mg or 75 mg at week 16 or 24, depending on clinical response. The primary end point was the proportion of patients with an American College of Rheumatology 20 (ACR20) response at week 24, defined as a 20% improvement from baseline in the number of tender and swollen joints and at least three other important domains.

RESULTS

ACR20 response rates at week 24 were significantly higher in the group receiving secukinumab at doses of 150 mg (50.0%) and 75 mg (50.5%) than in those receiving placebo (17.3%) ($P<0.001$ for both comparisons with placebo). Secondary end points, including the ACR50 response and joint structural damage, were significantly better in the secukinumab groups than in the placebo group. Improvements were sustained through 52 weeks. Infections, including candida, were more common in the secukinumab groups. Throughout the study (mean secukinumab exposure, 438.5 days; mean placebo exposure, 128.5 days), four patients in the secukinumab groups had a stroke (0.6 per 100 patient-years; 95% confidence interval [CI], 0.2 to 1.5), and two had a myocardial infarction (0.3 per 100 patient-years; 95% CI, 0.0 to 1.0), as compared with no patients in the placebo group.

CONCLUSIONS

Secukinumab was more effective than placebo in patients with psoriatic arthritis, which validates interleukin-17A as a therapeutic target. Infections were more common in the secukinumab groups than in the placebo group. The study was neither large enough nor long enough to evaluate uncommon serious adverse events or the risks associated with long-term use. (Funded by Novartis Pharma; ClinicalTrials.gov number, NCT01392326.)

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Psoriatic arthritis is a chronic, systemic inflammatory disease that affects peripheral joints, connective tissues, and the axial skeleton and is associated with psoriasis of the skin and nails.[1,2] Inhibitors of tumor necrosis factor (TNF) have significantly improved outcomes among patients with psoriatic arthritis.[3-6] However, some patients who have received these agents have not had adequate benefit, have not had a durable response, or have had adverse events.[1,2] Effective therapies with a different mechanism of action are needed.

Interleukin-17A is postulated to play a role in the pathogenesis of psoriatic arthritis. Increased levels of cells that produce interleukin-17A are found in the circulation, joints, and skin plaques of patients with psoriatic arthritis,[7-10] and these levels have been shown to correlate with measures of disease activity and structural damage.[11] A phase 2 study showed that the inhibition of the interleukin-17A receptor improved signs and symptoms of psoriatic arthritis.[12] Secukinumab, a high-affinity, human immunoglobulin G1 monoclonal antibody that selectively binds to and neutralizes interleukin-17A, has shown efficacy in a number of immune-mediated inflammatory diseases, including psoriasis and ankylosing spondylitis.[13,14]

FUTURE 1 is an ongoing, 2-year, phase 3 study assessing the effect of secukinumab on signs and symptoms, joint structural damage, physical function, and quality of life among patients with psoriatic arthritis. Here, we report efficacy data through week 24 (primary end point) and week 52 (interim follow-up analysis). Safety data are reported up to the interim follow-up analysis.

Methods

Study Population

Study patients were 18 years of age or older, fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR),[15] and had active disease, which was defined as three or more tender joints and three or more swollen joints, despite previous treatment with nonsteroidal antiinflammatory drugs, disease-modifying antirheumatic drugs, or TNF inhibitors. The concomitant use of oral glucocorticoids (at a dose of ≤10 mg per day of prednisone or its equivalent) and methotrexate (at a dose of ≤25 mg per week) was permitted, provided that the dose was stable. Patients who had previously received anti-TNF therapy were required either to have had an inadequate response or to have stopped treatment because of side effects. For patients who had received anti-TNF agents, a washout period of 4 to 10 weeks before randomization was required.

Key exclusion criteria included previous therapy with biologic drugs other than anti-TNF agents, treatment with more than three anti-TNF therapies, the presence of active inflammatory diseases other than psoriatic arthritis, and active infection in the 2 weeks before randomization or a history of ongoing, chronic, or recurrent infections. Additional information is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Study Oversight

The study was approved by the institutional review board or ethics committee at each participating site and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

The study was sponsored by Novartis Pharma and designed by the scientific steering committee and Novartis personnel. Data were collected according to Good Clinical Practice guidelines by the study investigators and were analyzed by the sponsor. Statistical analyses were performed by statisticians employed by the sponsor and were reviewed by all the authors. Agreements between the sponsor and the investigators included provisions relating to confidentiality of the study data. The first draft of the manuscript was written by a medical writer funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of this report to the study protocol, which is available at NEJM.org.

