

Efficacy of Subcutaneous Secukinumab in Patients with Active Psoriatic Arthritis Stratified by Prior Tumor Necrosis Factor Inhibitor Use: Results from the Randomized Placebo-controlled FUTURE 2 Study

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ABSTRACT. Objective. To determine the effect of prior tumor necrosis factor inhibitor (TNFi) therapy on secukinumab efficacy in psoriatic arthritis (PsA).

Methods. Patients were randomized to secukinumab 300 mg, 150 mg, 75 mg, or placebo.

Results. American College of Rheumatology 20 responses at Week 24 with secukinumab 300 mg, 150 mg, 75 mg, and placebo were 58.2%, 63.5%, 36.9%, and 15.9% in TNFi-naïve (n = 258), and 45.5%, 29.7%, 14.7%, and 14.3% in TNFi-exposed patients (n = 139), respectively. Week 52 responses with secukinumab 300 mg, 150 mg, and 75 mg were 68.7%, 79.4%, and 58.5% in TNFi-naïve, and 54.5%, 37.8%, and 35.3% in TNFi-exposed patients, respectively.

Conclusion. Secukinumab was efficacious in TNFi-naïve and TNFi-exposed patients with PsA, with greatest improvements in TNFi-naïve patients. (First Release June 15 2016; J Rheumatol 2016;43: 1713–17; doi:10.3899/jrheum.160275)

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SECUKINUMAB

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Tumor necrosis factor inhibitors (TNFi) have proven efficacy in psoriatic arthritis (PsA)^{1,2}. However, some patients are intolerant of TNFi or fail to achieve desired levels of disease control³. Alternative treatment options are therefore required.

The proinflammatory cytokine interleukin (IL)-17 is implicated in the pathophysiology of PsA^{4,5}. Secukinumab, a human anti-IL-17A monoclonal antibody of the immunoglobulin (Ig) G1/κ isotype, is approved for the treatment of moderate to severe psoriasis and active PsA.

In the phase III FUTURE 2 (NCT01752634) study, secukinumab significantly improved signs and symptoms of

disease, physical function, and quality of life in patients with PsA, with efficacy sustained through 52 weeks⁶. Here we describe efficacy outcomes in patients naïve to TNFi therapy (TNFi-naïve) and those previously treated with TNFi (TNFi-exposed).

MATERIALS AND METHODS

Patients and study design. FUTURE 2 is a 5-year, randomized, double-blind, multicenter, placebo-controlled, parallel-group study that is ongoing at the time of this analysis. Detailed patient eligibility criteria and study design have been reported previously⁶. Briefly, patients were ≥ 18 years old and had PsA fulfilling the CIASSification criteria for Psoriatic ARthritis

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(CASPAR) and active disease, defined as ≥ 3 tender and ≥ 3 swollen joints, despite previous treatment with conventional therapy. Patients were excluded if they had previously received biologics other than TNFi, or had received > 3 TNFi. Where applicable, TNFi were discontinued for 4–10 weeks before randomization. Concomitant methotrexate (MTX; ≤ 25 mg per week) was permitted.

Eligible patients were randomized (1:1:1:1) to receive subcutaneous (sc) doses of secukinumab 300 mg, 150 mg, 75 mg, or placebo at baseline, weeks 1, 2, 3, and 4, and every 4 weeks thereafter. At Week 16, placebo-treated patients were re-randomized (1:1) to receive secukinumab 300 mg or 150 mg sc from Week 16 (if they had $< 20\%$ improvement from baseline in tender and swollen joint counts) or Week 24. Randomization was stratified by previous TNFi use, with patients being TNFi-naive or TNFi-exposed (defined as having active disease despite having received an approved dose of a TNFi for ≥ 3 months or as having stopped treatment owing to safety and tolerability reasons).

The study was conducted in accordance with the Declaration of Helsinki principles and was approved by institutional review boards or independent ethics committees. Written informed consent was obtained from all patients.

