The Journal of Rheumatology 2022;49:894–902
doi:10.3899/jrheum.210912
First Release June 1 2022

The Journal of Rheumatology

Secukinumab in United States Biologic-Naïve Patients With Psoriatic Arthritis: Results From the Randomized, Placebo-Controlled CHOICE Study

Tien Nguyen[1], Melvin Churchill[2], Robert Levin[3], Guillermo Valenzuela[4], Joseph F. Merola[5], Alexis Ogdie[6], Ana-Maria Orbai[7], Jose U. Scher[8], Arthur Kavanaugh[9], Farid Kianifard[10], Chauncy Rollins[10], Renato Calheiros[10], and Olivier Chambenoit[10]

ABSTRACT. ***Objective***. To evaluate secukinumab (SEC) 300 mg and 150 mg vs placebo in a United States–only population of biologic-naïve patients with psoriatic arthritis (PsA).

Methods. CHOICE was a double-blind, randomized controlled trial conducted in the US. Biologic-naïve patients with PsA and psoriasis (PsO) were randomized 2:2:1 to SEC 300 mg (n = 103), SEC 150 mg (n = 103), or placebo (n = 52). The primary objective was to show superiority of SEC 300 mg vs placebo in American College of Rheumatology 20% (ACR20) response at week 16. Additional objectives included the effect of SEC on dactylitis, enthesitis, PsO, and safety.

Results. ACR20 response rates at week 16 were higher with SEC 300 mg than with placebo (51.5% vs 23.1%; odds ratio 3.51 [95% CI 1.65-7.45]; $P = 0.001$). SEC 300 mg also led to greater ACR50/70 responses and improvements in other variables vs placebo. Responses were generally sustained over time. Patients with inadequate response to SEC 150 mg at weeks 16, 28, or 40 who received dose escalation to 300 mg experienced improved clinical response after uptitration. The most common adverse events were upper respiratory tract infections and diarrhea. No inflammatory bowel disease was reported or new safety signals observed.

Conclusion. SEC 300 mg led to rapid and significant improvements over placebo in symptoms of PsA in this heavier population of US-only, biologic-naïve patients. Findings were consistent with previous studies and suggest that SEC 300 mg is a safe and efficacious first-line biologic treatment for patients with PsA. [ClinicalTrials.gov: NCT02798211]

Key Indexing Terms: biologicals, IL-17 inhibitors, psoriasis, psoriatic arthritis

This work was supported by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

[1]T. Nguyen, MD, First OC Dermatology, Irvine, California; [2]M. Churchill, MD, Arthritis Center of Nebraska, Lincoln, Nebraska; [3]R. Levin, MD, Clinical Research of West Florida, Inc., Clearwater, Florida, and University of South Florida, Tampa, Florida; [4]G. Valenzuela, MD, Integral Rheumatology & Immunology Specialists, Plantation, Florida, USA; [5]J.F. Merola, MD, Department of Dermatology and Medicine, Division of Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [6]A. Ogdie, MD, MSCE, Department of Medicine/Rheumatology and Department of Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; [7]A.M. Orbai, MD, MHS, Division of Rheumatology, Psoriatic Arthritis Program, Johns Hopkins University School of Medicine, Baltimore, Maryland; [8]J.U. Scher, MD, Division of Rheumatology, New York University School of Medicine and NYU Langone Orthopedic Hospital, New York, New York; [9]A. Kavanaugh, MD, Division of Rheumatology, Allergy and Immunology, Department of Medicine, University of California, San Diego, La Jolla, California; [10]F. Kianifard, PhD, C. Rollins, MS, R. Calheiros, MD, O. Chambenoit, PhD, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA.

TN has served as a consultant for AbbVie, Amgen, BMS, Celgene, Corrona, Lilly, Janssen, Novartis, Pfizer, Sanofi Regeneron, and UCB; as an investigator for AbbVie, Amgen, BMS, Biogen, Lilly, GSK, Merck, Novartis, Pfizer, and Sanofi Regeneron; and as a speaker for AbbVie, Almirall, Amgen, Celgene, Lilly, Novartis, Pfizer, Sanofi Regeneron, and Sun Pharma. MC has served as a clinical investigator for Novartis. RL has served as a consultant for Gilead and Myriad Genetics; has conducted clinical trials for AbbVie, Amgen, Lilly, Pfizer, Sanofi, and UCB; and is a speaker for AbbVie, BMS, and Sanofi. GV has served as a consultant for AbbVie, Celgene, GSK, Janssen, Lilly, Merck, Mallinckrodt Pharmaceuticals, Novartis, Pfizer, Sanofi Regeneron, and UCB; and as investigator for BMS, Lilly, Merck, Mallinckrodt Pharmaceuticals, Novartis, Pfizer, and Sanofi Regeneron. JFM has served as a consultant for AbbVie, Biogen, Celgene, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Biosplice Therapeutics, Sanofi Regeneron, Science 37, and UCB; as an investigator for Biogen, Incyte, Novartis, Pfizer, and Sanofi Regeneron; and as a speaker for AbbVie. AO has served as a consultant for AbbVie, Amgen, BMS, Celgene, Corrona, Lilly, Novartis, and Pfizer; has received research funding from Novartis and Pfizer to the University of Pennsylvania and from Amgen to Forward/NDB; has served as a speaker for AbbVie, Amgen, and Celgene; and her husband has received royalties from Novartis related to a patent. AMO has received research grants to Johns Hopkins University from AbbVie, Amgen, Celgene, Horizon, Janssen, Lilly, and Novartis; and consulting fees from BMS, Janssen, Lilly, Novartis, Pfizer, and UCB. JUS has received grant support from Novartis, Janssen and Pfizer; and consulting fees from AbbVie, Amgen, BMS, Janssen, Lilly, Novartis, Pfizer, and UCB. AK has served as a consultant for and conducted clinical research sponsored by Novartis. FK, CR, RC, and OC are employees and stockholders of Novartis Pharmaceuticals Corporation.

Address correspondence to Dr. T.Q. Nguyen, First OC Dermatology, 17305 Von Karman Avenue, Suite 107, Irvine, CA 92614, USA.
Email: tiennguyenmd82@gmail.com.

Accepted for publication April 5, 2022.

