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Secukinumab and Sustained Reduction in Fatigue in Patients With Ankylosing Spondylitis: Long-Term Results of Two Phase III Randomized Controlled Trials

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Objective. To investigate the longer-term effects of secukinumab 150 mg on fatigue in patients with ankylosing spondylitis (AS) in the MEASURE 1 study (up to 3 years) and the MEASURE 2 study (up to 2 years).

Methods. Patients with active AS were randomized to secukinumab or placebo in MEASURE 1 (10 mg/kg intravenous [IV] followed by 150 mg subcutaneous) and MEASURE 2 (150 mg subcutaneous). Patients were naive to treatment with anti–tumor necrosis factor (anti-TNF-naive) therapy or had an inadequate response/intolerance to anti-TNF therapy (anti-TNF-IR). Fatigue was measured using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale. Relationships between fatigue response and baseline characteristics and clinical/laboratory variables were explored.

Results. Significant improvements in FACIT-F scores from baseline were observed with secukinumab across both studies versus placebo at week 16 ($P < 0.05$). Improvements were sustained through week 156 (MEASURE 1) and week 104 (MEASURE 2). Significantly more patients reported fatigue responses (FACIT-F improvement ≥4; observed data) with secukinumab 150 mg than with placebo at week 16 in both MEASURE 1 ($P < 0.05$) and MEASURE 2 ($P < 0.01$). Fatigue responses were achieved by 75.6% of patients receiving secukinumab at week 156 (MEASURE 1) and 81.4% at week 104 (MEASURE 2); these results were consistent in patients who were anti-TNF-naive (74.3% and 84.6%, respectively) and anti-TNF-IR (81.3% and 75.0%, respectively). Baseline characteristics did not predict improvement in fatigue consistently. Fatigue responses were moderately to strongly correlated with responses in several clinical measures, including the Assessment of SpondyloArthritis international Society (ASAS) 20%/40% improvement, ASAS5/6 responses, the Ankylosing Spondylitis Disease Activity Score with C-reactive protein level, the Bath Ankylosing Spondylitis Disease Activity Index, and the Short Form 36 health questionnaire scores.

Conclusion. Secukinumab provided rapid and sustained improvements in fatigue for up to 3 years, regardless of prior anti-TNF exposure.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory condition predominantly affecting the spine and sacroiliac joints, which, if left untreated, can lead to progressive structural and functional impairment (1).

The main goals of AS therapy are to maximize long-term health-related quality of life (HRQoL) "through control of symptoms and inflammation, prevention of progressive structural damage, and preservation/normalization of function and social participation" (2). Fatigue is reported in up to 66% of patients with AS (3) and has been identified as a key patient priority in the

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SIGNIFICANCE & INNOVATIONS

- In this exploratory analysis of 2 phase III randomized placebo-controlled trials (MEASURE 1 and MEASURE 2), treatment with secukinumab provided rapid improvements in fatigue (assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue scale) that were sustained for up to 3 years in patients with active ankylosing spondylitis (AS); improvements were particularly prominent in patients who were naive to anti–tumor necrosis factor therapy.
- Fatigue responses correlated with responses in several other clinical measures, including signs and symptoms (Assessment of SpondyloArthritis international Society [ASAS] 20% improvement, ASAS 40% improvement, and ASAS5/6 responses), disease activity (Ankylosing Spondylitis Disease Activity Score with C-reactive protein level and Bath Ankylosing Spondylitis Disease Activity Index), and health-related quality of life (HRQoL; Short Form 36 health questionnaire scores), highlighting the close links between fatigue and other key aspects of disease.
- Efficacy in treating fatigue adds to the existing evidence base for secukinumab in AS, which already includes significant and sustained improvements in signs and symptoms, physical function, and HRQoL.

treatment of AS (4). Many patients report that fatigue negatively impacts HRQoL and social functioning (5–7); thus, reducing this symptom remains an important unmet need in AS.

Interleukin-17A (IL-17A) is one of the key cytokines driving the pathogenesis of AS (8). Secukinumab, a fully human monoclonal antibody that selectively binds to and inhibits IL-17A (9), is approved for the treatment of AS (10) based on the results of 2 randomized, double-blind, placebo-controlled, phase III trials, MEASURE 1 (NCT01358175 and NCT01863732) and MEASURE 2 (NCT01649375), that demonstrated significant improvements in the signs and symptoms of AS with secukinumab versus placebo (11).

Secukinumab has previously been shown to provide rapid improvements in fatigue (12). The aim of the current analysis of data from the MEASURE 1 and MEASURE 2 studies was to investigate the longer-term effects of the approved dose of secukinumab (150 mg) on fatigue in patients with AS who were naive to tumor necrosis factor (TNF) inhibitor therapy (anti-TNF-naive) or who had a previous inadequate response to or intolerance of TNF inhibitors (anti-TNF-IR). Potential predictors of fatigue response and the relationship between fatigue and other clinical response measures were also assessed.