Study Design

From September 29, 2011, to October 1, 2012, we conducted this multicenter, randomized, double-blind, placebo-controlled trial at 104 sites in North America and South America, Europe, the Middle East, Australia, and Asia. After a 4-week screening period, eligible patients were randomly assigned in a 1:1:1 ratio by means of an interactive voice–Web response system to one of two secukinumab dose groups or a placebo group. Patients in the secukinumab groups received an intravenous dose of 10 mg per kilogram

of body weight at baseline and weeks 2 and 4, followed by subcutaneous secukinumab at a dose of either 150 mg or 75 mg every 4 weeks thereafter. Patients in the placebo group were treated according to the same intravenous-to-subcutaneous administration schedule.

At week 16, investigators who were unaware of study-group assignments classified all the patients as having had a response (which was defined as an improvement of 20% or more from baseline in the number of tender and swollen joints) or no response. Placebo-treated patients underwent randomization for a second time in a 1:1 ratio to receive subcutaneous secukinumab at a dose of either 150 mg or 75 mg every 4 weeks, starting at week 16 (for patients who were classified as having had no response) or week 24 (for those who were classified as having had a response). In the efficacy analyses, the placebo-controlled period included data through week 24, with imputation for patients who switched to active treatment at week 16. In the safety analyses, the placebo-controlled period included data only through week 16, when patients received the originally assigned study medication.

The randomization of patients was stratified according to previous anti-TNF therapy. Approximately 70% of the patients were required to have received no previous anti-TNF therapy.

ASSESSMENTS

The primary objective was to assess the proportion of patients meeting the criteria for 20% improvement according to the criteria of the American College of Rheumatology (ACR20 response)[16] at week 24. The ACR20 response was defined as an improvement of 20% or more from baseline in the number of tender joints (from an analysis of 78 joints), in the number of swollen joints (from an analysis of 76 joints), and in three of the following five domains: a patient's global assessment of disease, a physician's global assessment of disease, and a patient's assessment of pain (with all three evaluations measured on a visual-analogue scale of 0 to 100); disability (as measured by the score on the Health Assessment Questionnaire–Disability Index [HAQ-DI], which ranges from 0 to 3, with higher scores indicating greater disability); and the level of acute-phase reactants (as measured by the level of high-sensitivity C-reactive protein or the erythrocyte sedimentation rate).

Secondary objectives included assessment of the following categories at week 24: the proportion of patients with improvement of at least 75% and 90% in the score on the psoriasis area-and-severity index (PASI 75 and PASI 90, respectively)[17] among patients with at least 3% of body-surface area that was affected by psoriasis at baseline; a change from baseline in the 28-joint Disease Activity Score on the basis of levels of C-reactive protein (DAS28-CRP), with scores ranging from 2 to 10, and a score of more than 5.1 indicating active disease, a score of up to 3.2 indicating low disease activity, and a score of less than 2.6 indicating remission)[18]; quality of life, as assessed with the use of the physical component summary score of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), version 2, with scores ranging from 0 to 100, and 0 indicating maximum disability and 100 indicating no disability, and a minimum clinically important difference of at least 2.5 points used for the analysis[19]; physical function, as assessed with the use of the HAQ-DI[20]; the proportion of patients with improvement of at least 50% according to the criteria of the ACR (ACR50 response); and radiographic progression. In addition, among patients who had either dactylitis or enthesitis at baseline, the presence of dactylitis was assessed by means of a dactylitic digit count, with a score of 1 for the presence of dactylitis and 0 for the absence in each digit, for an overall score ranging from 0 to 20; the presence of enthesitis was assessed by means of a 4-point enthesitis index to measure the presence (score of 1) or absence (score of 0) of tenderness at the lateral epicondyle humerus (left and right) and proximal achilles (left and right).

Radiographic progression was assessed with the use of the van der Heijde–modified total Sharp score (mTSS), which ranges from 0 to 528, with higher scores indicating greater erosion or narrowing of joint spaces.[21] Radiography of the hands, wrists, and feet was performed at baseline, at week 16 or 24 (depending on response), and at week 52. Two independent readers scored all images centrally. Exploratory objectives included assessment of the proportion of patients with improvement of at least 70% according to the criteria of the ACR (ACR70 response). Prespecified subgroup analyses on the basis of previous anti-TNF therapy were performed for key efficacy end points. Efficacy assessments were

conducted at baseline and throughout the study, with key assessments at week 24 (primary end point) and week 52 (interim follow-up analysis).

