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ORIGINAL ARTICLE

Ustekinumab Treatment and Improvement of Physical Function and Health-Related Quality of Life in Patients With Psoriatic Arthritis

PROTON RAHMAN,[1] LLUIS PUIG,[2] ALICE B. GOTTLIEB,[3] ARTHUR KAVANAUGH,[4]
IAIN B. McINNES,[5] CHRISTOPHER RITCHLIN,[6] SHU LI,[7] YUHUA WANG,[7] MICHAEL SONG,[7]
ALAN MENDELSOHN,[7] AND CHENGLONG HAN,[8] ON BEHALF OF THE PSUMMIT 1 AND 2 STUDY GROUPS

Objective. To examine the effects of ustekinumab on patient-reported outcomes (PROs) in PSUMMIT 1 and PSUMMIT 2 patients with active psoriatic arthritis (PsA) who were methotrexate (MTX) naive, MTX experienced, or anti–tumor necrosis factor (TNF) experienced.

Methods. Patients in the phase 3, PSUMMIT 1 (n = 615) and PSUMMIT 2 (n = 312) studies randomly (1:1:1) received placebo, ustekinumab 45-mg, or ustekinumab 90-mg subcutaneous injections at weeks 0, 4, 16, 28, 40, and 52. The PROs (Health Assessment Questionnaire [HAQ] disability index [DI], Dermatology Life Quality Index [DLQI], 36-Item Short Form [SF-36] health survey physical (PCS) and mental component summary scores, patient assessments of pain and disease activity, and impact of disease on productivity) were assessed at weeks 0, 24, and 52. In these post hoc analyses, outcomes were compared between the ustekinumab and placebo groups for 3 mutually exclusive antecedent-exposure populations from the combined studies: MTX/anti-TNF naive (placebo, n = 56; 45 mg, n = 58; and 90 mg, n = 66), MTX experienced, biologic agent naive (placebo, n = 192; 45 mg, n = 190; and 90 mg, n = 185), and anti-TNF experienced with or without MTX (placebo, n = 62; 45 mg, n = 60; and 90 mg, n = 58).

Results. At week 24, mean improvements from baseline in HAQ DI, DLQI, and SF-36 PCS scores were significantly greater in both ustekinumab groups versus placebo across antecedent-exposure groups. Greater proportions of ustekinumab-treated than placebo-treated patients (all $P < 0.05$) had clinically meaningful improvements in HAQ DI (≥0.3), DLQI (≥5), and SF-36 (≥5) scores at week 24, irrespective of drug exposure. Improvements in pain, disease activity, and impact of disease on productivity were similar, and benefits were maintained through week 52.

Conclusion. Significant improvements in PROs with ustekinumab versus placebo were observed in 3 antecedent-exposure populations of PsA patients, including those with prior MTX and anti-TNF use.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, systemic, inflammatory disease that can be characterized by peripheral joint pain and tenderness, skin and nail psoriasis, axial joint involvement, enthesitis, dactylitis, and other manifestations. The pain and discomfort associated with the joint and skin symptoms of PsA can limit a patient's physical function

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[1]Proton Rahman, MD: Memorial University, Newfoundland, Canada; [2]Lluis Puig, MD: Hospital de la Santa Creu i Sant Pau, Universitat Autònoa de Barcelona, Barcelona, Spain; [3]Alice B. Gottlieb, MD: Tufts University School of Medicine, Boston, Massachusetts (current address: New York Medical College, Valhalla); [4]Arthur Kavanaugh, MD: University of California, San Diego; [5]Iain B. McInnes, MD: University of Glasgow, Glasgow, Scotland; [6]Christopher Ritchlin, MD: University of Rochester, Rochester, New York; [7]Shu Li, PhD, Yuhua Wang, PhD, Michael Song, MD, Alan Mendelsohn, MD (current address: Pfizer Pharmaceuticals): Janssen Research & Development, LLC, Spring House, Pennsylvania; [8]Chenglong Han, PhD: Janssen Global Services, LLC, Malvern, Pennsylvania.

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Significance & Innovations

- Using pooled data from 2 phase 3 trials, this post hoc analysis was able to explore patient-reported outcome (PRO) benefits of the biologic agent ustekinumab, an anti–interleukin-12/23 monoclonal antibody with a mechanism of action differing from those of tumor necrosis factor antagonists, in patients with psoriatic arthritis (PsA) who had diverse prior treatment histories.
- Results of analyses presented herein indicated that although overall responses in a PRO end point may vary among PsA patients with different treatment histories, the overall effect sizes between active and placebo treatments were comparable.
- Reported findings indicate ustekinumab provides an additional treatment option for health care providers in the comprehensive management of PsA patients.

and ability to perform daily activities (1,2). The physical appearance of skin lesions also can cause psychological distress (3,4) that tends to increase with more severe disease (1). Several comorbidities, including cardiovascular, are commonly associated with PsA (5). Therefore, these patients often have a significantly compromised health-related quality of life (HRQoL) (1,6,7), including limitations in physical function and productivity (8).