PATIENTS AND METHODS

Participants. Detailed enrollment criteria and trial designs for MEASURE 1 and MEASURE 2 have been previously described (11). Inclusion criteria were the same for both trials. Briefly, patients were enrolled if they were age ≥18 years, had AS as defined by the modified New York criteria, had an inadequate response to or intolerance of nonsteroidal antiinflammatory drugs, and either had no previous treatment with anti-TNF therapy or an inadequate response/intolerance to not >1 anti-TNF agent. Exclusion criteria included total spinal ankylosis and active and ongoing systemic infections or inflammatory conditions, other than AS.

Trial design. Patients were randomized to secukinumab 75 mg, 150 mg, or placebo in both trials (intravenous loading, followed by subcutaneous maintenance dosing in MEASURE 1, and subcutaneous loading and maintenance dosing in MEASURE 2). At week 16 (or week 24 in MEASURE 1, depending on Assessment of SpondyloArthritis international Society [ASAS] 20% improvement response [ASAS20]), placebo patients were re-randomized to secukinumab. At week 104 of MEASURE 1, patients were invited to enter a long-term extension study for up to 3 additional years, continuing on the same treatment. Efficacy data from patients receiving secukinumab 75 mg are not presented in this article, as this dose is not approved.

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The studies were conducted in accordance with the Declaration of Helsinki (13). The institutional review board or independent ethics committee at each participating center approved the protocols. Written and informed consent was obtained for all patients.

Outcome measures. Improvements in fatigue, an exploratory endpoint of the MEASURE 1 and 2 trials, were evaluated using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale, a 13-item questionnaire that assesses self-reported fatigue and its impact on daily activities and function on a scale of 0–52, with higher scores indicating less fatigue (14). Assessments were performed at baseline and at weeks 4, 8, 12, 16, 24, 52, and 104 in both trials, and at week 156 in the MEASURE 1 extension. A fatigue response was defined as an improvement (increase) of ≥4 points in the FACIT-F score, corresponding to the minimum clinically important difference (14). Possible relationships between baseline characteristics and fatigue responses were explored using pooled data from MEASURE 1 and MEASURE 2. Prespecified subgroup analyses on the basis of anti-TNF response status (anti-TNF-naive or anti-TNF-IR) were performed for FACIT-F scores at weeks 16, 24, 52, and 104 for both trials, and at week 156 for the MEASURE 1 extension.

Statistical methods. Statistical analyses were performed using the software package SAS, version 9.4. Detailed sample size calculations have been previously reported (11). The mean change in FACIT-F score from baseline up to week 104 or 156 was assessed using a mixed model for repeated measures (MMRM) approach. Treatment regimen, analysis visit, and randomization stratum (anti-TNF-naive or anti-TNF-IR) were included as factors in the model, with weight and baseline score as continuous covariates, and treatment by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure. The proportions of patients with a fatigue response are presented as observed and were compared using Fisher's exact test.

A multivariate logistic regression model was used to explore the association between fatigue responses (dependent variable) and selected demographic and clinical baseline independent variables (age, sex, TNF inhibitor status, FACIT-F score, Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] total score, Bath Ankylosing Spondylitis Functional Index [BASFI] score, swollen/tender 44-joint count, patient global assessment of disease [visual analog scale (VAS)], spinal pain assessment, C-reactive protein [CRP] level, Ankylosing Spondylitis Disease Activity Score [ASDAS] with CRP level, and disease duration) at weeks 16, 52, and 104. Univariate linear regression models were also conducted for absolute FACIT-F scores at week 16 and week 104, with response variable and selected baseline factors as predictors.

Possible correlations between dichotomized clinical response measures and fatigue response at week 16 (the primary endpoint for clinical responses) and at weeks 52 and 104 were examined using polychoric (used to calculate the correlation coefficients between ordinal variables) and polyserial (used for an ordinal discrete variable and a continuous variable) correlation coefficients. The following were evaluated: ASAS20 and ASAS40 response, ASAS5/6 response, ASAS partial remission, ASDAS-CRP major improvement, BASDAI 50, Work Productivity and Activity Impairment (WPAI) change from baseline in percentage of overall work impairment due to health, WPAI change from baseline in

Table 1. Demographic and baseline characteristics of patients from MEASURE 1 study and MEASURE 2 study included in the analysis*