Safety was evaluated by means of open assessment of adverse events, serious adverse events, and routine laboratory values. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0,[22] was used to grade the severity of adverse events. Potential major adverse cardiac events were adjudicated by an independent expert committee. Blood samples were obtained at baseline and weeks 24 and 52 for assessment of secukinumab immunogenicity with the use of a homogeneous Meso Scale Discovery bridging assay.[23]

STATISTICAL ANALYSIS

We calculated that the enrollment of 600 patients (200 in each study group) would provide a power of more than 90% to detect a treatment difference between a secukinumab regimen and placebo with respect to the primary end point, assuming response rates for placebo and secukinumab of 22% and 49%, respectively, at a two-sided significance level of 0.025. Primary and secondary efficacy analyses included all patients according to the treatment assigned at randomization. Statistical analyses at week 24 used the imputation of missing values as a nonresponse for binary variables, a mixed-effects repeated-measures model for continuous variables, and linear extrapolation for radiographic data. Analyses followed a predefined hierarchical hypothesis-testing strategy to adjust for multiplicity to maintain a familywise type I error of 5%. According to this strategy, the statistical significance of each secondary end point could be investigated only if the previous end point was significant ($P<0.025$ for end points tested at individual doses; $P<0.05$ for pooled analyses). The statistical-hierarchy testing order was as follows: ACR20 response, PASI 75, PASI 90, DAS28-CRP, physical component summary of SF-36, HAQ-DI, ACR50, mTSS (for pooled secukinumab doses), dactylitis and enthesitis (for pooled secukinumab doses), and mTSS (for individual doses). Patients in the placebo group who were switched to active treatment at week 16 were imputed to have had no response in the analysis at week 24. To avoid bias, secukinumab-treated patients who had no response at week 16 were also imputed to have had no response at week 24.

For binary variables, P values are from a logistic-regression model with treatment and previous use of anti-TNF therapy as factors, with body weight at baseline as a covariate. The baseline score was a covariate in the analysis of some end points. For continuous variables, P values are from a repeated-measures mixed model, with treatment regimen, analysis visit, and previous use of anti-TNF therapy as factors and with body weight and baseline score as continuous covariates. Treatment according to analysis visit and baseline score according to analysis visit were used as interaction terms, and an unstructured covariance structure was assumed.

Both inferential analyses (with imputation) and descriptive summaries (on observed data) were performed on data from week 28 to week 52. In the inferential analysis of binary variables during this period, patients who withdrew from the study were considered to have had no response from the time of withdrawal. In contrast to the method that was used in the primary analysis, in the analyses from week 20 through week 52, no imputation was applied as a result of the clinical response of a patient at week 16. Patients for whom responses could not be calculated at a specific time point were classified as having had no response. Analyses of clinical responses to secukinumab from week 28 to week 52 include only patients who underwent the first randomization to active treatment.

Safety analyses included all patients who underwent randomization and who received at least one dose of a study drug. Additional information regarding the statistical analysis is provided in the Supplementary Appendix. All reported P values are two-sided.

RESULTS

PATIENTS

Of the 606 patients who underwent randomization (202 in each study group), 553 (91.3%) completed the 24-week evaluation period and 515 (85.0%) completed the 52-week evaluation period (Fig. S1 in the Supplementary Appendix). The patients' demographic and disease characteristics and previous or concomitant use of medications were similar across the study groups at baseline (Table 1). More than half the patients (53.6%) had psoriasis affecting at least 3% of their body-surface area; 53.5% had dactylitis,

and 61.4% had enthesitis. A total of 70.6% of the patients had received no previous anti-TNF therapy, and 60.7% were receiving concomitant methotrexate.