Ustekinumab, a monoclonal antibody targeting the common p40 subunit of interleukin (IL)–12 and IL-23, is approved for treating plaque psoriasis and PsA in adult patients (9). The safety and efficacy of ustekinumab in adult patients with active PsA were evaluated in the pivotal phase 3, PSUMMIT 1 (10) and PSUMMIT 2 (11) trials. These studies also demonstrated that ustekinumab treatment can significantly inhibit radiographic progression of

joint damage in patients with active PsA (12). Patients enrolled into both trials had active disease despite prior therapies; however, patients who had previously received anti–tumor necrosis factor (anti-TNF) agents were excluded from PSUMMIT 1, but eligible for PSUMMIT 2 enrollment.

In both PSUMMIT trials, significant improvements in patient-reported outcomes (PROs), including in physical function measured by the Health Assessment Questionnaire (HAQ) disability index (DI), were observed at week 24 in the ustekinumab groups (10,11). Here we report the results of a post hoc analysis of combined data from PSUMMIT 1 and PSUMMIT 2, evaluating the effects of ustekinumab on PROs among patients in 3 mutually exclusive antecedent-exposure groups: 1) patients who were biologic agent- and methotrexate (MTX) naive, 2) patients who were biologic agent naive, but had been treated with MTX, and 3) patients who had been treated with an anti-TNF agent with or without MTX.

PATIENTS AND METHODS

Patients and study design. PSUMMIT 1 (NCT01009086) and PSUMMIT 2 (NCT01077362) were conducted according to the principles of the Declaration of Helsinki. Governing ethical bodies at each study site approved the protocols, and patients provided written informed consent prior to the conduct of any study-specific procedures.

Patient eligibility criteria and the study designs of the phase 3, randomized, placebo-controlled PSUMMIT 1 (10) and PSUMMIT 2 (11) trials have been described. Briefly, both trials enrolled adult patients with active PsA for ≥6 months despite previous treatment with disease-modifying antirheumatic drugs (DMARDs; ≥3 months) or nonsteroidal antiinflammatory drugs (NSAIDs; ≥4 weeks), or <3 months or 4 weeks, respectively, if DMARDS or NSAIDs were discontinued due to intolerance. Active PsA was defined as having 5 or more swollen joints (0–66), 5 or more tender joints (0–68), and a C-reactive protein level ≥0.3 mg/dl at screening. Patients also had to have a documented history of plaque psoriasis or signs of active psoriatic disease. Patients who had received anti-TNF therapy (i.e., etanercept, adalimumab, infliximab, golimumab, certolizumab pegol) were excluded from the PSUMMIT 1 trial. However, patients with prior biologic anti-TNF therapy for ≥8 (etanercept, adalimumab, golimumab, certolizumab pegol) or ≥14 (infliximab) continuous weeks (or shorter duration if patient was intolerant of anti-TNF therapies) were eligible for enrollment in the PSUMMIT 2 trial. Concomitant use of other biologic agents was prohibited in both trials.

In both the PSUMMIT 1 (10) and PSUMMIT 2 (11) trials, enrolled patients were randomized (1:1:1) to receive subcutaneous injections of placebo, ustekinumab 45 mg, or ustekinumab 90 mg at weeks 0, 4, and every 12 weeks thereafter through week 24, the primary end point visit. At week 16, patients with <5% improvement in tender and swollen joints entered blinded early escape such that patients randomized to placebo began receiving ustekinumab 45 mg, those randomized to ustekinumab 45 mg had their dose increased to 90 mg, and patients randomized to

Table 1. Odds ratios (ORs) of ustekinumab (combined) vs. placebo groups for achieving specified HAQ DI and DLQI outcomes at week 24: results from logistic regression modeling*

Outcomes at week 24 (dependent variable)	Biologic agent and MTX naive				Prior MTX treatment/biologic agent naive				Prior anti-TNF treatment ± MTX			
	No.	OR	95% CI	*P*	No.	OR	95% CI	*P*	No.	OR	95% CI	*P*
HAQ DI												
HAQ DI score improvement ≥0.3 points	179	4.2	1.9–9.0	< 0.001	565	2.2	1.5–3.3	< 0.001	180	3.9	1.6–9.3	0.002
HAQ DI score ≤0.5 points	179	6.8	2.7–17.4	< 0.001	565	1.7	1.1–2.7	0.018	180	3.2	1.2–8.5	0.02
DLQI												
DLQI score improvement ≥5 points	179	12.3	4.1–37.1	< 0.001	556	6.4	3.8–11.0	< 0.001	180	8.4	3.0–23.2	< 0.001
DLQI score = 0/1	177	8.2	3.5–19.4	< 0.001	541	3.5	2.3–5.4	< 0.001	164	3.0	1.4–6.2	0.003