Psoriatic arthritis (PsA) is a chronic inflammatory disease that occurs in up to 30% of patients with psoriasis (PsO)[1,2] and is associated with functional disability and reduced quality of life.[3-5] The disease is progressive and, if untreated, can result in destruction of cartilage and bone as well as new bone formation, leading to permanent joint damage.[6,7] Patients can experience peripheral arthritis, dactylitis, enthesitis, axial involvement, and/or skin and nail PsO.[8] Additionally, patients with PsA are at an increased risk of several comorbidities, such as obesity and diabetes, which correlate with disease severity.[9]

Secukinumab (SEC), a human monoclonal antibody that selectively targets interleukin 17A, has proven to be efficacious and safe for the treatment of PsA.[10-14] Responses to therapy include resolution of enthesitis and dactylitis; improvement in skin and nail PsO and in axial manifestations of PsA[10-16]; and prevention of radiographic progression in these patients,[14] and response rates were sustained through 5 years.[17] Overall, SEC was well tolerated and demonstrated a favorable safety profile.[10-14] However, US patients were a minority of those enrolled in these studies. Additionally, US patients in these studies had a baseline clinical profile indicating harder-to-treat disease than the total study population, including higher BMI, higher tender and swollen joint counts, increased prevalence of enthesitis and dactylitis, and more tumor necrosis factor inhibitor (TNFi) experience.[11-14,18]

To gather additional data on the effect of SEC in US biologic-naïve patients with PsA and psoriatic skin lesions, the CHOICE study evaluated the efficacy and safety of SEC 300 mg and 150 mg vs placebo. We report primary findings and 52-week results of the CHOICE study.

METHODS

Study design and participants. CHOICE was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase IV trial that evaluated the efficacy and safety of SEC vs placebo in treating patients with PsA (ClinicalTrials.gov: NCT02798211). The study was conducted from July 20, 2016, to October 1, 2018, in 67 centers in the US, was approved by a central institutional review board (IRB; Chespeake IRB, now Advarra; IRB#00000971) and by the IRB or independent ethics committee at each participating institution, and was conducted in accordance with the Declaration of Helsinki. Patients were recruited over a 15-month period beginning July 2016 and provided written informed consent before starting any study-related procedures. Eligible patients had moderate to severe active PsA by the Classification Criteria for Psoriatic Arthritis, with symptoms for ≥ 6 months, the presence of ≥ 3 tender joints of 78 and ≥ 3 swollen joints of 76, and psoriatic skin lesions with a Psoriasis Area and Severity Index (PASI) ≥ 1. Patients with active ongoing inflammatory diseases other than PsA were excluded from this study. Previous treatment with any biologic agent was not permitted, and disease-modifying antirheumatic drugs other than methotrexate (MTX) were discontinued 4 weeks prior to randomization (8 weeks for leflunomide). Investigational treatments were prohibited.

Patients were randomized 2:2:1 to receive SEC 300 mg, SEC 150 mg, or placebo. Patients received treatment every 4 weeks (Q4W) to week 16, with a weekly loading phase from baseline to week 4 (treatment period 1). At week 16, patients randomized to SEC 300 mg continued receiving the same dose and patients randomized to placebo began receiving SEC 300 mg Q4W to week 52 (treatment period 2). Patients receiving SEC 150 mg who achieved < 20% improvement from baseline in both tender and swollen joint counts (nonresponders) at weeks 16, 28, or 40 started receiving SEC 300 mg Q4W, while responders continued receiving SEC 150 mg Q4W to week 52. Patients were allowed concomitant treatment with nonsteroidal antiinflammatory drugs or corticosteroids (≤ 10 mg/day prednisone or equivalent) up to week 16, or with MTX (≤ 25 mg/week) up to week 52, provided the dose was stable.

Objectives and outcomes. The primary objective was to show superiority of SEC 300 mg vs placebo based on the proportion of patients achieving 20% improvement in the American College of Rheumatology score (ACR20) at week 16. Secondary objectives included the evaluation of efficacy of SEC 150 mg vs placebo based on the proportion of patients achieving ACR20 at week 16, and to evaluate the efficacy of SEC 300 mg and 150 mg vs placebo based on the proportion of patients achieving ACR50; ACR70; resolution of dactylitis (based on the Leeds Dactylitis Index [LDI]); resolution of enthesitis (based on the combined Leeds Enthesitis Index [LEI] and Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index); minimal disease activity (MDA); 75%, 90%, or 100% improvement from baseline in PASI (PASI75, PASI90, and PASI100, respectively); change from baseline in Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP); Psoriatic Arthritis Disease Activity Score (PASDAS); and Health Assessment Questionnaire–Disability Index (HAQ-DI). Exploratory objectives included achievement of ACR20/50/70, low disease activity (DAS28-CRP < 2.6), and HAQ-DI responses through week 52, as well as change from baseline over time in DAS28-CRP, HAQ-DI score, PASDAS, dactylitis count, enthesitis count, and the Multidimensional HAQ/Routine Assessment of Patient Index Data 3 (RAPID3). Subgroup analyses evaluating the efficacy of SEC by MTX use (yes or no), BMI (calculated as weight in kilograms divided by height in meters squared; ≤ 30 or > 30), and number of tender and swollen joints (< 10 or ≥ 10) at baseline were also conducted. Safety and tolerability of SEC were assessed during the 52-week study by monitoring adverse events (AEs), serious AEs, laboratory assessments, and vital signs.

Statistical analysis. The sample size was calculated based on ACR20 response for the primary comparison. ACR20 response rates of 50% for SEC 300 mg and 20% for placebo (odds ratio [OR] of 4) at week 16 were assumed. Using a continuity-corrected chi-square test, an allocation ratio of 2:1, a 2-sided significance level of 0.05, and a power of 0.90, approximately 88 patients in the SEC 300-mg group and 44 patients in the placebo group were needed. Assuming a loss to follow-up rate of 10% and a 2:2:1 allocation ratio, the total number of randomized patients was approximately 250 (100 receiving SEC 300 mg, 100 receiving SEC 150 mg, and 50 receiving placebo).

All statistical tests were conducted against a 2-sided alternative hypothesis, using a significance level of 0.05. Comparative efficacy analyses focused on the first 16 weeks of treatment (placebo-controlled period) and were performed based on the full analysis set. The primary efficacy variable (ACR20 response) was analyzed at week 16 using a logistic regression model with treatment (3 treatment groups), MTX use at baseline (yes, no), and body weight (in kg) as explanatory variables; nonresponder imputation was used for missing values. The percentages of patients achieving ACR20 at each timepoint up to week 16 were also estimated using multiple imputation. This analysis was also performed for binary secondary and exploratory efficacy variables using nonresponder imputation. No adjustment for multiple comparisons was made, and *P* values resulting from analyses addressing the secondary and exploratory objectives should be considered nominal.