EFFICACY

Secukinumab was superior to placebo with respect to all the primary and secondary end points that were prespecified in the hierarchical statistical testing. At week 24, the proportion of patients with an ACR20 response was significantly higher among patients receiving secukinumab at either the 150-mg dose or the 75-mg dose than among those receiving placebo (50.0% and 50.5%, respectively, vs. 17.3%) ($P<0.001$ for both comparisons with placebo) (Table 2 and Fig. 1). At week 24, the proportion of patients with an ACR50 response was significantly higher in the secukinumab groups than in the placebo group (Table 2), as was the proportion of patients with an ACR70 response in prespecified exploratory analyses (Fig. S2 in the Supplementary Appendix). Significant improvements with secukinumab versus placebo were observed for all other secondary end points at week 24 that were prespecified in hierarchical statistical testing, including PASI 75 and PASI 90 responses, the change from baseline in DAS28-CRP, the SF-36 physical component summary, HAQ-DI scores, and the proportion of patients who had resolution of dactylitis and enthesitis (Table 2). Patients in the secukinumab groups also had significantly less radiographic progression, as measured by the change from baseline on the mTSS at week 24, than did patients in the placebo group ($P<0.05$ for both comparisons) (Table 2, and Fig. S3 in the Supplementary Appendix).

In prespecified exploratory subgroup analyses, improvements in ACR response rates and disease activity at week 24 in the secukinumab groups, as compared with the placebo group, were observed regardless of previous exposure to anti-TNF agents (Table S1 in the Supplementary Appendix). At week 24, among patients who had received no previous anti-TNF therapy, an ACR20 response was reported in 78 of 143 patients (54.5%) who received 150 mg of secukinumab and in 79 of 142 patients (55.6%) who received 75 mg of secukinumab, as compared with 25 of 143 patients (17.5%) in the placebo group. At the same time, among patients who had a previous inadequate response to anti-TNF therapy or who had unacceptable side effects, an ACR20 response was reported in 23 of 59 patients (39.0%) who received 150 mg of secukinumab, 23 of 60 patients (38.3%) who received 75 mg of secukinumab, and 10 of 59 patients (16.9%) in the placebo group. In a post hoc analysis, ACR20 response rates were better in the secukinumab groups than in the placebo group at week 24, regardless of concomitant methotrexate use (Fig. S4 in the Supplementary Appendix).

Clinical benefits in the secukinumab groups were sustained through 52 weeks of therapy (Table S2 in the Supplementary Appendix). On the basis of a conservative estimate of efficacy with missing values imputed as no response, at week 52 in the secukinumab groups, an ACR20 response was reported in 121 of 202 patients (59.9%) among those receiving 150 mg and in 115 of 202 patients (56.9%) among those receiving 75 mg (Fig. 1). On the basis of observed data, the corresponding numbers for the ACR20 response were 121 of 174 patients (69.5%) and 115 of 172 patients (66.9%), respectively (Table S2 and Fig. S5 in the Supplementary Appendix). ACR50 and ACR70 results are presented in Table S2 and Figures S2 and S5 in the Supplementary Appendix. Patients in the placebo group had improvements in ACR20 response rates after switching to secukinumab (Fig. S6 in the Supplementary Appendix).

SAFETY

During the 16-week placebo-controlled period, adverse events were reported in 64.9% of patients receiving 150 mg of secukinumab, in 60.4% of those receiving 75 mg of secukinumab, and in 58.4% of those receiving placebo. Rates of nonfatal serious adverse events and discontinuations were similar across the study groups (Table 3). Nasopharyngitis, headache, and upper respiratory tract infection were the most common adverse events and were more frequent among patients in the secukinumab groups than among those in the placebo group. During the placebo-controlled period, infections were more common among patients in the secukinumab groups.

Across the entire safety-data reporting period, the maximum exposure to secukinumab was 103 weeks, with a mean exposure of 438.5 days and a median exposure of 456 days. During this period, the exposure-adjusted rates of serious