Characteristics	MEASURE 1		MEASURE 2	
	SEC IV, 150 mg (n = 125)	Placebo (n = 122)	SEC, 150 mg (n = 72)	Placebo (n = 74)
Age, years	40.1 ± 11.6	43.1 ± 12.4	41.9 ± 12.5	43.6 ± 13.2
Female, no. (%)	41 (32.8)	37 (30.3)	26 (36.1)	18 (24.3)
Weight, kg	74.7 ± 16.2	76.7 ± 14.4	82.3 ± 18.0	80.3 ± 15.2
Time since AS diagnosis, years	6.5 ± 6.9	8.3 ± 8.9	7.0 ± 8.2	6.4 ± 8.9
Anti-TNF-naive, no. (%)	92 (73.6)	89 (73.0)	44 (61.1)	45 (60.8)
MTX use at randomization, no. (%)	17 (13.6)	16 (13.1)	8 (11.1)	9 (12.2)
hsCRP, median (range) mg/liter	7.4 (0.2–147.7)	7.9 (0.2–146.8)	7.5 (0.4–237.0)	8.3 (0.5–84.6)
PtGA VAS (0–100 mm)	64.0 ± 19.4	66.3 ± 18.6	67.5 ± 16.8	70.5 ± 15.8
BASDAI total score	6.4 ± 1.6	6.5 ± 1.5	6.6 ± 1.5	6.8 ± 1.3
BASFI score	5.6 ± 2.2	5.8 ± 2.0	6.2 ± 2.1	6.1 ± 2.0
Swollen 44-joint count at baseline	2.3 ± 4.4	2.3 ± 4.1	1.6 ± 3.3	2.0 ± 5.3
Tender 44-joint count at baseline	5.5 ± 7.7	6.5 ± 8.4	5.5 ± 7.6	4.8 ± 7.7
Subject spinal pain assessment	64.0 ± 18.6	66.7 ± 16.5	66.2 ± 16.7	69.2 ± 18.8
ASDAS-CRP	3.6 ± 0.9	3.7 ± 0.9	3.7 ± 0.9	3.8 ± 0.8
FACIT-F score	25.6 ± 10.7	24.5 ± 9.4	22.6 ± 8.8	24.3 ± 9.0

* Values are the mean ± SD unless indicated otherwise. Anti-TNF = anti–tumor necrosis factor; AS = ankylosing spondylitis; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score with C-reactive protein; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; FACIT-F = Fatigue Functional Assessment of Chronic Illness Therapy–Fatigue; hsCRP = high-sensitivity CRP; IV = intravenous; MTX = methotrexate; PtGA = patient global assessment; SEC = secukinumab; TNF = tumor necrosis factor; VAS = visual analog scale.

percentage of impairment while working due to health, hemoglobin, patient's total back pain intensity VAS, and the Short Form 36 (SF-36) health questionnaire mental component score (MCS) and physical component score (PCS). FACIT-F scores were stratified by selected clinical response measures. Degrees of association between clinical response measures were determined based on Cohen's criteria for correlation coefficients, in which 0.1–0.29 indicates a weak association, 0.3–0.49 indicates a moderate association, and ≥0.5 indicates a strong association. Analyses of fatigue are presented separately from MEASURE 1 (up to 104 weeks), MEASURE 1 extension (156 weeks), and MEASURE 2 (up to 104 weeks) for the approved dose of secukinumab (150 mg).

RESULTS

Baseline characteristics. In MEASURE 1, of the 125 patients randomized to secukinumab 150 mg at baseline, 97 (77.6%) completed the 2-year core trial; 87 of these patients entered the extension study, of which 83 patients (95.4%) completed week 156. In MEASURE 2, of the 72 patients randomized to secukinumab 150 mg at baseline, 60 patients (83.3%) completed week 104. Patient demographics and baseline characteristics were comparable across groups (Table 1). The majority of patients were male (~70%), and ~70% were anti-TNF-naive and 30% were anti-TNF-IR across both trials. Mean FACIT-F scores were low at baseline in both studies (range 22.6–25.6 across MEASURE 1 and MEASURE 2), indicating severe fatigue.

Fatigue: overall populations. In this analysis, the least mean squares improvements in FACIT-F total scores from baseline were significantly higher with secukinumab 150 mg compared with placebo at week 16 in both MEASURE 1 and MEASURE 2 (MMRM: $P < 0.001$ [MEASURE 1] and $P < 0.01$ [MEASURE 2]) for secukinumab 150 mg versus placebo (Figure 1). Signficant