The changes from baseline at each timepoint through week 16 for all continuous secondary and exploratory efficacy variables were assessed using an analysis of covariance model with treatment, baseline, MTX use at baseline, and body weight as explanatory variables; missing data were imputed using last observation carried forward. Analyses for dactylitis included patients with an LDI ≥ 1 at baseline, and analyses of enthesitis included patients who had an enthesitis score ≥ 1 when sites from LEI and SPARCC were assessed together at baseline. Analyses of PASI75/90/100 responses included patients with ≥ 3% of their body surface area affected by psoriatic skin involvement at baseline.

All safety analyses were performed on all patients who received ≥ 1 dose of study medication. Treatment-emergent AEs, serious AEs, and risks based on AEs were summarized.

RESULTS

Patients. A total of 258 patients were randomized to receive SEC 300 mg (n = 103), SEC 150 mg (n = 103), or placebo (n = 52; Figure 1). At week 52, a higher proportion of patients in the SEC 300-mg group completed treatment period 2 (80.6%) compared with patients in the SEC 150-mg group (74.8%) and those who were originally randomized to placebo and switched to SEC 300 mg after week 16 (76.9%). The main reasons for discontinuation in treatment period 1 were withdrawal of informed consent (300 mg, 1.9%; 150 mg, 6.8%; placebo, 5.8%) and loss to follow-up (300 mg, 1.9%; 150 mg, 1.0%; placebo, 0%). The main reasons for discontinuation in treatment period 2 were withdrawal of informed consent (300 mg, 1.0%; 150 mg, 3.9%; placebo-to-300 mg, 5.8%) and AEs (300 mg, 4.9%; 150 mg, 1.9%; placebo-to-300 mg, 0%).

The age of patients at baseline ranged from 19 to 82 years and the mean time since diagnosis of PsA ranged from 3.0 to 3.9 years (Table 1). The mean baseline BMI of patients was > 30 in all treatment groups, indicating an obese population. Most patients (73.3%) had enthesitis, and 48.1% had dactylitis. Approximately one-third of patients were receiving MTX at baseline.

Efficacy. The study met its primary objective, with a greater percentage of patients treated with SEC 300 mg achieving an ACR20 response at week 16 vs placebo (51.5% vs 23.1% using nonresponder imputation); the OR of 3.51 was statistically significant (95% CI 1.65-7.45; $P = 0.001$; Figure 2A). SEC 150 mg led to a numerically higher ACR20 response rate (36.9%) than placebo, although the OR of 1.92 was not statistically significant (95% CI 0.89-4.15; $P = 0.10$; Figure 2A). Results were similar when multiple imputation was used (SEC 300 mg, 55.0%; SEC 150 mg, 38.2%; placebo, 23.1%).

SEC also led to higher ACR50 (Figure 2B) and ACR70 (Figure 2C) response rates at week 16 than placebo. ACR50 response rates were higher with significant ORs for SEC 300 mg (28.2%; OR 6.30, 95% CI 1.81-21.88; $P = 0.004$) and SEC 150 mg (24.3%; OR 4.77, 95% CI 1.36-16.77; $P = 0.02$) vs placebo (5.8%; Figure 2B). Both SEC doses led to higher ACR70 response rates than placebo, although only SEC 300 mg resulted in a significant OR (17.5% vs 1.9%; OR 10.50, 95% CI 1.36-81.30; $P = 0.02$; Figure 2C). Overall, ACR20/50/70 and Disease Activity in Psoriatic Arthritis–based remission or low disease activity response rates with SEC at week 16 were higher in patients who had < 10 tender joints and < 10 swollen joints at baseline than in those with more swollen and tender joints (Supplementary Tables S1-S2, available with the online version of this article).

When assessed by concomitant MTX use at baseline (no MTX vs MTX), ACR20 response rates at week 16 were comparable in both SEC groups; in contrast, patients in the placebo group who received MTX had higher response rates than those who received placebo alone (38.9% vs 14.7%; Supplementary Figure S1, available with the online version of this article). No consistent patterns of differences were observed in ACR50 or ACR70 response rates by baseline MTX use. A greater percentage of patients treated with SEC vs placebo had resolution of enthesitis at week 16 based on the combined LEI and SPARCC, with a significant OR (SEC 300 mg, 37.8% vs 17.9%, OR 2.85 [95% CI 1.08-7.50], $P = 0.03$; SEC 150 mg, 39.5% vs 17.9%, OR 2.65 [95% CI 1.01-6.93]; $P = 0.047$; Table 2). Treatment with SEC also resulted in numerically higher rates of

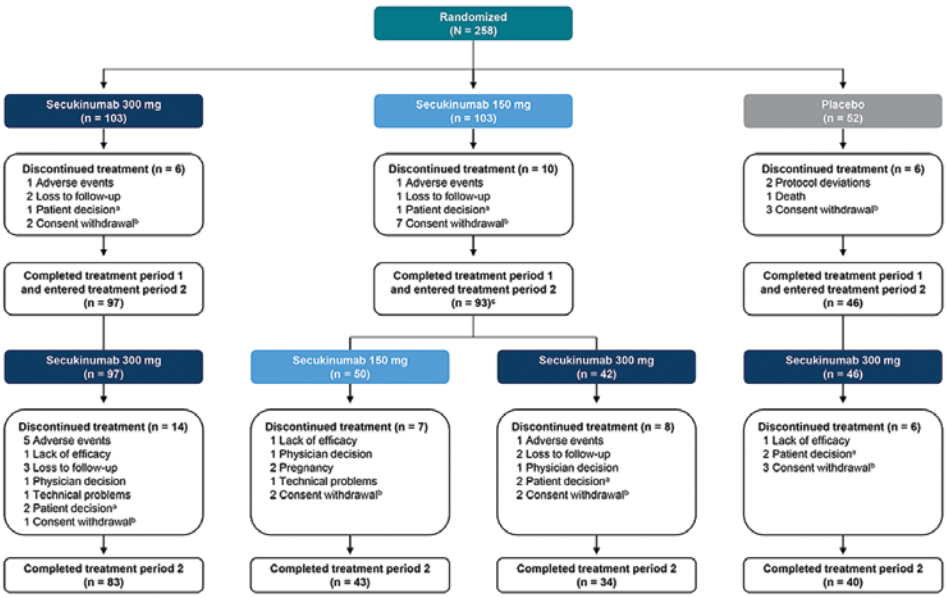

Figure 1. Patient disposition. [a] Patients who discontinued study treatment were considered to have withdrawn due to patient decision if other possible underlying causes such as adverse events or lack of efficacy were excluded. [b] Patients who chose to stop participating in the study and wanted no further visits or assessments and no further study-related contact were considered to have withdrawn consent. [c] One patient discontinued treatment period 2 before receiving study drug due to a positive pregnancy test.