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Secukinumab, 150 mg (N=202)	Secukinumab, 75 mg (N=202)	Placebo (N=202)
Age — yr	49.6±11.8	48.8±12.2	48.5±11.2
Female sex — no. (%)	106 (52.5)	118 (58.4)	106 (52.5)
Weight — kg	84.2±21.1	84.5±19.6	80.0±20.5
Race — no. (%)†			
White	162 (80.2)	165 (81.7)	154 (76.2)
Black	3 (1.5)	2 (1.0)	0
Asian	36 (17.8)	33 (16.3)	46 (22.8)
Other	1 (0.5)	1 (0.5)	2 (1.0)
No. of previous anti-TNF drugs — no. (%)			
0	143 (70.8)	142 (70.3)	143 (70.8)
1	39 (19.3)	35 (17.3)	35 (17.3)‡
≥2	20 (9.9)	25 (12.4)	24 (11.9)
Use of methotrexate at randomization — no. (%)	121 (59.9)	122 (60.4)	125 (61.9)
Use of systemic glucocorticoid at randomization — no. (%)	34 (16.8)	34 (16.8)	27 (13.4)
Patients with specific disease characteristics — no. (%)			
Psoriasis affecting ≥3% of body-surface area	108 (53.5)	108 (53.5)	109 (54.0)
Dactylitis	104 (51.5)	104 (51.5)	116 (57.4)
Enthesitis	126 (62.4)	129 (63.9)	117 (57.9)
Disease and quality-of-life scores			
Tender-joint count (of 78 joints)	23.8±16.4	23.4±17.2	25.1±18.4
Swollen-joint count (of 76 joints)	12.5±9.4	12.7±11.1	14.9±13.1
DAS28-CRP§	4.8±1.1	4.9±1.2	4.9±1.1
PASI¶	15.6±13.9	10.7±8.8	15.1±11.6
Physician's global assessment of disease activity‖	58.3±18.9	54.3±18.0	56.7±18.8
Modified total Sharp score**	21.9±47.5	20.0±38.8	28.1±62.8
HAQ-DI score††	1.2±0.7	1.3±0.7	1.2±0.6
Psoriatic arthritis pain‖	55.7±24.2	55.1±22.1	56.7±21.1
Patient's global assessment of disease activity‖	55.2±24.0	56.1±22.6	55.6±21.7
SF-36 physical component summary‡‡	36.2±8.1	36.9±8.1	36.8±8.0

* Plus–minus values are means ±SD. There were no significant differences among the three groups except for the psoriasis area-and-severity index (PASI) score (P=0.003) and weight (P=0.048). TNF denotes tumor necrosis factor.

† Race was self-reported. Race was not reported for one patient in the group receiving 75 mg of secukinumab.

‡ One patient in this group received one dose of infliximab, which was subsequently discontinued for logistic reasons rather than because of an inadequate response. The patient was reported as having received no previous anti-TNF therapy.

§ The 28-joint Disease Activity Score (DAS28), which is based on the level of C-reactive protein (CRP), ranges from 2 to 10, with higher scores indicating more severe disease activity (with >5.1 indicating active disease, ≤3.2 indicating low disease activity, and <2.6 remission).

¶ PASI scores range from 0 to 72, with higher scores indicating more severe disease. PASI was assessed only in patients in whom psoriasis affected at least 3% of the body-surface area at baseline.

‖ This evaluation is based on a visual-analogue scale of 0 to 100, with higher scores indicating greater disease activity or pain.

** The van der Heijde–modified total Sharp score ranges from 0 to 528, with higher scores indicating more articular damage.

†† Scores on the Health Assessment Questionnaire–Disability Index (HAQ-DI) range from 0 to 3, with higher scores indicating greater disability.

‡‡ Scores on the physical component summary of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with 0 representing maximum disability and 100 no disability; scores lower than 50 reflect less-than-average health, and scores greater than 50 reflect better-than-average health.

Table 2. Comparison of Efficacy at Week 24 during the Placebo-Controlled Phase.*

Outcome	Secukinumab, 150 mg (N=202)	Secukinumab, 75 mg (N=202)	Placebo (N=202)
ACR20 response: primary end point — no. (%)†	101 (50.0)‡	102 (50.5)‡	35 (17.3)
Prespecified secondary end points			
PASI 75 response — no./total no. (%)§	66/108 (61.1)‡	70/108 (64.8)‡	9/109 (8.3)
PASI 90 response — no./total no. (%)§	49/108 (45.4)‡	53/108 (49.1)‡	4/109 (3.7)
Change from baseline in DAS28-CRP	−1.62±0.08‡	−1.67±0.09‡	−0.77±0.12
Change from baseline in SF-36 physical component summary	5.91±0.53‡	5.41±0.52‡	1.82±0.72
Change from baseline in disability assessment (HAQ-DI score)	−0.40±0.04‡	−0.41±0.04‡	−0.17±0.05
ACR50 response — no. (%)	70 (34.7)‡	62 (30.7)‡	15 (7.4)
Change from baseline in joint structural damage (mTSS score)¶	0.13±0.09‖	0.02±0.12‖	0.57±0.19
Patients with resolution of dactylitis — no./total no. (%)**	109/208 (52.4)‖		18/116 (15.5)
Patients with resolution of enthesitis — no./total no. (%)**	121/255 (47.5)‖		15/117 (12.8)