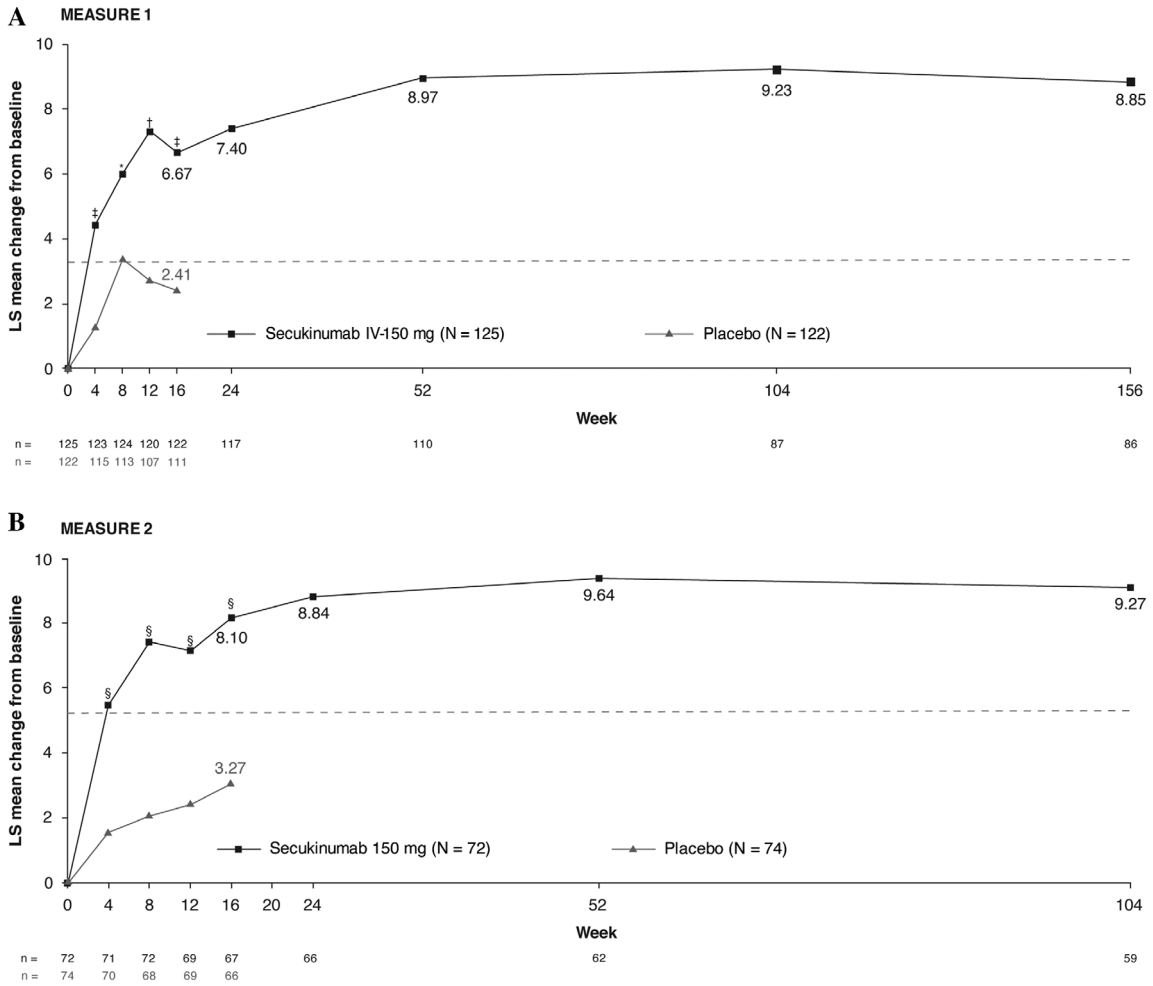

Figure 1. Least mean squares (LS) change from baseline in Functional Assessment of Chronic Illness Therapy–Fatigue scores in overall populations of **A**, MEASURE 1, and **B**, MEASURE 2 (mixed model repeated-measures analysis). Broken lines indicate minimum clinically important difference. * = $P < 0.05$; † = $P < 0.0001$; ‡ = $P < 0.001$; § = $P < 0.01$ versus placebo. IV = intravenous; N = number of randomized patients; n = number of patients in treatment group with evaluation.