* In the logistic regression model for the Health Assessment Questionnaire (HAQ) disability index (DI) improvement ≥0.3 points or HAQ DI ≤0.5 points at week 24, the independent variables were age, sex, baseline patient global assessment of disease activity, and baseline HAQ DI. In the logistic regression model for the Dermatology Life Quality Index (DLQI) improvement ≥5 points or DLQI = 0 or 1 at week 24, the independent variables were age, sex, baseline patient global assessment of disease activity, and baseline DLQI score. MTX = methotrexate; anti-TNF = anti–tumor necrosis factor; 95% CI = 95% confidence interval.

ustekinumab 90 mg continued the 90-mg dose. At week 24, all patients who were randomized to placebo at baseline were switched to ustekinumab 45 mg. All patients would continue receiving ustekinumab every 12 weeks through week 52.

Assessments. In both PSUMMIT 1 and PSUMMIT 2, PROs were assessed at weeks 0 and 24. Physical function was assessed using the HAQ DI (13), with a minimal clinically important difference (MCID) defined as an improvement from baseline ≥0.3 (14). HRQoL was assessed with the Dermatology Life Quality Index (DLQI) (15) in patients with ≥3% body surface area affected by psoriasis, as well as with the physical and mental component summary (PCS/MCS) scores of the 36-Item Short-Form (SF-36) health survey (16). The MCIDs were defined as an improvement from baseline ≥5 points for both the DLQI and SF-36 PCS/MCS scores (17,18). Additionally, a DLQI score ≤1 was defined as no impact of disease on HRQoL. The impact of disease on daily productivity at work, school, or home was evaluated using a visual analog scale (VAS; where 0 = did not affect at all and 10 = affected very much). Patient assessments of pain and disease activity also were assessed with a VAS ranging from 0 to 10.

Statistical analysis. Data from the PSUMMIT 1 and PSUMMIT 2 trials were pooled for these post hoc analyses. Descriptive statistics, including counts (percentages), means (SDs), and mean changes from baseline are reported. Outcomes were analyzed according to 3 mutually exclusive antecedent-exposure groups: 1) patients who were biologic agent- and MTX naive, 2) patients who were biologic agent naive, but had been treated with MTX, and 3) patients who had been treated with an anti-TNF agent with or without MTX. Within each of these groups, treatment group comparisons were performed between each ustekinumab dose group and the placebo group using Cochran-Mantel-Haenszel tests for binary variables and analyses of variance on the van der Waerden normal scores for continuous variables. Patients who qualified for early escape in all 3 treatment groups had their week-16 outcome data carried forward to week 24 for analysis.

To adjust for potential differences in demographic and baseline disease characteristics between the ustekinumab and placebo groups, logistic regression models were employed to derive the odds ratio (OR) for achieving dichotomous outcomes of DLQI and HAQ DI (see Table 1 for analysis details). Summary statistics were provided for changes in PROs at week 52.

RESULTS

Baseline characteristics and patient disposition. A total of 927 patients were randomized and treated in PSUMMIT 1 (n = 615) and PSUMMIT 2 (n = 312, of which 180 had prior anti-TNF exposure). As previously reported, baseline demographic and disease characteristics were generally well-balanced among the treatment groups within each trial (10,11).

In the pooled analysis, 180 patients were MTX- and biologic agent naive (n = 56/58/66 for placebo/45 mg/90 mg, respectively), 567 patients had received treatment with MTX, but not biologic agents (n = 192/190/185 for placebo/45 mg/90 mg, respectively), and 180 patients had received prior treatment with an anti-TNF agent with or without MTX (n = 62/60/58 for placebo/45 mg/90 mg, respectively) (Table 2). Baseline demographic, physical functions, and HRQoL were generally comparable across the placebo and ustekinumab dose groups within and across the 3 antecedent-exposure groups, although patients with prior anti-TNF experience appeared to have more active disease at study outset than those who did not have prior anti-TNF exposure (Table 2). Note that the numbers of patients included in each of the various post hoc analyses are provided with the reported data.