* Plus–minus values are means ±SE. The change from baseline in the DAS28-CRP and the SF-36 physical component summary were calculated as least-squares means in inferential analysis. Prespecified primary and secondary end points were analyzed according to a statistical hierarchy. End points are shown in the order of testing, except the effect of individual doses of secukinumab on joint structural damage, which was tested after dactylitis and enthesitis end points.

† The primary end point was an improvement of at least 20% in the American College of Rheumatology response criteria (ACR20 response).

‡ P<0.001 for the comparison with placebo.

§ PASI 75 and PASI 90 denote improvements of 75% and 90%, respectively, in the score on the psoriasis area-and-severity index.

¶ Joint structural damage was measured by means of the van der Heijde–modified total Sharp score (mTSS). Data are shown for 185 patients who received 150 mg of secukinumab, 181 patients who received 75 mg of secukinumab, and 179 patients who received placebo. For the pooled secukinumab groups, the mean change from baseline in the mTSS score was 0.08±0.07 (P=0.01).

‖ P<0.05 for the comparison with placebo.

** For this analysis, data for the two secukinumab groups were pooled.

adverse events among patients receiving secukinumab were 11.5 and 7.4 per 100 patient-years among those receiving 150 mg and 75 mg, respectively (Table 3). Serious adverse events are listed in Table S3 in the Supplementary Appendix. Through 16 weeks, one patient receiving 75 mg of secukinumab had a stroke. After week 16, an additional three patients had a stroke, totaling four patients for the entire safety reporting period; all these patients were receiving 75 mg of secukinumab (exposure-adjusted rate, 0.6 per 100 patient-years; 95% confidence interval [CI], 0.2 to 1.5). In addition, two patients (one in each secukinumab group) had a myocardial infarction (rate, 0.3 per 100 patient-years; 95% CI, 0.0 to 1.0). Of these six patients, four continued to participate in the study. Additional details regarding these patients are provided in Table S4 in the Supplementary Appendix. No strokes or myocardial infarctions were observed in the placebo group (rate, 0 per 100 patient-years; 95% CI, 0.0 to 5.2). The maximum exposure to placebo was 33 weeks (mean exposure, 128.5 days; median exposure, 112 days).

Overall, adverse events leading to discontinuations of a study drug were noted in less than 5% of the patients and were similar among the three groups. Oral candidiasis was reported in 4 patients each in the secukinumab 150-mg and 75-mg groups; in the 150-mg group, there were reports of esophageal candidiasis in 1 patient and a candida infection of the skin in another. All cases of candidiasis, including one serious case, responded to oral therapy, and patients continued in the study. No other serious opportunistic infections or cases of active tuberculosis

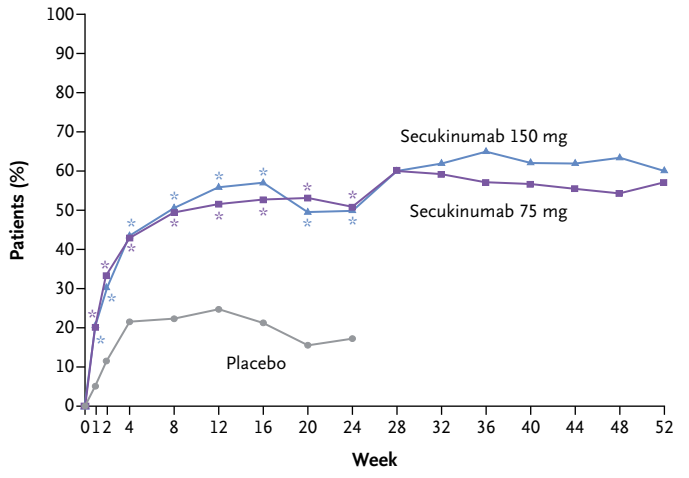

Figure 1. Responses to Secukinumab at 24 Weeks and 52 Weeks.