Efficacy outcomes. Primary and secondary efficacy endpoints in the overall study population have been published⁶. Efficacy outcomes included proportion of patients with $\geq 20\%$, $\geq 50\%$ or $\geq 70\%$ improvement in American College of Rheumatology response criteria (ACR20, ACR50, and ACR70 responses, respectively); proportion of patients with $\geq 75\%$ or $\geq 90\%$ improvement in Psoriasis Area and Severity Index score (PASI75 and PASI90 responses, respectively); evaluated in patients with $\geq 3\%$ body surface area affected with psoriasis); change in 28-joint Disease Activity Score using C-reactive protein (DAS28-CRP); physical component summary score of the Medical Outcomes Study Short Form-36 health survey (SF36-PCS); Health Assessment Questionnaire–Disability Index (HAQ-DI); resolution of dactylitis and enthesitis among patients with these symptoms at baseline.

Assessment of efficacy in TNFi-naive and TNFi-exposed patients was prespecified, with analyses performed by intent-to-treat. Exploratory posthoc analyses were performed in TNFi-naive and TNFi-exposed patients based on concomitant MTX use, baseline weight (≥ 90 kg and < 90 kg), and disease activity (DAS28-CRP > 5.1 and ≤ 5.1).

Statistical analysis. Sample size calculations and analysis of primary and other efficacy endpoints have been reported⁶. For binary variables, patients with missing values and those with $< 20\%$ improvement in tender and swollen joint counts at Week 16 were imputed as nonresponders in the Week 24 analyses (nonresponder imputation). P values were computed for comparisons of secukinumab doses versus placebo from a logistic regression model with treatment and previous TNFi use as factors and the covariate being baseline weight. Baseline PASI score was a covariate in PASI75 and PASI90 analyses. For continuous variables at Week 24, a mixed-effect model repeated measures model was used, with treatment regimen, analysis visit, and previous TNFi use as factors, and weight and baseline score as continuous covariates.

Efficacy analyses at Week 52 are presented for patients originally randomized to secukinumab. Both imputed analyses and descriptive summaries (observed data) were performed on efficacy endpoints at Week 52.

RESULTS

Of 397 patients randomized, 258 (65.0%) were TNFi-naive and 139 (35.0%) were TNFi-exposed. The majority of patients completed 52 weeks of treatment [secukinumab 300 mg: 92/100 (92.0%); secukinumab 150 mg: 86/100 (86.0%); secukinumab 75 mg: 75/99 (75.8%)]. Lack of efficacy was the most common reason for discontinuation: 1 (1.0%) secukinumab 300 mg, 6 (6.0%) secukinumab 150 mg; 12 (12.1%) secukinumab 75 mg. More than half [13/19 (68.4%)] of the

patients who discontinued because of lack of efficacy at Week 52 were in the TNFi-exposed subgroup.

Demographic and baseline characteristics were generally similar between TNFi-naive and TNFi-exposed, although some differences were noted in terms of weight and MTX use at baseline between the subgroups (Table 1).

In the overall population, ACR20 response rates (primary endpoint) were significantly higher in the secukinumab 300 mg (54.0%; $p < 0.0001$), 150 mg (51.0%; $p < 0.0001$), and 75 mg (29.3%; $p < 0.05$) groups versus placebo (15.3%) at Week 24. In the TNFi-naive subgroup, ACR20 response rates at Week 24 were 58.2% for secukinumab 300 mg group ($p < 0.0001$); 63.5% for the 150 mg group ($p < 0.0001$); and 36.9% for the 75 mg group ($p < 0.01$), compared with 15.9% in the placebo group (Table 2; Supplementary Figure 1, available online at jrheum.org). Improvements in multiple secondary endpoints were observed with secukinumab 300 mg and 150 mg versus placebo at Week 24 (Table 2).