Improvements in physical function and HRQoL. At week 24, patients in the ustekinumab groups had

Table 2. Baseline demographics, physical function, and quality of life for patients who had not received treatment with MTX or a biologic agent, patients who had received prior MTX treatment, but were biologic agent naive, and patients who had received treatment with an anti-TNF agent with or without MTX*

	Biologic agent and MTX naive				Prior MTX treatment/biologic agent naive				Prior anti-TNF treatment ± MTX			
	Placebo	Ust. 45 mg	Ust. 90 mg	Ust. combined	Placebo	Ust. 45 mg	Ust. 90 mg	Ust. combined	Placebo	Ust. 45 mg	Ust. 90 mg	Ust. combined
Patients randomized, no.	56	58	66	124	192	190	185	375	62	60	58	118
Age, years	45.6 ± 13.1	48.4 ± 12.3	47.3 ± 13.2	47.8 ± 12.8	48.0 ± 11.7	47.1 ± 12.5	47.1 ± 47.1	47.1 ± 11.3	47.6 ± 11.4	47.4 ± 11.1	47.7 ± 12.6	47.5 ± 11.8
Male, no. (%)	34 (60.7)	38 (65.5)	43 (65.2)	81 (65.3)	94 (49.0)	93 (48.9)	100 (54.1)	193 (51.5)	31 (50.0)	23 (38.3)	22 (37.9)	45 (38.1)
Patient assessment of pain (0–10)	6.0 ± 2.1	6.1 ± 2.0	6.3 ± 1.9	6.2 ± 1.9	6.1 ± 2.0	6.3 ± 1.9	6.5 ± 1.8	6.4 ± 1.9	6.8 ± 1.9	7.1 ± 1.7	7.1 ± 1.9	7.1 ± 1.8
Patient global assessment of disease activity (0–10)	6.1 ± 2.0	6.2 ± 2.1	6.1 ± 2.0	6.2 ± 2.0	6.1 ± 2.0	6.3 ± 1.9	6.4 ± 1.9	6.4 ± 1.9	6.5 ± 2.0	7.1 ± 1.8	6.9 ± 2.1	7.0 ± 1.9
HAQ DI score (0–3)	1.09 ± 0.69	1.08 ± 0.65	1.05 ± 0.62	1.06 ± 0.63	1.28 ± 0.65	1.27 ± 0.61	1.27 ± 0.62	1.27 ± 0.61	1.26 ± 0.70	1.41 ± 0.71	1.41 ± 0.72	1.41 ± 0.71
Patients with HAQ DI score >0.5, no. (%)	43 (76.8)	45 (77.6)	51 (77.3)	96 (77.4)	162 (84.4)	161 (84.7)	159 (85.9)	320 (85.3)	50 (80.6)	52 (86.7)	48 (82.8)	100 (84.7)
DLQI score (0–30)	12.2 ± 8.2	11.3 ± 7.3	10.0 ± 6.2	10.6 ± 6.7	11.8 ± 7.5	11.2 ± 7.2	10.8 ± 7.5	11.0 ± 7.3	11.4 ± 7.9	12.3 ± 8.3	13.3 ± 8.4	12.8 ± 8.3
SF-36 PCS score (0–100)	32.8 ± 8.9	33.4 ± 8.1	33.8 ± 9.2	33.6 ± 8.6	30.8 ± 8.4	30.3 ± 8.4	30.5 ± 7.4	30.4 ± 7.9	30.1 ± 10.5	27.4 ± 8.6	27.2 ± 8.9	27.3 ± 8.7
SF-36 MCS score (0–100)	44.1 ± 11.0	42.9 ± 11.3	45.6 ± 11.2	44.3 ± 11.3	42.2 ± 11.2	42.7 ± 11.3	42.6 ± 11.6	42.6 ± 11.4	44.6 ± 12.4	43.8 ± 13.0	42.7 ± 12.5	43.2 ± 12.7
Impact of disease on productivity (0–10)	5.7 ± 2.7	5.9 ± 3.3	5.4 ± 2.9	5.6 ± 3.1	6.0 ± 2.6	6.1 ± 2.7	6.5 ± 2.6	6.3 ± 2.6	6.0 ± 2.9	6.9 ± 2.6	7.0 ± 2.3	7.0 ± 2.4