Shown is the proportion of 606 patients who had an improvement of at least 20% in the American College of Rheumatology response criteria (ACR20 response), among those receiving 150 mg of secukinumab, 75 mg of secukinumab, or placebo. Data are shown for patients in the placebo-controlled portion of the efficacy study, which was conducted from baseline to week 24, and for patients who were randomly assigned to receive secukinumab at baseline through week 52. Missing data were imputed as no response to treatment through week 52. P values at week 24 were adjusted for multiplicity of testing. In the primary analysis through week 24, patients who had less than 20% improvement in the number of tender and swollen joints at week 16 were imputed to have had no response at weeks 20 and 24. There was no imputation on the basis of the response at week 16 for analyses performed at week 28 and for subsequent analyses. Asterisks indicate P<0.001 for the comparison with placebo.

(new or reactivation of latent infection) were reported. Malignant or unspecified tumors were reported in 1 of 295 patients (0.3%) receiving 150 mg of secukinumab, 3 of 292 patients (1.0%) receiving 75 mg of secukinumab, and 1 of 202 patients (0.5%) receiving placebo. Three of 10 patients with anti-secukinumab antibodies at baseline showed anti-secukinumab antibodies and neutralizing antibodies in all or most post-baseline samples. Treatment-emergent anti-secukinumab antibodies were detected in 1 of 587 patients (0.2%) receiving secukinumab.

DISCUSSION

In this phase 3 study, we found that selective inhibition of interleukin-17A with secukinumab was significantly better than placebo in improving the signs and symptoms of psoriatic arthritis, along with patient-reported physical functioning and quality of life, with responses sustained during 52 weeks of therapy. In addition, there was a small reduction in the progression of measures of structural joint damage among patients receiving secukinumab. Preclinical data implicate the interleukin-17 pathway in the irreversible structural damage observed in inflammatory arthritis.[11,24-26] Our data provide further evidence that interleukin-17A may be a mediator of this process.

It is noteworthy that there was no apparent dose–response relationship between the two secukinumab groups with respect to efficacy assessments up to week 24, although such an analysis was not a predefined end point. This lack of difference may be at least partly due to the same intravenous loading dose that was administered to patients in the two secukinumab groups. Further evaluation of the dose–response relationship in subsequent subcutaneous administration of secukinumab is needed.

Even though many patients with psoriatic arthritis benefit from anti-TNF therapy, unmet needs remain, including an unacceptable side-effect profile in some patients, lack of primary efficacy, loss of efficacy, and immunogenicity with these agents in some patients.[4,27-30] Secukinumab showed efficacy among patients who had received previous anti-TNF therapy and those who had received no such therapy, although improvements were smaller among patients who had received previous anti-TNF therapy.

The safety profile of secukinumab was consistent with the findings in previous studies involving patients with psoriatic arthritis and moderate-to-severe plaque psoriasis.[13,31] Elevated cardiovascular risk among patients with psoriatic arthritis has been reported previously.[32-34] In our study, two patients who were receiving secukinumab had a myocardial infarction and four had a stroke (mean exposure to secukinumab across the study, 438.5 days). No myocardial infarctions or strokes were observed in the placebo group during the shorter placebo-controlled period (mean exposure, 128.5 days). Consistent with observations from phase 3 studies involving patients with psoriasis,[13] candida infections were more frequent among patients receiving secukinumab than among those receiving placebo, since interleukin-17 plays a role in host defense against bacterial and fungal infections, particularly at mucosal sites.[35]

Table 3. Adverse Events through Week 16 (Placebo-Controlled Period) and the Entire Safety-Data Period.*