In the TNFi-exposed subgroup, ACR20 response rates at Week 24 were 45.5% in the secukinumab 300 mg group ($p < 0.01$), 29.7% in the 150 mg group ($p = 0.12$), and 14.7% in the 75 mg group ($p = 0.96$), versus 14.3% in the placebo group (Table 2; Supplementary Figure 1, available online at jrheum.org). Secukinumab 300 mg improved a number of secondary endpoints at Week 24 versus placebo (Table 2).

Clinical improvements observed with secukinumab at Week 24 were sustained or continued to improve through Week 52 in both TNFi-naive and TNFi-exposed patients (Table 2 and Table 3; Supplementary Figure 1, available online at jrheum.org). Using a conservative estimate of efficacy with missing values imputed as nonresponse, 68.7%, 79.4%, and 58.5% of TNFi-naive and 54.5%, 37.8%, and 35.3% of TNFi-exposed patients in the 300 mg, 150 mg, and 75 mg group, respectively, achieved an ACR20 response at Week 52 (Table 2). Observed data are presented in Table 3.

In the posthoc analyses, improvements in ACR20 response rates in TNFi-naive patients at Week 24 versus placebo were observed with secukinumab 300 mg and 150 mg, irrespective of concomitant MTX use, body weight or baseline disease activity (Supplementary Figures 2, 3, and 4, available online at jrheum.org). In TNFi-exposed patients, improved ACR20 response rates at Week 24 versus placebo were achieved with secukinumab 300 mg in patients receiving concomitant MTX, patients weighing ≥ 90 kg, and patients with baseline DAS28-CRP ≤ 5.1 . Across all of these subgroups, the clinical responses observed with secukinumab at Week 24 were generally sustained or improved through Week 52 (Supplementary Figures 2, 3, and 4, available online at jrheum.org).

DISCUSSION

Previous results from the FUTURE 2 study demonstrated that secukinumab 300 mg and 150 mg sc provide clinically meaningful and sustained improvements in key clinical

Table 1. Demographic and baseline characteristics.

Characteristic	TNFi-naive		TNFi-exposed	
	Pooled secukinumab, n = 195	Placebo, n = 63	Pooled secukinumab, n = 104	Placebo, n = 35
Age, yrs, mean (SD)	47.1 (11.7)	49.1 (12.3)	47.7 (12.3)	51.3 (13.0)
Female, % (n)	49.2 (96)	63.5 (40)	48.1 (50)	54.3 (19)
Weight, kg ₂ , mean (SD)	85.8 (19.1)	82.7 (19.8)	90.4 (20.6)	92.5 (18.4)
BMI, kg/m ² , mean (SD)	29.7 (5.9)	29.3 (6.3)	31.3 (6.7)	31.6 (5.2)
White, % (n)	93.8 (183)	93.7 (59)	89.4 (93)	100.0 (35)
MTX use at randomization, % (n)	49.2 (96)	63.5 (40)	40.4 (42)	34.3 (12)
Systemic glucocorticoids use at randomization, % (n)	21.0 (41)	22.2 (14)	21.2 (22)	22.9 (8)
Disease history				
DAS28-CRP, mean (SD)	4.7 (1.0)	4.6 (1.0)	5.0 (1.1)	4.9 (1.1)
TJC (78 joints), mean (SD)	20.3 (14.7)	21.9 (18.1)	25.6 (19.1)	26.1 (20.4)
SJC (76 joints), mean (SD)	10.8 (8.6)	10.6 (8.3)	12.4 (9.7)	14.7 (13.7)
HAQ-DI, mean (SD)	1.2 (0.6)	1.2 (0.7)	1.3 (0.6)	1.1 (0.7)
Enthesitis, % (n)	61.0 (119)	66.7 (42)	66.3 (69)	65.7 (23)
Dactylitis, % (n)	40.0 (78)	27.0 (17)	31.7 (33)	28.6 (10)
Psoriasis ≥ 3% of BSA, % (n)	50.8 (99)	49.2 (31)	48.1 (50)	34.3 (12)

BSA: body surface area; BMI: body mass index; DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; HAQ-DI: Health Assessment Questionnaire–Disability Index; MTX: methotrexate; SJC: swollen joint count; TNFi: tumor necrosis factor inhibitor; TJC: tender joint count.