* Values are the mean ± SD unless otherwise indicated. MTX = methotrexate; anti-TNF = anti–tumor necrosis factor; Ust. = ustekinumab; HAQ = Health Assessment Questionnaire; DI = disability index; DLQI = Dermatology Life Quality Index; SF-36 = 36-Item Short Form health survey; PCS = physical component summary; MCS = mental component summary.
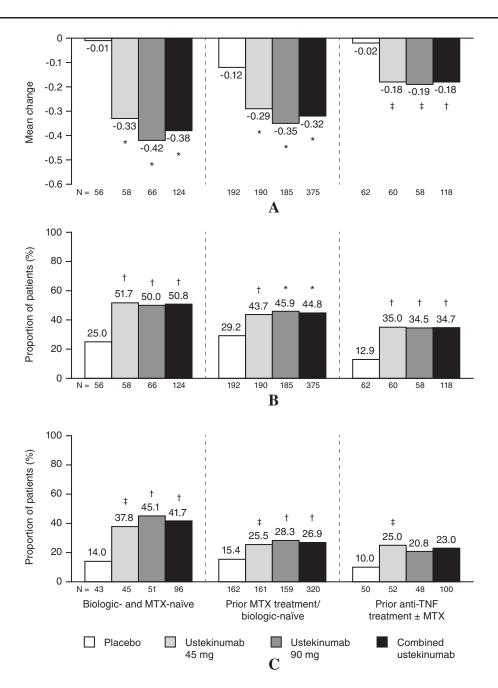
Figure 1. Mean change from baseline in the Health Assessment Questionnaire (HAQ) disability index (DI) score (**A**), the proportion of patients with an improvement in HAQ DI score ≥0.3 (**B**) at week 24, and the proportion of patients with a HAQ DI score ≤0.5 at week 24 among patients with baseline HAQ DI score >0.5 (**C**). * = $P < 0.001$; † = $P < 0.01$; ‡ = $P < 0.05$; MTX = methotrexate; TNF = tumor necrosis factor.

significantly greater improvements from baseline in HAQ DI scores when compared with the placebo group for patients who were MTX- and biologic agent naive (45 mg: −0.33, 90 mg: −0.42 versus placebo: −0.01; $P < 0.001$), patients previously treated with MTX but biologic agent naive (45 mg: −0.29, 90 mg: −0.35 versus placebo: −0.12; $P < 0.001$), and for patients previously treated with an anti-TNF agent with or without MTX (45 mg: −0.18, 90 mg: −0.19 versus placebo: −0.02; $P < 0.05$) (Figure 1A). In addition, significantly greater proportions of ustekinumab than placebo-treated patients had a clinically meaningful

improvement in HAQ DI (≥0.3) in each antecedent-exposure group (Figure 1B). Consistent findings were generally observed when the proportions of patients with a HAQ DI score ≤0.5 at week 24, among those with baseline HAQ DI >0.5, were compared (Figure 1C).

HRQoL was evaluated with both the DLQI and SF-36 measures. Mean changes from baseline to week 24 in DLQI were significantly greater for patients in the ustekinumab groups than those in the placebo group among MTX- and biologic agent–naive patients (45 mg: −7.6, 90 mg: −7.7 versus placebo: −1.3; $P < 0.001$), patients previously treated with
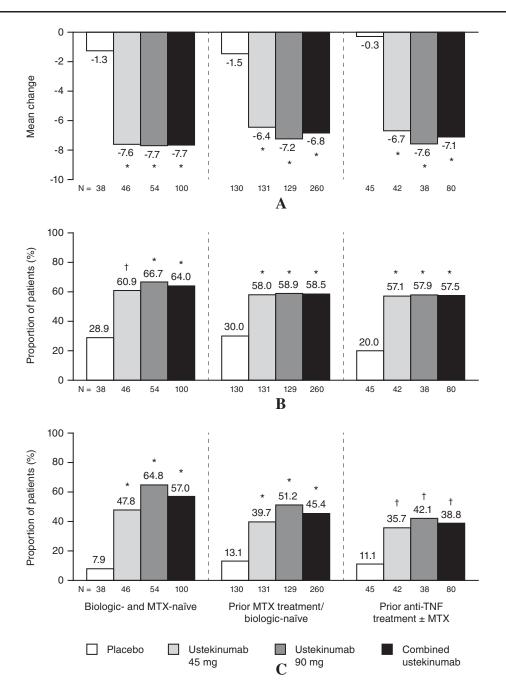
Figure 2. Mean change from baseline in Dermatology Life Quality Index (DLQI) score (**A**), the proportion of patients with an improvement in DLQI score ≥5 (**B**), and the proportion of patients with a DLQI score = 0 or 1 (**C**) at week 24. Note that DLQI was assessed in patients with ≥3% body surface area affected by psoriasis at baseline. * = $P < 0.001$; † = $P < 0.01$; MTX = methotrexate; TNF = tumor necrosis factor.

MTX but biologic naive (45 mg: −6.4, 90 mg: −7.2 versus placebo: −1.5; $P < 0.001$), and patients previously treated with an anti-TNF agent with or without MTX (45 mg: −6.7, 90 mg: −7.6 versus placebo: −0.3; $P < 0.001$) (Figure 2A). Results of this analysis showed that greater proportions of ustekinumab-treated patients in each of the 3 antecedent-exposure groups had an improvement in DLQI score ≥5 or achieved a DLQI score of 0 or 1 compared with placebo (Figures 2B, 2C).