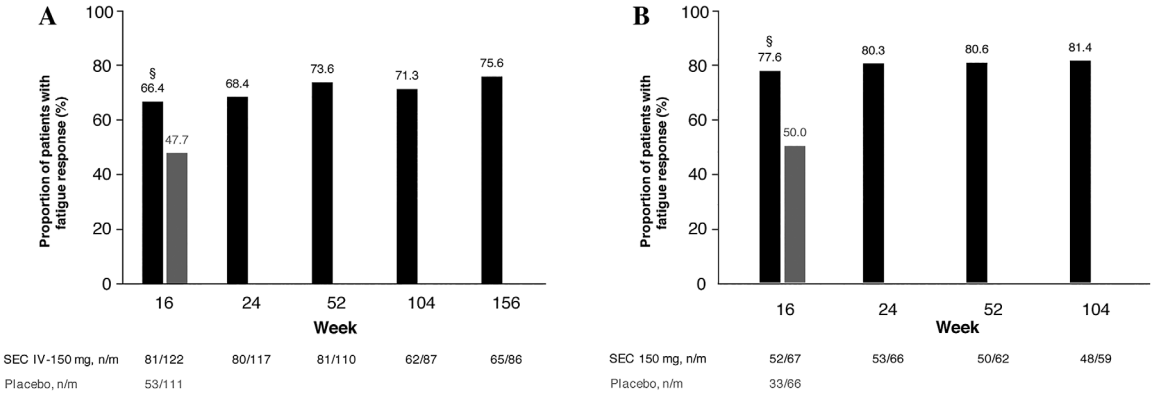

Figure 2. Fatigue responses in the overall populations of **A**, MEASURE 1, and **B**, MEASURE 2 (data shown as observed). Fatigue response was defined as an increase from baseline of ≥4 points in the Functional Assessment of Chronic Illness Therapy–Fatigue score. § = $P < 0.01$ versus placebo. IV = intravenous; m = total number of patients in treatment group with evaluation; n = number of patients who were responders; SEC = secukinumab.

improvements from baseline in FACIT-F total scores were reported as early as week 4 (the first postbaseline assessment) with secukinumab 150 mg in both studies. Improvements were sustained up to week 156 in the MEASURE 1 extension and week 104 in MEASURE 2 (observed data) (Figure 1).

Significantly more patients reported fatigue responses with secukinumab 150 mg than placebo at week 16 in both trials (observed data; both $P < 0.01$ in MEASURE 1 and MEASURE 2) (Figure 2). Fatigue responses were sustained in 75.6% of patients through week 156 in the MEASURE 1 extension and 81.4% through week 104 in MEASURE 2 (observed data) (Figure 2).

Fatigue: anti-TNF-naive and anti-TNF-IR patients. Improvements in FACIT-F scores were reported with