Table 1. Patient characteristics at baseline.

	SEC 300 mg, n = 103	SEC 150 mg, n = 103	Placebo, n = 52
Age, yrs			
Mean (SD)	51.9 (12.6)	51.3 (14.6)	53.1 (12.7)
Median (min, max)	53.0 (29, 82)	52.0 (19, 80)	56.0 (20, 74)
Male sex, n (%)	53 (51.5)	56 (54.4)	23 (44.2)
Race, n (%)			
White	88 (85.4)	88 (85.4)	45 (86.5)
Black	2 (1.9)	2 (1.9)	3 (5.8)
Asian	9 (8.7)	10 (9.7)	1 (1.9)
Native American	0	1 (1.0)	1 (1.9)
Pacific Islander	1 (1.0)	1 (1.0)	0
Other	2 (1.9)	0	2 (3.8)
Unknown	1 (1.0)	1 (1.0)	0
Weight, kg, mean (SD)	93.4 (23.0)	86.9 (23.3)	97.2 (26.5)
BMI, kg/m^2, mean (SD)	32.8 (8.2)	30.7 (7.6)	34.1 (7.8)
10th percentile	23.7	21.9	24.9
25th percentile	26.4	25.4	27.8
50th percentile	32.4	29.0	32.4
75th percentile	38.1	35.1	40.7
90th percentile	42.8	40.7	44.9
Time since first PsA diagnosis, yrs, mean (SD)	3.0 (4.4)	3.8 (5.6)	3.9 (5.0)
Methotrexate use, n (%)	34 (33.0)	23 (22.3)	18 (34.6)
Dose, mg/week, mean (SD)	17.1 (4.6)	16.4 (4.2)	16.3 (6.1)
Corticosteroid use, n (%)	12 (11.7)	11 (10.7)	3 (5.8)
NSAID use, n (%)	33 (32.0)	35 (34.0)	18 (34.6)
Presence of dactylitis, LDI, n (%)	49 (47.6)	52 (50.5)	23 (44.2)
Presence of enthesitis, SPARCC + LEI, n (%)	74 (71.8)	76 (73.8)	39 (75.0)
TJC78, mean (SD)	27.1 (19.6)	25.6 (18.6)	25.2 (15.0)
SJC76, mean (SD)	17.7 (16.4)	14.4 (13.9)	13.8 (11.9)
PASI score, mean (SD)	8.3 (8.0)	9.0 (10.0)	5.9 (5.4)
DAS28-CRP score, mean (SD)	4.9 (1.2)	4.7 (1.3)	5.0 (1.1)
PASDAS score, mean (SD)	6.2 (1.3)	6.0 (1.3)	6.2 (1.3)
SF-12 MCS, mean (SD)	46.5 (11.0)	45.7 (10.8)	46.0 (11.6)
SF-12 PCS, mean (SD)	36.9 (10.1)	38.3 (9.7)	35.9 (8.8)
HAQ-DI, mean (SD)	1.1 (0.6)	1.0 (0.6)	1.3 (0.7)
RAPID3, mean (SD)	14.6 (5.6)	13.9 (5.7)	15.6 (5.7)

DAS28-CRP: Disease Activity Score in 28 joints using C-reactive protein; HAQ-DI: Health Assessment Questionnaire–Disability Index; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; NSAID: nonsteroidal antiinflammatory drug; MCS: mental component summary score; PASI: Psoriasis Area and Severity Index; PASDAS: Psoriatic Arthritis Disease Activity Score; PCS: physical component summary score; PsA: psoriatic arthritis; RAPID3: Routine Assessment of Patient Index Data 3; SF-12: 12-item Short Form Health Survey; SEC: secukinumab; SJC76: swollen joint count in 76 joints; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Index; TJC78: tender joint count in 78 joints.

resolution of dactylitis than placebo, although the ORs were not significant. Patients treated with SEC had substantial improvements in PsO and achieved higher PASI75/90/100 response rates than patients taking placebo, with significant ORs. SEC also led to improvements in other secondary and exploratory efficacy variables vs placebo, including MDA, DAS28-CRP, and PASDAS (Table 2). Patients receiving either dose of SEC experienced significant improvements vs those taking placebo as measured by RAPID3 at week 16 (SEC 300 mg, least-squares mean [LSM] of treatment difference −3.80 [95% CI −5.65 to −1.94], $P < 0.001$; SEC 150 mg, LSM of treatment difference −2.89 [95% CI −4.78 to −1.00]; $P = 0.003$). Sustained clinical responses in several efficacy variables were seen with continued SEC treatment to week 52 (Figure 2; Supplementary Table S3, available with the online version of this article).

In addition, the proportion of patients achieving ACR responses at any timepoint between weeks 16 and 52 increased in patients for whom SEC was uptitrated from 150 mg to 300 mg (Figure 3A). Before uptitration, only 2.4% of patients in the uptitration subset had achieved an ACR20 response; this proportion increased to 65.9% after dose escalation. Additionally, although no patients in the uptitration subset had achieved an ACR50 or ACR70 response before uptitration, 34.1% of patients achieved an ACR50 response following uptitration, and 12.2% achieved an ACR70 response. Improvements were also observed in dactylitis, enthesitis, and MDA in patients with uptitration,