Improvements in SF-36 PCS scores from baseline to week 24 were significantly greater in both ustekinumab dose groups than in the placebo group in each of the 3 antecedent-exposure groups (see Supplementary Figure 1A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23000/abstract). Likewise, significantly greater proportions of patients in the ustekinumab groups achieved an improvement from baseline to week 24 ≥5 points in SF-36 PCS

Table 3. Median ± SD percent improvements in patient assessments of pain, global disease activity, and impact of disease on productivity at week 24*

	Biologic agent and MTX naive				Prior MTX treatment/biologic agent naive				Prior anti-TNF treatment ± MTX			
	Placebo	Ust. 45 mg	Ust. 90 mg	Ust. combined	Placebo	Ust. 45 mg	Ust. 90 mg	Ust. combined	Placebo	Ust. 45 mg	Ust. 90 mg	Ust. combined
Patients randomized, no.	56	58	66	124	192	190	185	375	62	60	58	118
Pain	0.0 ± 42.6	25.7 ± 46.6†	56.8 ± 38.0†	48.4 ± 43.0†	1.6 ± 47.0	31.9 ± 52.1†	32.1 ± 40.0†	32.1 ± 46.6†	0.0 ± 31.9	17.0 ± 42.7†	21.2 ± 39.4†	20.6 ± 41.0†
Global disease activity	4.8 ± 52.2	42.6 ± 40.2‡	61.2 ± 40.2†	49.6 ± 40.7†	3.9 ± 56.3	30.2 ± 48.5†	28.9 ± 50.2†	28.9 ± 49.3†	0.0 ± 34.9	17.1 ± 45.1‡	16.4 ± 44.5§	17.0 ± 44.7‡
Impact of disease on productivity	0.0 ± 94.1	39.6 ± 42.7†	66.7 ± 127.2†	53.3 ± 97.4†	7.8 ± 186.7	27.3 ± 481.0‡	39.5 ± 182.7†	35.9 ± 369.5†	0.0 ± 106.3	14.9 ± 187.1‡	30.5 ± 35.5†	20.2 ± 1,395.0†

* Values are the median ± SD unless otherwise indicated. MTX = methotrexate; anti-TNF = anti–tumor necrosis factor; Ust. = ustekinumab.
† $P < 0.001$.
‡ $P < 0.05$.
§ $P < 0.01$.

score (Supplementary Figure 1B, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23000/abstract).

Improvements from baseline in SF-36 MCS scores were significantly greater in the ustekinumab 45-mg and combined dose groups when compared with placebo among patients who were MTX- and anti-TNF naive, and were significantly greater in the ustekinumab 90-mg and combined dose groups when compared with placebo among the MTX-experienced patients (see Supplementary Figure 2A, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23000/abstract). The proportion of patients who had an improvement in SF-36 MCS score ≥5 points was generally numerically greater in the ustekinumab groups than in the placebo group in each antecedent-exposure group (Supplementary Figure 2B, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23000/abstract).

Patient perception of pain and disease activity improved at week 24. The median percent improvements from baseline in pain and patient global assessment of disease activity were significantly greater in the ustekinumab groups than in the placebo groups within each of the 3 antecedent-exposure groups (Table 3). Similarly, median percent improvements in the impact of disease on daily productivity were significantly greater in the ustekinumab groups within each antecedent-exposure group (Table 3).

Logistic regression analyses were employed to adjust for differences in demographic and baseline disease characteristics, including patient global disease activity, DLQI, or HAQ DI, between the ustekinumab and placebo groups. After these adjustments, patients in the ustekinumab groups were more likely to achieve clinically meaningful improvement in DLQI (≥5) or HAQ DI (≥0.3) score and more likely to achieve a normal DLQI (≤1) or HAQ DI (≤0.5) score at week 24 than those in the placebo groups within each antecedent-exposure group (Table 1).

Improvements in all outcomes were numerically lower in patients with increasing therapeutic experience. However, although the trials were not designed for this purpose, the overlapping 95% confidence intervals (95% CIs) surrounding the ORs determined via logistic regression (Table 1) suggest the differences between antecedent-exposure groups in efficacy response are not statistically significant.

The improvements in PROs observed in ustekinumab-treated patients through week 24 were generally maintained through week 52 (Table 4). Additionally, patients randomized to placebo who crossed over to ustekinumab 45 mg at week 24 had improvements in PROs that were generally comparable to week-24 improvement among patients randomized to ustekinumab at baseline (Table 4).