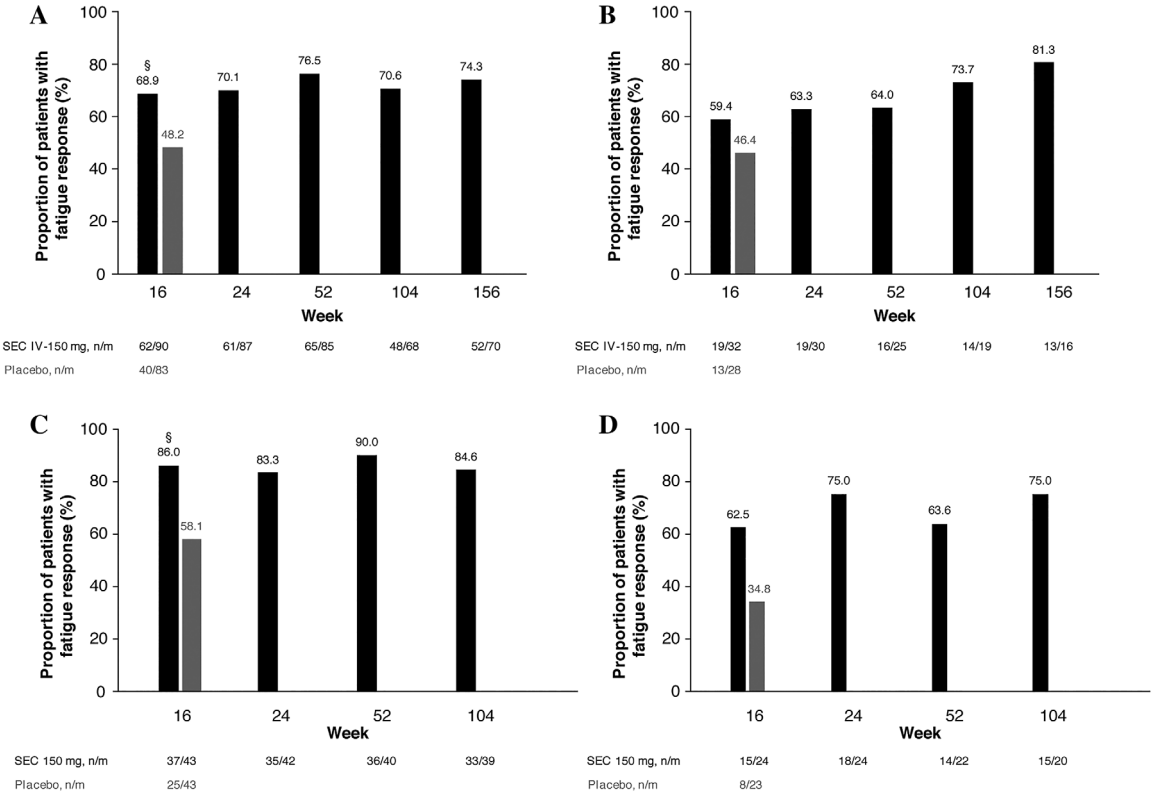

Figure 3. Fatigue responses over time. **A**, Anti–tumor necrosis factor (anti-TNF) naive, and **B**, Anti-TNF inadequate responder (IR) patients in MEASURE 1; **C**, Anti-TNF-naive, and **D**, Anti-TNF-IR patients in MEASURE 2 (data shown as observed). Fatigue response was defined as an increase from baseline of ≥4 points in the Functional Assessment of Chronic Illness Therapy–Fatigue score. § = $P < 0.01$ versus placebo. IV = intravenous; m = total number of patients in treatment group with evaluation; n = number of patients who were responders; SEC = secukinumab.

secukinumab treatment in both MEASURE 1 and MEASURE 2, regardless of anti-TNF treatment status (observed data; see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24517/abstract). In MEASURE 1, least mean squares improvements from baseline in FACIT-F scores were reported with secukinumab 150 mg at week 16 in anti-TNF-naive patients (MMRM: 8.42 versus 2.95 with placebo; $P < 0.0001$) and anti-TNF-IR patients (MMRM: 3.61 versus 2.57 with placebo; $P = 0.68$); however, these improvements only reached statistical significance in the anti-TNF-naive group. Observed improvements were sustained or further increased up to week 156 (MMRM: 9.57 and 9.28 in anti-TNF-naive and anti-TNF-IR patients, respectively). Similarly, in MEASURE 2, improvements in least mean squares FACIT-F scores from baseline were evident with secukinumab in both anti-TNF-naive (MMRM: week 16: 9.96 versus 5.15 with placebo [$P = 0.01$]; week 104: 9.85) and anti-TNF-IR patients (MMRM: week 16: 5.66 versus 0.54 with placebo [$P = 0.0560$]; week 104: 9.13), although they only reached statistical significance in the anti-TNF-naive group.

At week 16 in both MEASURE 1 and MEASURE 2, the proportions of anti-TNF-naive patients reporting fatigue responses were significantly greater with secukinumab versus placebo (observed data; $P < 0.01$); more anti-TNF-IR patients receiving secukinumab reported fatigue responses at week 16 versus placebo, although differences were not statistically significant (observed data) (Figure 3). The proportions of patients reporting fatigue responses were sustained in both studies through weeks 104 and 156 (observed data) (Figure 3). Fatigue responses were numerically higher in anti-TNF-naive patients than anti-TNF-IR patients, particularly at week 16 in the MEASURE 2 study.

Association between other variables and fatigue response. *Baseline predictors of fatigue response.* Results of univariate linear regression models demonstrated that several baseline factors, including age, sex, BASDAI score, inadequate responses to anti-TNF, and SF-36 PCS and MCS scores were predictive of absolute FACIT-F scores at week 16 (see Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24517/abstract) and week 104 (see Supplementary Table 2, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24517/abstract).

In multivariate logistic regression analysis, although no baseline or disease characteristics predicted improvement in fatigue across all time points assessed, several variables were noted to be predictive at either week 16 (see Supplementary Table 3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24517/abstract) or week 104 (Table 2). At week 16, older patients had significantly lower odds of fatigue responses and patients with higher baseline ASDAS-CRP had significantly increased odds of fatigue responses ($P < 0.05$ for both, see Supplementary Table 3, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24517/abstract). No baseline or disease characteristics were significant predictors for fatigue responses at week 52 (data not shown). BASFI and FACIT-F scores at baseline were identified as significant predictive factors for achieving fatigue responses at week 104; no other predictors were identified (Table 2). Anti-TNF-IR

Table 2. Multivariate logistic regression analysis examining baseline predictors of FACIT-F response at week 104 in a pooled population from MEASURE 1 study and MEASURE 2 study*

Baseline variable	Odds ratio (95% CI)	*P*
Age (est. odds ratio for a 10-unit increase)	0.882 (0.711–1.094)	0.252
Female	0.603 (0.336–1.081)	0.089
Anti-TNF-IR	1.007 (0.552–1.834)	0.983
FACIT-F score at baseline	0.897 (0.864–0.931)	<0.0001†
BASDAI total score at baseline	1.111 (0.828–1.492)	0.482
BASFI score at baseline	0.752 (0.631–0.895)	0.0014†
Swollen 44-joint count at baseline	0.977 (0.889–1.075)	0.637
Tender 44-joint count at baseline	0.998 (0.953–1.045)	0.927
Patient global assessment VAS at baseline	0.992 (0.972–1.014)	0.479
Patient spinal pain assessment at baseline	1.008 (0.987–1.029)	0.449
CRP, mg/liter at baseline	1.001 (0.984–1.018)	0.911
ASDAS-CRP at baseline	1.690 (0.919–3.110)	0.092
Disease duration, time since diagnosis	1.007 (0.975–1.040)	0.682