Table 2. Efficacy of secukinumab at weeks 24 and 52.

		TNFi-naive				TNFi-exposed ^a			
		300 mg, N = 67	150 mg, N = 63	75 mg, N = 65	Placebo, N = 63	300 mg, N = 33	150 mg, N = 37	75 mg, N = 34	Placebo, N = 35
ACR20%, (n/N)	Week 24	58.2* (39/67)	63.5* (40/63)	36.9 [§] (24/65)	15.9 (10/63)	45.5 [§] (15/33)	29.7 (11/37)	14.7 (5/34)	14.3 (5/35)
	Week 52	68.7 (46/67)	79.4 (50/63)	58.5 (38/65)	NA	54.5 (18/33)	37.8 (14/37)	35.3 (12/34)	NA
ACR50%, (n/N)	Week 24	38.8* (26/67)	44.4* (28/63)	24.6 [§] (16/65)	6.3 (4/63)	27.3 [‡] (9/33)	18.9 (7/37)	5.9 (2/34)	8.6 (3/35)
	Week 52	52.2 (35/67)	49.2 (31/63)	36.9 (24/65)	NA	27.3 (9/33)	21.6 (8/37)	17.6 (6/34)	NA
ACR70%, (n/N)	Week 24	22.4 [†] (15/67)	27.0* (17/63)	6.2 (4/65)	1.6 (1/63)	15.2 [‡] (5/33)	10.8 (4/37)	5.9 (2/34)	0.0 (0/35)
	Week 52	26.9 (18/67)	23.8 (15/63)	20.0 (13/65)	NA	18.2 (6/33)	13.5 (5/37)	8.8 (3/34)	NA
PASI75 ^b %, (n/N)	Week 24	63.3 [†] (19/30)	55.6 [§] (20/36)	30.3 (10/33)	19.4 (6/31)	63.6 [‡] (7/11)	36.4 (8/22)	23.5 (4/17)	8.3 (1/12)
	Week 52	76.7 (23/30)	61.1 (22/36)	51.5 (17/33)	NA	63.6 (7/11)	50.0 (11/22)	41.2 (7/17)	NA
PASI90 ^b %, (n/N)	Week 24	53.3 [†] (16/30)	38.9 [§] (14/36)	12.1 (4/33)	9.7 (3/31)	36.4 (4/11)	22.7 (5/22)	11.8 (2/17)	8.3 (1/12)
	Week 52	60.0 (18/30)	44.4 (16/36)	24.2 (8/33)	NA	45.5 (5/11)	40.9 (9/22)	23.5 (4/17)	NA
Resolution of enthesitis %, (n/N)	Week 24 ^c	45.9 (17/37)	45.9 (17/37)	35.6 (16/45)	28.6 (12/42)	52.6 [§] (10/19)	37.0 [‡] (10/27)	26.1 (6/23)	8.7 (2/23)
	Week 52 ^c	62.2 (23/37)	56.8 (21/37)	48.9 (22/45)	NA	36.8 (7/19)	37.0 (10/27)	39.1 (9/23)	NA
Resolution of dactylitis %, (n/N)	Week 24 ^d	54.8 [‡] (17/31)	57.1 [‡] (12/21)	30.8 (8/26)	17.6 (3/17)	60.0 [‡] (9/15)	36.4 (4/11)	28.6 (2/7)	10.0 (1/10)
	Week 52 ^d	71.0 (22/31)	71.4 (15/21)	57.7 (15/26)	NA	66.7 (10/15)	54.5 (6/11)	85.7 (6/7)	NA
DAS28-CRP, mean change from baseline ± SE									
	Week 24	-1.76 ± 0.13 [§]	-1.69 ± 0.13 [§]	-1.27 ± 0.13	-1.11 ± 0.18	-1.39 ± 0.20 [‡]	-1.45 ± 0.19 [‡]	-0.89 ± 0.20	-0.69 ± 0.27
	Week 52	-1.91 ± 0.13	-1.87 ± 0.14	-1.57 ± 0.14	NA	-1.56 ± 0.23	-1.45 ± 0.23	-1.26 ± 0.27	NA
SF-36 PCS, mean change from baseline ± SE									
	Week 24	8.05 ± 0.92*	7.91 ± 0.93 [†]	5.37 ± 0.94 [‡]	2.08 ± 1.20	6.56 ± 1.20	4.21 ± 1.15	3.15 ± 1.20	2.65 ± 1.66
	Week 52	8.40 ± 0.94	8.11 ± 0.95	5.63 ± 0.96	NA	7.34 ± 1.39	4.63 ± 1.39	0.58 ± 1.5	NA
HAQ-DI, mean change from baseline ± SE									
	Week 24	-0.59 ± 0.06 [‡]	-0.55 ± 0.06 [‡]	-0.37 ± 0.06	-0.35 ± 0.07	-0.53 ± 0.09 [‡]	-0.35 ± 0.08	-0.23 ± 0.09	-0.23 ± 0.11
	Week 52	-0.60 ± 0.06	-0.54 ± 0.06	-0.36 ± 0.06	NA	-0.51 ± 0.10	-0.38 ± 0.09	-0.26 ± 0.10	NA