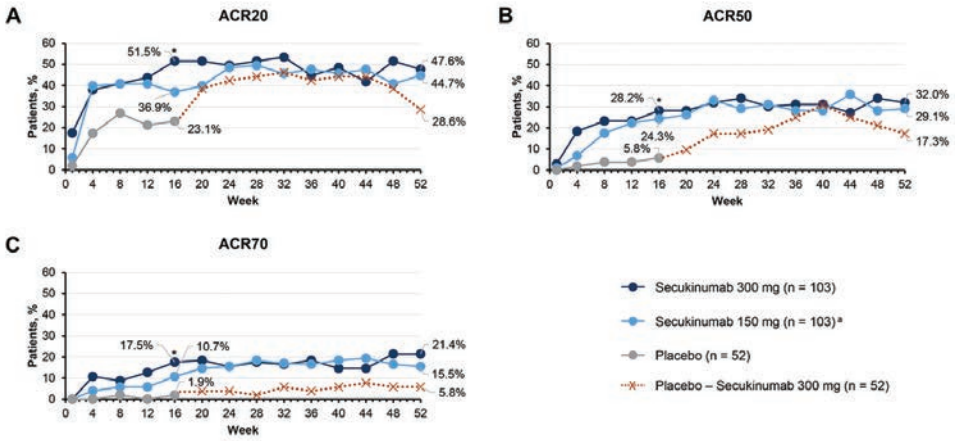

Figure 2. (A) ACR20, (B) ACR50, and (C) ACR70 response rates through week 52. [a] Includes patients with uptitration to secukinumab 300 mg at weeks 16, 28, or 40. * $P < 0.05$; statistically significant odds ratio in favor of secukinumab dose vs placebo based on logistic regression using nonresponder imputation. ACR: American College of Rheumatology.

with response rates increasing almost 2-fold after uptitration (Figure 3B-D). Interestingly, 11.9% of patients with uptitration (those who had not achieved ≥ 20% improvement from baseline in both tender and swollen joint counts) were classified as being in MDA at the time of dose escalation; the proportion in MDA increased to 31.0% after uptitration, between weeks 16 and 52. Most patients (83.3%) achieved dactylitis resolution after dose escalation, compared with 44.4% who achieved response prior to uptitration. Similarly, patients initially receiving placebo had increased ACR20/50/70 response rates after switching to SEC 300 mg (Figure 2).

Efficacy by BMI subgroups. Given that the mean BMI at baseline indicated an obese patient population, the efficacy of SEC was evaluated in patients with BMI ≤ 30 and in those with BMI > 30. SEC led to achievement of ACR20/50/70 responses in both subgroups, regardless of BMI at baseline, and these responses were sustained from week 16 to week 52 (Supplementary Figure S2, available with the online version of this article). However, ACR50 and ACR70 response rates at week 52 were numerically lower in patients with BMI > 30 than in those with BMI ≤ 30. An analysis of PASI response by BMI subgroups was also conducted (Supplementary Figure S3). PASI responses, including PASI100 responses, were achieved by patients receiving SEC regardless of BMI at baseline, although patients with BMI > 30 had numerically lower PASI responses at week 16 than those with BMI ≤ 30.

Safety. The most commonly reported AEs up to week 16 were diarrhea (SEC 300 mg, 5.8%; SEC 150 mg, 5.8%; placebo, 1.9%), hypertension (300 mg, 4.9%; 150 mg, 3.9%; placebo, 0%), and upper respiratory tract infections (300 mg, 5.8%; 150 mg, 1.9%; placebo, 0%; Table 3). Most AEs were mild (SEC 300 mg, 30.1%; SEC 150 mg, 35.9%; placebo, 38.5%) or moderate (300 mg, 23.3%; 150 mg, 20.4%; placebo, 11.5%). By week 16, serious AEs were reported in 2 patients in each treatment group (SEC 300 mg, 1.9%; SEC 150 mg, 1.9%; placebo, 3.8%; Table 3 and Supplementary Table S4, available with the online version of this article). At week 16, 1 patient in the SEC 300-mg group and 1 patient in the SEC 150-mg group had discontinued due to PsO.

Throughout the 52-week study, the most common AEs in patients receiving SEC were upper respiratory tract infection (any SEC 300-mg group, 13.7%; any SEC 150-mg group, 13.6%) and diarrhea (any SEC 300-mg group, 7.6%; any SEC 150-mg group, 6.8%; Supplementary Table S5, available with the online version of this article). At week 52, serious AEs were reported in 9.6% of patients in the any SEC 300-mg group and in 7.8% of patients in the any SEC 150-mg group (Supplementary Table S5). *Candida* infection through week 52 was reported in 0.5% of patients in the SEC 300-mg group and 1.9% of patients in the SEC 150-mg group. There was 1 report of myocardial infarction in a patient receiving SEC 150 mg, and 1 report of ischemic stroke during placebo treatment in a patient included in the week 52 SEC 300-mg group. Transient Common Terminology Criteria for Adverse Events grade 2 neutropenia was reported in 1 patient (SEC 300-mg group), during 1 visit, and was not associated with concomitant infection. One case of breast cancer and 1 case of prostate cancer occurred in patients treated with SEC 300 mg (Supplementary Tables S5-S6). No cases of inflammatory bowel disease (Crohn disease or ulcerative colitis) or tuberculosis were reported in any group throughout the study. Among the observed cases of diarrhea, none were hemorrhagic. Serious AEs through week 52 are listed in Supplementary Table S6. The most frequently reported types of serious AEs through week 52 were infections (any SEC 300-mg group, 2.5%; any SEC 150-mg group, 1.9%) and nervous system disorders (including syncope, cerebral cyst, ischemic stroke, and seizure; any SEC 300-mg group, 2.5%; any SEC 150-mg group, 1.0%). Over the entire treatment period, AEs leading to treatment discontinuation were reported in 8 patients (4.1%) receiving any SEC 300-mg dose and 1 patient (1.0%) receiving any SEC 150-mg dose. One death, due to cardiac arrest, was reported in a patient who received placebo prior to week 16 and who was randomized to but did not yet receive SEC 300 mg; no other deaths were reported.

Table 2. Summary of primary and key secondary and exploratory efficacy results at week 16[a].