Variable	Through Week 16 (Placebo-Controlled Period)†				Entire Safety-Data Period		
	Secukinumab, 150 mg (N=202)	Secukinumab, 75 mg (N=202)	Any Secukinumab (N=404)	Placebo (N=202)	Secukinumab, 150 mg (N=295)	Secukinumab, 75 mg (N=292)	Any Secukinumab (N=587)
	no. of patients (%)				*no. of patients (no. of events/100 patient-yr)*		
Any adverse event	131 (64.9)	122 (60.4)	253 (62.6)	118 (58.4)	243 (229.0)	228 (183.2)	471 (204.3)
Any serious adverse event‡	9 (4.5)	5 (2.5)	14 (3.5)	10 (5.0)	38 (11.5)	25 (7.4)	63 (9.4)
Myocardial infarction	0	0	0	0	1 (0.3)	1 (0.3)	2 (0.3)
Stroke	0	1 (0.5)	1 (0.2)	0	0	4 (1.1)	4 (0.6)
Death	0	0	0	0	0	1	1
Discontinuation of study treatment owing to any adverse event§	3 (1.5)	4 (2.0)	7 (1.7)	5 (2.5)	10 (3.4)‡	13 (4.5)‡	23 (3.9)‡
Infection or infestation	67 (33.2)	53 (26.2)	120 (29.7)	47 (23.3)	166 (81.8)	159 (71.3)	325 (76.3)
Candida infection	2 (1.0)	1 (0.5)	3 (0.7)	0	6 (1.7)	4 (1.2)	10 (1.4)
Common adverse events¶							
Nasopharyngitis	19 (9.4)	14 (6.9)	33 (8.2)	9 (4.5)	46 (14.8)	54 (17.8)	100 (16.3)
Headache	11 (5.4)	11 (5.4)	22 (5.4)	6 (3.0)	23 (6.9)	25 (7.7)	48 (7.3)
Upper respiratory tract infection	13 (6.4)	9 (4.5)	22 (5.4)	10 (5.0)	49 (15.5)	43 (13.4)	92 (14.5)
Hypercholesterolemia	6 (3.0)	8 (4.0)	14 (3.5)	5 (2.5)	9 (2.6)	11 (3.3)	20 (2.9)
Diarrhea	6 (3.0)	4 (2.0)	10 (2.5)	6 (3.0)	17 (5.0)	13 (3.8)	30 (4.4)
Hypertension	3 (1.5)	7 (3.5)	10 (2.5)	5 (2.5)	13 (3.8)	19 (5.7)	32 (4.7)
Nausea	4 (2.0)	5 (2.5)	9 (2.2)	2 (1.0)	7 (2.0)	13 (3.8)	20 (2.9)
Back pain	3 (1.5)	5 (2.5)	8 (2.0)	2 (1.0)	17 (5.0)	23 (6.9)	40 (5.9)

* During the placebo-controlled period, the mean (±SD) exposure to a study drug was 113.0±16.1 days in the group receiving 150 mg of secukinumab, 112.3±15.6 days in the group receiving 75 mg of secukinumab, and 110.3±14.6 days in the group receiving placebo. The safety-data period was defined as the period from baseline through the week 52 visit of the last patient (maximum secukinumab exposure, 103 weeks; mean and median exposure, 438.5 days and 456 days, respectively). In the analysis of the entire study period, the secukinumab groups include any patients who received the stated dose of secukinumab and those who were randomly assigned to the placebo group at baseline and who underwent a second randomization to active treatment at week 16 or 24.

† In the efficacy analyses, the placebo-controlled period included data through week 24, with imputation for patients who switched to active treatment at week 16. In the safety analyses, the placebo-controlled period included data only through week 16, when patients received the originally assigned study medication.

‡ A list of the most common serious adverse events is provided in Table S3 in the Supplementary Appendix.

§ Exposure-adjusted incidence rates were not calculated for study-drug discontinuations owing to adverse events. Percentages are shown, as indicated.

¶ The most common adverse events, which are expressed according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, were reported in at least 2% of patients in the pooled secukinumab groups through week 16.

Several different statistical methods have been applied to trials involving patients with psoriatic arthritis. We used a rigorous assessment of efficacy at week 24, with the imputation of missing data as no response, which provided a conservative estimate. One limitation of our study is that it did not include assessment of axial disease. In addition, the use of the same high intravenous loading dose in the two secukinumab groups made it difficult to identify any potential dose–response relationships. For ethical reasons and consistent with clinical trials of other biologic agents, the placebo-controlled period of this trial was short. Thus, the long-term efficacy and safety of secukinumab as compared with placebo cannot be determined.

In conclusion, the use of secukinumab showed efficacy in the key clinical domains of psoriatic arthritis. Adverse events that were associated with secukinumab included infections and cardiovascular events. Longer and larger studies will be required to assess uncommon serious adverse effects and adverse effects associated with long-term use of secukinumab. These results suggest an important role for interleukin-17A in the pathogenesis of psoriatic arthritis and validate inhibition of this cytokine as a therapeutic approach in this disease.

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