*p < 0.0001. †p < 0.001. §p < 0.01. ‡p < 0.05 vs placebo. ^aPatients who had previously used up to 3 TNFi and had experienced an inadequate response or discontinued treatment owing to safety or tolerability reasons. ^bPatients who had psoriasis affecting ≥ 3% body surface area at baseline. ^cResolution of enthesitis among those patients (N = 253) with this symptom at baseline. ^dResolution of dactylitis among those patients (N = 138) with this symptom at baseline. Missing values were imputed as nonresponse for binary variables. Least-square mean change from baseline was used for continuous variables where mixed-model repeated-measures analysis was performed. n/N for NRI analysis: no. patients who are responders with corresponding imputation approach in the treatment group/randomized patients. ACR: American College of Rheumatology; DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; HAQ-DI: Health Assessment Questionnaire–Disability Index; NA: not applicable; NRI: nonresponder imputation; PASI: Psoriasis Area and Severity Index; SF36-PCS: Medical Outcomes Study Short Form-36 health survey physical component summary; SE: standard error; TNFi: tumor necrosis factor inhibitor.

Table 3. Efficacy of secukinumab at Week 52 (observed data).

	TNFi-naive Secukinumab Dose			TNFi-exposed ^a Secukinumab Dose		
	300 mg	150 mg	75 mg	300 mg	150 mg	75 mg
ACR20, % (n/N)	78.0 (46/59)	84.7 (50/59)	67.9 (38/56)	62.1 (18/29)	48.3 (14/29)	63.2 (12/19)
ACR50, % (n/N)	59.3 (35/59)	52.5 (31/59)	42.9 (24/56)	31.0 (9/29)	27.6 (8/29)	31.6 (6/19)
ACR70, % (n/N)	30.5 (18/59)	25.4 (15/59)	23.2 (13/56)	20.7 (6/29)	17.2 (5/29)	15.8 (3/19)
PASI75 ^b , % (n/N)	88.5 (23/26)	62.9 (22/35)	54.8 (17/31)	63.6 (7/11)	61.1 (11/18)	70.0 (7/10)
PASI90 ^b , % (n/N)	69.2 (18/26)	45.7 (16/35)	25.8 (8/31)	45.5 (5/11)	50.0 (9/18)	40.0 (4/10)
No enthesitis ^c , % (n/N)	79.4 (50/63)	74.6 (44/59)	60.3 (35/58)	56.7 (17/30)	58.6 (17/29)	73.7 (14/19)
No dactylitis ^d , % (n/N)	88.9 (56/63)	89.8 (53/59)	86.2 (50/58)	86.7 (26/30)	93.1 (27/29)	94.7 (18/19)
DAS28-CRP, mean change from baseline ± SD	-2.00 ± 1.1, n = 59	-1.88 ± 1.10, n = 58	-1.62 ± 1.38, n = 56	-1.61 ± 1.39, n = 30	-1.56 ± 1.22, n = 29	-1.47 ± 1.29, n = 19
SF-36 PCS, mean change from baseline ± SD	8.30 ± 8.32, n = 62	7.97 ± 8.69, n = 59	6.18 ± 7.83, n = 58	7.44 ± 8.71, n = 32	4.90 ± 9.24, n = 30	1.43 ± 7.63, n = 24
HAQ-DI, mean change from baseline ± SD	-0.65 ± 0.55, n = 59	-0.55 ± 0.47, n = 59	-0.35 ± 0.58, n = 56	-0.53 ± 0.64, n = 30	-0.43 ± 0.49, n = 29	-0.40 ± 0.68, n = 19

^aPatients who had previously used up to 3 TNFi and had experienced an inadequate response or discontinued treatment owing to safety or tolerability reasons.