Outcome	Placebo, n = 52, n/N (%)	SEC, 300 mg, n = 103, n/N (%)	OR (95% CI)	*P*	SEC 150 mg, n = 103, n/N (%)	OR (95% CI)	*P*
Primary efficacy variable							
ACR20	12/52 (23.1)	53/103 (51.5)	3.51 (1.65-7.45)	0.001	38/103 (36.9)	1.92 (0.89-4.15)	0.10
Secondary binary efficacy variables							
ACR50	3/52 (5.8)	29/103 (28.2)	6.30 (1.81-21.88)	0.004	25/103 (24.3)	4.77 (1.36-16.77)	0.02
ACR70	1/52 (1.9)	18/103 (17.5)	10.50 (1.36-81.30)	0.02	11/103 (10.7)	5.42 (0.67-43.64)	0.11
Resolution of enthesitis, LEI + SPARCC[b]	7/39 (17.9)	28/74 (37.8)	2.85 (1.08-7.50)	0.03	30/76 (39.5)	2.65 (1.01-6.93)	0.047
Resolution of dactylitis[c]	4/23 (17.4)	20/49 (40.8)	3.27 (0.96-11.20)	0.06	20/52 (38.5)	3.40 (0.98-11.76)	0.05
PASI75[d]	7/43 (16.3)	51/79 (64.6)	9.49 (3.73-24.16)	< 0.001	45/83 (54.2)	6.38 (2.51-16.24)	< 0.001
PASI90[d]	4/43 (9.3)	39/79 (49.4)	9.86 (3.19-30.45)	< 0.001	30/83 (36.1)	5.21 (1.68-16.21)	0.004
PASI100[d]	1/43 (2.3)	20/79 (25.3)	14.38 (1.86-111.53)	0.01	15/83 (18.1)	9.82 (1.24-77.90)	0.03
MDA	2/52 (3.8)	27/103 (26.2)	8.75 (1.99-38.45)	0.004	27/103 (26.2)	8.34 (1.89-36.85)	0.005
	Placebo, LSM, n = 52	SEC 300 mg, LSM, n = 103	LSM of Treatment Difference, (SE)[e] [95% CI]	*P*	SEC 150 mg, LSM, n = 103	LSM of Treatment Difference, (SE)[e] [95% CI]	*P*
Secondary and exploratory continuous efficacy variables[f]							
Change from baseline in DAS28-CRP	−0.35	−1.39	−1.05 (0.203) [−1.45 to −0.65]	< 0.001	−1.18	−0.83 (0.207) [−1.24 to −0.43]	< 0.001
Change from baseline in PASDAS	−0.36	−1.04	−0.68 (0.085) [−0.85 to −0.52]	< 0.001	−0.92	−0.57 (0.086) [−0.74 to −0.40]	< 0.001
Change from baseline in SF-12 MCS	1.54	3.05	1.51 (1.334) [−1.12 to 4.14]	0.26	1.77	0.23 (1.353) [−2.43 to 2.90]	0.86
Change from baseline in SF-12 PCS	−0.63	4.82	5.45 (1.363) [2.76 to 8.13]	< 0.001	4.32	4.94 (1.385) [2.22 to 7.67]	< 0.001
Change from baseline in HAQ-DI	−0.11	−0.32	−0.21 (0.081) [−0.37 to −0.05]	0.01	−0.24	−0.13 (0.083) [−0.30 to 0.03]	0.11
Change from baseline in RAPID3	−0.78	−4.57	−3.80 (0.941) [−5.65 to −1.94]	< 0.001	−3.67	−2.89 (0.960) [−4.78 to −1.00]	0.003

[a] ORs, 95% CIs, and *P* values are based on logistic regression using nonresponder imputation. [b] Results are from the combined LEI and SPARCC subset. Enthesitis was determined in patients who had an enthesitis score ≥ 1 when sites from LEI and SPARCC were assessed together at baseline: SEC 300 mg, n = 74; SEC 150 mg, n = 76; placebo, n = 39. [c] Dactylitis was determined in patients who had a Leeds Dactylitis Index ≥ 1 at baseline: SEC 300 mg, n = 49; SEC 150 mg, n = 52; placebo, n = 23. [d] Results are from patients having psoriatic skin involvement in ≥ 3% of their body surface area at baseline: SEC 300 mg, n = 79; SEC 150 mg, n = 83; placebo, n = 43. [e] LSM of the treatment difference vs placebo. [f] LSM, LSM of treatment differences, 95% CI, and *P* values are based on an ANCOVA model; missing data were imputed using last observation carried forward. ACR: American College of Rheumatology; DAS28-CRP: Disease Activity Score in 28 joints using C-reactive protein; HAQ-DI: Health Assessment Questionnaire–Disability Index; LEI: Leeds Enthesitis Index; LSM: least-squares mean; MCS: mental component summary score; MDA: minimal disease activity; OR: odds ratio; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PCS: physical component summary score; RAPID3: Routine Assessment of Patient Index Data 3; SE: standard error; SEC: secukinumab; SF-12: 12-item Short Form Health Survey; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Index.

DISCUSSION

In this randomized study of biologic-naïve US patients with PsA, SEC 300 mg was superior to placebo in achieving rapid and significant improvements in symptoms of PsA, including achievement of stringent binary outcomes such as ACR50, ACR70, PASI90, PASI100, and MDA. Benefits were also observed with SEC 150 mg, although responses were generally higher with SEC 300 mg. An analysis of ACR responses by baseline MTX use showed higher response rates with SEC 300 mg compared with placebo, regardless of MTX use. Differences between patients receiving SEC vs placebo in achievement of ACR20, a modest outcome compared with ACR50 or ACR70, were greatest among patients not receiving MTX at baseline. Response rates with SEC were higher in patients with a tender or swollen joint count < 10 than in patients with more tender or swollen joints, likely reflecting a patient population with a lower baseline disease activity that was more responsive to treatment.

SEC also led to sustained or improved responses over time. Further, uptitrating the dose of patients to SEC 300 mg led to improvements in ACR and PASI responses, as well as to a greater percentage of patients achieving response in dactylitis, enthesitis, and MDA. These findings show the benefits of dose escalation in patients whose symptoms are not adequately controlled with SEC 150 mg and suggest potential benefit from increasing