* *P* values are from a multivariate logistic regression model with baseline factors including age, sex, tumor necrosis factor (TNF) inhibitor status, Fatigue Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score at baseline, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) total score, Bath Ankylosing Spondylitis Functional Index (BASFI) score, swollen 44-joint count, tender 44-joint count, patient global assessment (visual analog scale [VAS]), patient spinal pain assessment, C-reactive protein (CRP) level, Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP), and disease duration. Patients randomized to secukinumab 75 mg or 150 mg or placebo are included. The model includes N = 402 observations. Fatigue response was defined as an increase from baseline of ≥4 points in the FACIT-F score. Parameter estimates and odds ratios apply to a 1-unit increase in all continuous variables unless otherwise specified. 95% CI = 95% confidence interval; Anti-TNF-IR = anti-TNF inadequate responder.
† *P* values < 0.05.

Table 3. Correlations between fatigue responses at weeks 16, 52, and 104 and measures of clinical response at the corresponding time points in a pooled population from MEASURE 1 study and MEASURE 2 study*

Measure of clinical response	Week 16	Week 52	Week 104
ASAS20 response	0.66	0.62	0.70
ASAS40 response	0.71	0.57	0.60
ASAS5/6 response	0.62	0.52	0.58
ASAS partial remission	0.44	0.46	0.33
ASDAS-CRP major improvement	0.56	0.60	0.49
BASDAI 50	0.55	0.52	0.52
WPAI change from baseline in percentage of overall work impairment due to health	−0.47	−0.50	−0.51
WPAI change from baseline in percentage of impairment while working due to health	−0.49	−0.50	−0.55
Hemoglobin, gm/liter	−0.04†	0.02†	−0.08†
Patient's total back pain intensity VAS	0.47	0.41	0.38
SF-36 MCS	−0.41	−0.35	−0.36
SF-36 PCS	−0.42	−0.42	−0.35

* Values are the correlation coefficient. All $P < 0.01$ except for hemoglobin (P values calculated by the chi-square likelihood ratio test). Fatigue response was defined as an increase from baseline of ≥4 points in the Fatigue Functional Assessment of Chronic Illness Therapy–Fatigue score. Polychoric correlations (used to calculate the correlation coefficients between ordinal variables) were calculated for ASAS20, ASAS40, ASAS5/6, and ASAS partial remission, Ankylosing Spondylitis Disease Activity Score with C-reactive protein ≥2.0 (ASDAS-CRP) major improvement, and 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50) score. Polyserial correlations (used to calculate the correlation coefficients between an ordinal discrete variable and a continuous variable) were calculated for Work Productivity and Activity Impairment (WPAI) percentage of overall work impairment due to health and WPAI percentage of impairment while working due to health. Degrees of association between variables were determined based on Cohen's criteria for correlation coefficients (0.1–0.29 = weak association, 0.3–0.49 = moderate association, and ≥ 0.5 = strong association). ASAS20 = Assessment of SpondyloArthritis international Society 20% improvement and absolute improvement of at least 1 unit (scale 0–10) in ≥3 of the 4 main ASAS domains, with no worsening by ≥20% in the remaining domain; ASAS40 = 40% improvement and absolute improvement of ≥2 units (scale 0–10) in ≥3 of the 4 main ASAS domains, with no worsening in the remaining domain; ASAS5/6 = ≥20% improvement in 5 of the 6 ASAS response criteria; ASAS partial remission = score ≤2 units (scale 0–10) in each of the 4 core ASAS domains; MCS = mental component score; PCS = physical component score; SF-36 = Short Form 36; VAS = visual analog scale.
† P values were not < 0.05.

status was not a significant predictor of fatigue responses based on regression analysis.