^bPatients who had psoriasis affecting ≥ 3% body surface area at baseline. ^cAbsence of enthesitis (includes patients without the symptoms at baseline). ^dAbsence of dactylitis (includes patients without the symptoms at baseline). n/N for observed data: no. patients who are responders/total no. patients in the treatment group with evaluation. ACR: American College of Rheumatology; DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; HAQ-DI: Health Assessment Questionnaire–Disability Index; PASI: Psoriasis Area and Severity Index; SF36-PCS: Medical Outcomes Study Short Form-36 health survey physical component summary; TNFi: tumor necrosis factor inhibitor.

domains of PsA⁶. Here, we expand upon those findings, demonstrating that secukinumab is effective in TNFi-naive patients and those who are intolerant of or who fail to achieve adequate disease control with TNFi. These data suggest that secukinumab 150 mg appears to be the most appropriate dose for TNFi-naive patients, but among the TNFi-exposed patients, the 300 mg dose seems to be more appropriate, especially among those patients with high levels of disease activity.

Despite the proven benefits of TNFi, not all treated patients achieve desired levels of disease control, and loss of efficacy can be a clinically relevant problem⁷. In an analysis of data from the Danish DANBIO registry, about 40% of patients with PsA receiving a TNFi switched to a second biologic within a median followup of 2.3 years⁸. Moreover, switching biologics was associated with decreasing ACR response rates and drug survival times; 47% of patients achieved an ACR20 response after 3–6 months of first-line TNFi therapy, reducing to 22% and 18% among patients switching to a second or third biologic, respectively⁸. These data suggest that targeting IL-17A with secukinumab may be a viable treatment option for patients with PsA, including those previously treated with TNFi.

Posthoc analyses indicate that secukinumab 300 mg and 150 mg was effective in TNFi-naive patients regardless of concomitant MTX use, weight, or baseline disease activity. In TNFi-exposed patients, the 300 mg dose appeared to be effective in those patients with concomitant MTX, increased weight (≥ 90 kg), and lower baseline disease activity.

The main limitation of these analyses is the small number

of patients within each subgroup. This, along with the posthoc nature of some of the exploratory analyses by baseline disease characteristics, means these findings should be interpreted with caution.

Secukinumab 300 mg and 150 mg provided sustained improvements in the signs and symptoms of PsA in TNFi-naive patients. In TNF-exposed patients, improved clinical responses were consistently observed only with the 300 mg dose.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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