DISCUSSION

Psoriatic diseases affect 2% to 3% of the world's population, and both psoriasis and PsA can carry significant burdens of pain and physical disability, psychological distress, depression, and impaired productivity. Reflecting the disability that accompanies concurrent joint disease, patients with PsA have been shown to have significantly worse HRQoL than psoriasis patients, both overall (19) and in terms of physical disability and pain, even in the context of more aggressive DMARD treatment of PsA (20). In psoriasis patients, quality of life as assessed by the DLQI has been found to be more strongly associated with overall costs of care than the extent of disease as assessed by the Psoriasis Area and Severity Index score (21). Additional factors that correlate with cost of psoriasis, most notably due to costs of time away from work, are the presence of joint involvement (i.e., concurrent PsA) and receipt of systemic therapy (21).

As previously reported, ustekinumab-treated patients had significantly greater improvements in physical function and HRQoL measures from baseline to week 24 when compared with the placebo groups in both PSUMMIT 1 and PSUMMIT 2 (10,11). Given the heterogeneity of treatment and disease courses that can be observed in PsA patients, we performed post hoc analyses combining patient data from the PSUMMIT 1 and PSUMMIT 2 trials according to 3 mutually exclusive antecedent-exposure groups: 1) patients who were biologic agent and MTX naive, 2) patients who were biologic agent naive, but had been treated with MTX, and 3) patients who had been treated with an anti-TNF agent with or without MTX.

Significant improvements in physical function (HAQ DI) and HRQoL (DLQI) from baseline to week 24 with ustekinumab versus placebo were observed in all 3 antecedent-exposure populations. Notably, greater proportions of ustekinumab-treated patients in each of the 3 antecedent-exposure groups had an improvement in HAQ DI score ≥0.3, had an improvement in DLQI score ≥5, or achieved a DLQI score of 0 or 1 compared with placebo, indicating clinically meaningful improvements in physical function and HRQoL. Similar patterns of improvement were observed for the SF-36 MCS and PCS scores, impact of disease on daily productivity, and patient assessments of pain and global disease activity. Importantly, improvements in function and quality of life accrued through week 24 appeared to be sustained through week 52. The SF-36 findings are particularly salient given that PsA patients experience significant impairment in HRQoL, with higher levels of bodily pain and more role limitations due to emotional problems than patients with rheumatoid arthritis after adjusting for observed differences in vitality (6). Also of note, our overall findings were consistent with those from analyses employing logistic regression models, i.e., after adjustment for baseline and other demographic characteristics, ustekinumab treatment was consistently associated with positive treatment outcomes related to HAQ DI and DLQI, and no significant interactions were found between treatment and prior treatment histories (data not shown).While patients in the prior–anti-TNF group overall had relatively smaller improvements in HRQoL across treatment groups, the active treatment versus placebo deltas were generally comparable to those observed in the MTX-naive group. In addition, the overlapping 95% CIs surrounding the ORs determined via logistic regression analysis for key efficacy outcomes suggest the differences observed among antecedent-exposure groups are not statistically significant.

A slight difference in baseline disease severity between ustekinumab groups versus placebo patients in each of the