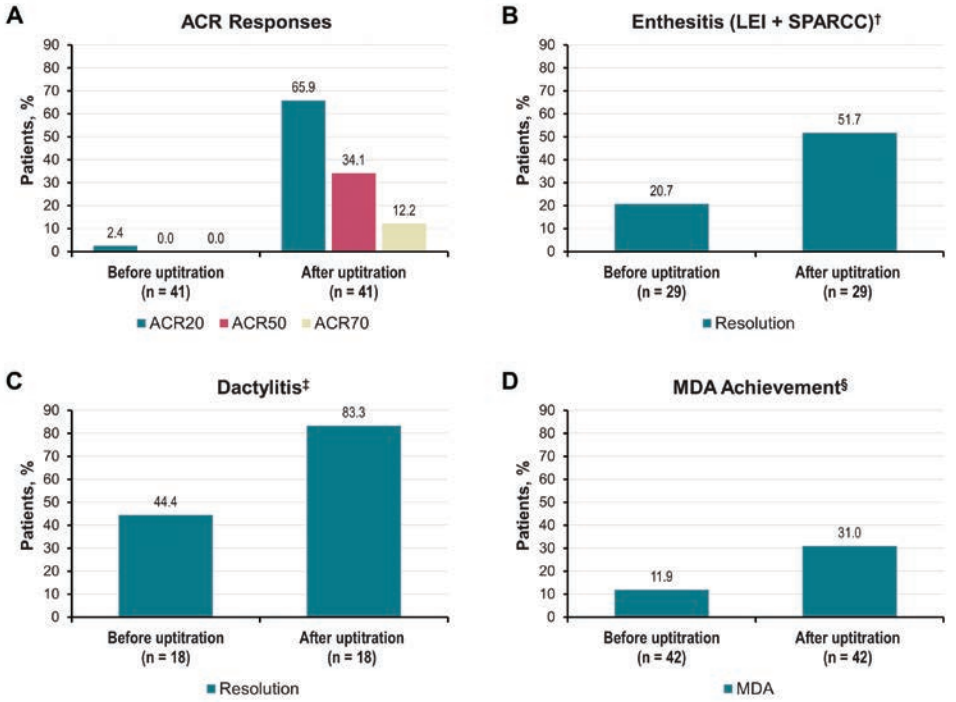

Figure 3. (A) ACR, (B) enthesitis, (C) dactylitis, and (D) MDA responses at any timepoint between weeks 16 and 52 following uptitration from secukinumab 150 mg to 300 mg among nonresponders.[a] [a] Patients defined as nonresponders were those who had < 20% improvement from baseline in both tender and swollen joint counts, at weeks 16, 28, or 40. Unless otherwise noted, these analyses included all patients with uptitration from secukinumab 150 mg to 300 mg and completed the study. [b] Patients included in the LEI + SPARCC subset were included in this analysis. [c] Patients included in the dactylitis subset were included in this analysis. [d] MDA is defined as achievement of ≥ 5 of the following 7 criteria: tender joint count ≤ 1; swollen joint count ≤ 1; Psoriasis Area and Severity Index ≤ 1 or body surface area ≤ 3; patient pain VAS ≤ 15; patient global disease activity VAS ≤ 20; Health Assessment Questionnaire ≤ 0.5; tender entheseal points ≤ 1. ACR: American College of Rheumatology; LEI: Leeds Enthesitis Index, MDA: minimal disease activity; SPARCC: Spondyloarthritis Research Consortium of Canada Enthesitis Index; VAS: visual analog scale.

the dose of SEC over the course of treatment. RAPID3 is a patient-reported outcome developed for the assessment of rheumatoid arthritis disease activity.[19] It is commonly used in clinical practice to assess patients with PsA but has not been evaluated in randomized controlled trials of PsA despite having been evaluated in post hoc analyses and cohort studies.[20,21] Here, RAPID3 improvements from either dose of SEC at week 16 were significant vs placebo.

Overall, ACR response rates in CHOICE were lower than those seen in the TNFi-naïve patient population of the FUTURE studies.[14,22] These findings may have been due to patients in CHOICE having higher disease activity scores at baseline compared with TNFi-naïve patients in the FUTURE studies.[23] For instance, patients in CHOICE had a higher mean tender joint count (SEC 300 mg, 27.1 vs 17.9; SEC 150 mg, 25.6 vs 20.0; placebo, 25.2 vs 19.8) and mean swollen joint count (SEC 300 mg, 17.7 vs 9.3; SEC 150 mg, 14.4 vs 10.6; placebo, 13.8 vs 10.7) compared with patients in the FUTURE studies. More patients in CHOICE had concomitant PsO affecting ≥ 3% of their body surface area compared with TNFi-naïve patients in the FUTURE studies (SEC 300 mg, 76.7% vs 46.8%; SEC 150 mg, 80.6% vs 55.1%; placebo, 82.7% vs 50.5%), suggestive of a more difficult-to-treat disease. Additionally, patients in the CHOICE study were more likely to be obese than TNFi-naïve patients in the FUTURE studies (mean BMI, SEC 300 mg, 32.8 vs 28.7; SEC 150 mg, 30.7 vs 29.2; placebo, 34.1 vs 29.1), which is associated with faster clearance of SEC[24] and with lower treatment responses.[25,26] In our study, SEC led to improvements in symptoms of PsA regardless of BMI, although patients with BMI ≤ 30 treated with SEC had generally higher ACR response rates than those with BMI > 30. Finally, patients with fibromyalgia or osteoarthritis were not excluded and could contribute to lower response rates observed here based on the potential residual effect of noninflammatory disease not targeted by SEC treatment.

The safety profile of SEC in CHOICE was consistent with previous reports.[10-14] AEs were generally mild or moderate and led to few discontinuations; no relation to dose was apparent. No deaths in patients treated with SEC were reported; 1 patient in the placebo group died due to cardiac arrest. *Candida* infections were more common in patients treated with SEC than in those receiving placebo. No cases of inflammatory bowel disease were reported, and no new safety signals were observed.

Overall, the findings from CHOICE were consistent with previous studies and demonstrated that SEC provides significant and sustained improvements in signs and symptoms of PsA.

Table 3. Safety profile of SEC until week 16 (placebo-controlled period)

Patients with AEs, n (%)	SEC 300 mg, n = 103	SEC 150 mg, n = 103	Placebo, n = 52
Any AE	59 (57.3)	61 (59.2)	27 (51.9)
Serious AEs	2 (1.9)	2 (1.9)	2 (3.8)
Death	0	0	1 (1.9)
Discontinuation due to AEs	1 (1.0)	1 (1.0)	0
Common AEs (≥ 3% in any treatment group)			
Diarrhea	6 (5.8)	6 (5.8)	1 (1.9)
Upper respiratory tract infection	6 (5.8)	2 (1.9)	0
Hypertension	5 (4.9)	4 (3.9)	0
Sinus congestion	4 (3.9)	0	0
Fatigue	3 (2.9)	5 (4.9)	0
Headache	3 (2.9)	4 (3.9)	2 (3.8)
Nasopharyngitis	3 (2.9)	4 (3.9)	1 (1.9)
Abdominal pain	2 (1.9)	2 (1.9)	2 (3.8)
Musculoskeletal pain	2 (1.9)	1 (1.0)	3 (5.8)
Sinusitis	2 (1.9)	1 (1.0)	2 (3.8)
Arthralgia	1 (1.0)	2 (1.9)	4 (7.7)
Back pain	1 (1.0)	4 (3.9)	0
Pain in extremity	1 (1.0)	3 (2.9)	3 (5.8)
Peripheral edema	1 (1.0)	0	2 (3.8)
Psoriasis	1 (1.0)	4 (3.9)	0
Psoriatic arthropathy	1 (1.0)	4 (3.9)	0
Respiratory tract congestion	0	0	2 (3.8)
Selected AEs of interest			
Candidiasis			
Candida infection	1 (1.0)	2 (1.9)	0
Skin *Candida*	0	1 (1.0)	0
Major cardiac AEs			
Myocardial infarction	0	1 (1.0)	0
Ischemic stroke	0	0	1 (1.9)
Neutropenia	1 (1.0)	0	0

Values are expressed as n (%) unless otherwise stated. AE: adverse event; SEC: secukinumab.