Association between clinical/laboratory variables and fatigue response. Correlation analyses based on pooled data from both trials revealed moderate positive correlations (correlation coefficients 0.33–0.49) between fatigue responses and ASAS partial remission at weeks 16, 52, and 104, and ASDAS-CRP major improvements at week 104. Strong correlations (correlation coefficients 0.52–0.71) were observed between fatigue and ASAS20, ASAS40, ASAS5/6 responses, and BASDAI 50 at weeks 16, 52, and 104, and ASDAS-CRP major improvements at weeks 16 and 52 (Table 3). No correlations were observed with hemoglobin levels, while moderate negative correlations were observed between fatigue and total back pain VAS and SF-36 scores, and moderate to strong negative correlations were observed for WPAI change from baseline (in percentage of overall work impairment and impairment while working due to health). There were significant differences in FACIT-F scores between responders and nonresponders across selected clinical response measures, including ASAS20, ASAS40, ASAS5/6, ASAS partial remision, ASDAS inactive disease, and BASDAI 50 (see Supplementary Table 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24517/abstract).

DISCUSSION

Secukinumab treatment provided rapid and sustained improvements in fatigue for up to 3 years in the MEASURE 1 and MEASURE 2 randomized controlled trials (RCTs). Reducing fatigue, one of the most common symptoms in patients with AS, represents an important unmet need. Patients with AS have lower employment rates and experience more absenteeism from work than the general population (15). Fatigue has also been shown to contribute to reduced work productivity (16,17) and is one of the key treatment priorities for patients with AS (4). Previous short-term studies (ranging from 12 to 24 weeks) evaluating the effects of other therapies including adalimumab, etanercept, and infliximab have reported improvements in fatigue from baseline following treatment (18–20); however, to date, long-term data on the effects of biologic treatment on fatigue have been lacking.

Baseline fatigue levels were high in both MEASURE 1 and MEASURE 2, highlighting the need for better control of fatigue, among other symptoms of AS. Previously, secukinumab has been shown to rapidly improve signs and symptoms, physical function, HRQoL, and fatigue in patients with AS (11, 12, 21), with a low long-term rate of structural progression as measured by the modified Stoke Ankylosing Spondylitis Spinal Score (22). Results presented here build upon these findings, demonstrating significant and sustained improvements in fatigue, as measured using the FACIT-F score, compared with placebo in the overall population and particularly in the anti-TNF-naive population for up to 3 years. Across both trials, although fatigue responses were numerically greater in both anti-TNF-naive and anti-TNF-IR patients treated with secukinumab 150 mg compared with placebo, statistical significance was only evident in the anti-TNF-naive subgroup. However, the small numbers of patients in the anti-TNF-IR subgroups limit interpretation of these results; furthermore, these patients had previously failed treatment with 1 anti-TNF therapy, thus reflecting a more challenging population to treat. Whether prior treatment with anti-TNF therapy changes the course of disease or whether this is simply a more refractory patient population is not known; this question remains an area of further research.

In multivariate logistic regression analyses, age, prior treatment with anti-TNF therapy and FACIT-F, BASDAI, and ASDAS-CRP scores at baseline were significant predictors of short-term fatigue responses at week 16, and BASFI and FACIT-F scores of long-term fatigue responses at week 104. Univariate regression analyses showed that several baseline factors were predictive for short- and long-term absolute FACIT-F scores, including age, sex, BASDAI score, anti-TNF status, and HRQoL (SF-36 scores). Fatigue responses were moderately to strongly correlated with responses in several clinical measures, including ASAS20, ASAS40, ASAS5/6 responses, ASDAS-CRP, BASDAI score, and SF-36 PCS and MCS scores, highlighting the link between fatigue and other measures of disease in AS. Correlations between the FACIT-F, BASDAI, and SF-36 scores are to be expected owing to conceptual overlaps between these questionnaires (14,23,24) but serve to support the clinical relevance and reliability of these metrics in assessing and monitoring fatigue in patients with AS. Moderate to strong correlations were observed between WPAI outcomes and fatigue responses. This finding would appear consistent with reports in patients with rheumatoid arthritis where correlations between work productivity and fatigue levels have been observed (25).

Potential limitations of this study include the lack of a control group after week 16, the fact that long-term fatigue response data are presented as observed (missing data were not imputed), and the potential selection bias toward patients who elected to remain on long-term secukinumab treatment. However, retention of patients receiving secukinumab was high through 3 years, and withdrawals due to lack of efficacy were rare (26). Some FACIT-F questionnaire items are known to have the potential for misinterpretation due to their phrasing or limited relevance to the concept of fatigue in the context of arthritis (27). However, this questionnaire covers a range of fatigue concepts in easy-to-understand language and has been shown to confer good internal consistency and reliability, construct and criterion validity, and sensitivity to change (27), hence its selection for this investigation. In conclusion, results of the current analyses from 2 phase III RCTs showed that secukinumab 150 mg provided rapid and sustained reductions in fatigue through up to 3 years in patients with AS that were particularly prominent in patients who were anti-TNF-naive.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Kvien had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Kvien, Conaghan, Gossec, Strand, Østergaard, Poddubnyy, Williams, Porter, Shete, Gilloteau, Deodhar.

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