Table 4. Improvements in patient-reported outcomes at week 52*

Change (improvement)	Biologic agent and MTX naive				Prior MTX treatment/biologic agent naive				Prior anti-TNF treatment ± MTX			
	Placebo →45 mg	Ust. 45 mg	Ust. 90 mg	Ust. combined	Placebo →45 mg	Ust. 45 mg	Ust. 90 mg	Ust. combined	Placebo →45 mg	Ust. 45 mg	Ust. 90 mg	Ust. combined
HAQ DI score, no.	49	55	61	116	170	179	169	348	40	54	54	108
Mean ± SD	−0.3 ± 0.6	−0.3 ± 0.6	−0.4 ± 0.5	−0.4 ± 0.5	−0.4 ± 0.4	−0.3 ± 0.6	−0.4 ± 0.6	−0.4 ± 0.6	−0.1 ± 0.4	−0.2 ± 0.5	−0.2 ± 0.5	−0.2 ± 0.5
DLQI score, no.	6	6	7	13	21	27	25	52	30	36	39	75
Mean ± SD	−8.2 ± 9.1	−10.2 ± 6.2	−9.0 ± 6.1	−9.5 ± 5.9	−8.2 ± 7.8	−6.2 ± 6.6	−8.1 ± 7.4	−7.1 ± 7.0	−5.2 ± 7.7	−6.4 ± 7.9	−6.9 ± 8.2	−6.7 ± 8.0
SF-36 PCS score, no.	49	55	61	116	168	177	168	345	40	53	54	107
Mean ± SD	6.5 ± 9.6	5.7 ± 9.9	7.8 ± 9.2	6.8 ± 9.6	6.8 ± 8.6	6.2 ± 9.0	6.0 ± 9.3	6.1 ± 9.1	3.8 ± 9.4	4.5 ± 7.9	5.4 ± 7.6	5.0 ± 7.7
SF-36 MCS score, no.	49	55	61	116	168	177	168	345	40	53	54	107
Mean ± SD	4.2 ± 10.9	5.8 ± 10.7	5.3 ± 12.0	5.6 ± 11.3	4.8 ± 10.6	3.3 ± 10.1	4.8 ± 10.1	4.0 ± 10.1	0.5 ± 6.5	0.8 ± 10.5	2.4 ± 10.6	1.6 ± 10.6
Impact of disease on productivity, no.	46	53	58	111	167	170	161	331	39	51	54	105
Median ± SD %	43.3 ± 78.0	48.5 ± 81.4	68.6 ± 51.0	62.7 ± 67.8	47.2 ± 136.2	31.6 ± 101.6	40.8 ± 199.6	37.7 ± 156.9	0.0 ± 171.3	6.6 ± 127.0	28.5 ± 80.6	12.1 ± 105.7
Pain, no.	49	55	61	116	171	179	169	348	39	53	54	107
Median ± SD %	43.9 ± 40.6	50.0 ± 41.5	57.5 ± 42.2	53.5 ± 41.7	50.0 ± 45.6	37.3 ± 41.9	40.2 ± 45.3	37.8 ± 43.6	6.5 ± 37.8	6.9 ± 40.7	19.8 ± 36.5	8.9 ± 38.6
Global disease activity, no.	49	55	61	116	171	179	169	348	39	53	54	107
Median ± SD %	35.6 ± 51.2	33.3 ± 40.8	57.6 ± 38.8	47.5 ± 40.1	41.0 ± 44.7	38.4 ± 41.1	37.0 ± 51.2	37.2 ± 46.2	8.9 ± 39.9	12.2 ± 46.2	17.1 ± 71.8	13.7 ± 60.2

* MTX = methotrexate; anti-TNF = anti-tumor necrosis factor; Ust. = ustekinumab; HAQ = Health Assessment Questionnaire; DI = disability index; DLQI = Dermatology Life Quality Index; SF-36 = 36-Item Short Form health survey; PCS = physical component summary; MCS = mental component summary.

3 antecedent-exposure groups was observed. To adjust for difference in demographic and baseline disease characteristics, including patient global disease activity, DLQI, or HAQ DI between the ustekinumab and placebo groups, logistic regression models were employed to derive ORs for dichotomous outcomes in DLQI and HAQ DI (dependent variable). Overall, the results were consistent between univariate and regression models, i.e., ORs for achieving clinically meaningful improvements in, and normalized, DLQI or HAQ DI scores in the ustekinumab group versus the placebo group were comparable between the prior–anti-TNF and MTX-naive groups.

A potential limitation of these post hoc analyses is the difference in sample sizes among the antecedent-exposure groups, with more than 3 times as many patients (n = 567) having received treatment with MTX but not biologic agents than being MTX and biologic agent naive (n = 180) or having received prior treatment with and anti-TNF agent with or without MTX (n = 180). A randomized trial designed to prospectively assess differences among patients with specific treatment histories may help to further validate the findings from this post hoc analysis. As another limitation, productivity was assessed using a single rating scale. Future evaluations should include additional and more comprehensive measures of productivity. Results related to mental health should also be interpreted with caution based on the fact that these post hoc analyses did not include information related to comorbidities such as major depression or concomitant antidepressant treatment. Also, the SF-36 is a generic tool for assessing HRQoL. As such, use of a PsA-specific tool for assessing HRQoL would provide valuable information and should be included in future research. Formal testing of interactions should be performed to determine if prior treatment differentially influences responses on these PRO measures in these trials. Finally, due to differences in patient populations and trial designs, our results cannot be directly compared with those from other studies. In the future, a meta-analysis and/or trial with a head-to-head comparison design would be appropriate for drawing such conclusions. In summary, the results of the pooled analysis of PsA patients by antecedent-exposure groups support the earlier findings from the primary analyses of the individual PSUMMIT 1 and PSUMMIT 2 clinical trials that showed significant improvements in patient HRQoL with ustekinumab versus placebo. Findings reported herein indicate that significant improvements in these PROs with ustekinumab were observed regardless of prior PsA treatment. However, given that delays in effective treatment of PsA patients can result in more refractory disease, earlier treatment is more likely to lessen the high prevalence of the disease burdens of PsA.

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. Han 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.

ROLE OF THE STUDY SPONSOR

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