Our findings suggest that SEC 300 mg is safe and efficacious as a first-line biologic treatment for patients with PsA. Further studies will also help determine the optimal dose of SEC for treating overweight patients or those with high disease activity at treatment initiation.

ACKNOWLEDGMENT

Medical writing support was provided by Karen Chinchilla, PhD, of ArticulateScience LLC, Hamilton, NJ, USA, and Rich Karpowicz, PhD, CMPP of Health Interactions, Inc, Hamilton, NJ, USA, and was funded by Novartis Pharmaceuticals Corporation. This manuscript was developed in accordance with Good Publication Practice (GPP3) guidelines. Authors had full control of the content and made the final decision on all aspects of this publication.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Alinaghi F, Calov M, Kristensen LE, et al. Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. J Am Acad Dermatol 2019;80:251-65.e19.
2. Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. J Am Acad Dermatol 2013;69:729-35.
3. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:2095-6.
4. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64 Suppl 2:ii14-7.
5. Kavanaugh A, Helliwell P, Ritchlin CT. Psoriatic arthritis and burden of disease: patient perspectives from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey. Rheumatol Ther 2016;3:91-102.
6. Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology 2003;42:1460-8.
7. Haroon M, Gallagher P, Fitzgerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis 2015;74:1045-50.
8. Coates LC, Helliwell PS. Psoriatic arthritis: state of the art review. Clin Med 2017;17:65-70.
9. Ogdie A, Schwartzman S, Husni ME. Recognizing and managing comorbidities in psoriatic arthritis. Curr Opin Rheumatol 2015;27:118-26.
10. Mease PJ, McInnes IB, Kirkham B, et al; FUTURE 1 Study Group. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 2015;373:1329-39.

11. McInnes IB, Mease PJ, Kirkham B, et al; FUTURE 2 Study Group. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;386:1137-46.
12. Nash P, Mease PJ, McInnes IB, et al; FUTURE 3 Study Group. Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3). Arthritis Res Ther 2018;20:47.
13. Kivitz AJ, Nash P, Tahir H, et al. Efficacy and safety of subcutaneous secukinumab 150 mg with or without loading regimen in psoriatic arthritis: results from the FUTURE 4 study. Rheumatol Ther 2019;6:393-407.
14. Mease P, van der Heijde D, Landewé R, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. Ann Rheum Dis 2018;77:890-7.
15. Reich K, Sullivan J, Arenberger P, et al. Effect of secukinumab on the clinical activity and disease burden of nail psoriasis: 32-week results from the randomized placebo-controlled TRANSFIGURE trial. Br J Dermatol 2019;181:954-66.
16. Baraliakos X, Gossec L, Pournara E, et al. Secukinumab in patients with psoriatic arthritis and axial manifestations: results from the double-blind, randomised, phase 3 MAXIMISE trial. Ann Rheum Dis 2021;80:582-90.
17. Mease PJ, Kavanaugh A, Reimold A, et al; FUTURE 1 study group. Secukinumab provides sustained improvements in the signs and symptoms in psoriatic arthritis: final 5 year efficacy and safety results from the phase 3 FUTURE 1 study. ACR Open Rheumatol 2020;2:18-25.
18. Kivitz A, Kremer J, Legerton C, et al. Efficacy of secukinumab in a US patient population with psoriatic arthritis: a subgroup analysis of the phase 3 FUTURE studies [abstract]. Arthritis Rheumatol 2019;71 Suppl 10.
19. Pincus T, Yazici Y, Bergman MJ. RAPID3, an index to assess and monitor patients with rheumatoid arthritis, without formal joint counts: similar results to DAS28 and CDAI in clinical trials and clinical care. Rheum Dis Clin North Am 2009;35:773-8, viii.
20. Coates LC, Tillett W, Shaddick G, Pincus T, Kavanaugh A, Helliwell PS. Value of the Routine Assessment of Patient Index Data 3 in patients with psoriatic arthritis: results from a tight-control clinical trial and an observational cohort. Arthritis Care Res 2018;70:1198-205.
21. Vakil-Gilani KM, Dinno A, Rich-Garg N, Deodhar A. Routine Assessment of Patient Index Data 3 Score and Psoriasis Quality of Life assess complementary yet different aspects of patient-reported outcomes in psoriasis and psoriatic arthritis. J Clin Rheumatol 2018;24:319-23.
22. Gottlieb AB, Mease PJ, Kirkham B, et al. Secukinumab efficacy in psoriatic arthritis: individual patient meta-analysis of four phase 3 trials in 2049 patients [abstract]. Arthritis Rheumatol 2018;70 Suppl 10.
23. Orbai AM, Husni ME, Gladman DD, et al. Secukinumab efficacy on psoriatic arthritis GRAPPA-OMERACT core domains in patients with or without prior tumor necrosis factor inhibitor use: pooled analysis of four phase 3 studies. Rheumatol Ther 2021;8:1223-1240.
24. Bruin G, Loesche C, Nyirady J, Sander O. Population pharmacokinetic modeling of secukinumab in patients with moderate to severe psoriasis. J Clin Pharmacol 2017;57:876-85.
25. Klingberg E, Bilberg A, Björkman S, et al. Weight loss improves disease activity in patients with psoriatic arthritis and obesity: an interventional study. Arthritis Res Ther 2019;21:17.
26. Ogdie A, Schwartzman S, Eder L, et al. Comprehensive treatment of psoriatic arthritis: managing comorbidities and extraarticular manifestations. J Rheumatol 2014;41:2315-22.