Original Article | Annals of Dermatology 2022;34(1):14-21 • https://doi.org/10.5021/ad.2022.34.1.14

Differences in Clinical Responses to Ustekinumab Treatment among Body Regions: Results from a Real-World Prospective, Observational, and Multi-Center Study in Korea

Sang Wook Son[1,*], Dae Young Yu[2,3,*], Youngdoe Kim[3], Hyo Hyun Ahn[4], Yong Hyun Jang[5], Joo Young Roh[6], Young Bok Lee[7], Ji Yeoun Lee[8], Myung Hwa Kim[9], YoungJa Lee[3], Gyeong-Hun Park[10], Hyun-Sun Yoon[11], Sang Woong Youn[12]; on behalf of the Stelara PMS investigators

[1]Department of Dermatology, Korea University Ansan Hospital, Ansan, [2]Department of Public Health, Korea University College of Medicine, [3]Medical Affairs, Janssen Korea, [4]Department of Dermatology, Korea University Anam Hospital, Seoul, [5]Department of Dermatology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, [6]Department of Dermatology, Gachon University Gil Medical Center, Incheon, [7]Department of Dermatology, Uijeongbu St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, [8]Department of Dermatology, Chungbuk National University Hospital, Cheongju, [9]Department of Dermatology, Dankook University Hospital, Cheonan, [10]Department of Dermatology, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, [11]Department of Dermatology, SMG-SNU Boramae Medical Center, Seoul, [12]Department of Dermatology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Received March 30, 2021
Revised July 14, 2021
Accepted July 25, 2021

Corresponding Author
Sang Woong Youn
Department of Dermatology, Seoul National University Bundang Hospital,
82 Gumi-ro 173beon-gil, Bundang-gu,
Seongnam 13620, Korea
Tel: +82-31-787-7312
Fax: +82-31-787-4058
E-mail: swyoun@snu.ac.kr
https://orcid.org/0000-0002-5602-3530

*These authors have equally contributed to the article.

Background: In psoriasis treatment, not all body regions improve simultaneously after clinical interventions.
Objective: This study was aimed at evaluating clinical responses across body regions, which may differentially influence patient treatment plans.
Methods: This prospective, observational, and multi-center study was conducted in Koreans who adhered to ustekinumab treatment based on criteria per local label and reimbursement guidelines. A total of 581 were included in this analysis.
Results: The mean (±standard deviation) psoriasis area severity index (PASI) score at baseline, age, disease duration, and body surface area (%) were 18.9±9.69, 44.2±13.29 years, 11.3±9.65 years, and 27.8±17.83, respectively. Across the head and neck, upper extremities, trunk, and lower extremities, the correlation between the PASI sub-scores for the upper and lower extremities was the highest (r=0.680). The mean PASI sub-score for the lower extremities was the highest at baseline. PASI90 and PASI100 scores were the highest for the head and neck region, indicating the highest response rates, while those for the lower extremities were consistently low at all visits.
Conclusion: We found differences in regional ustekinumab responses, with the lower extremities being the most difficult to treat. These findings should be considered in psoriasis treatment.

Keywords: Body regions, Psoriasis, Treatment, Ustekinumab

INTRODUCTION

Psoriasis is a chronic inflammatory disease characterized by plaques that display erythema (redness), infiltration (thickness), and desquamation (scaliness) on the skin due to a systemic immune system abnormality and may affect many aspects of a patient' life[1]. Ustekinumab (Stelara®; Janssen-Cilag International NV, Beerse, Belgium) is a fully human monoclonal antibody that inhibits interleukin (IL)-12 and IL-23 by binding to their shared p40 protein subunit[2,3]. Ustekinumab

represents one of a number of biologics that have been approved and demonstrated improved treatment outcomes for psoriasis over the past 10 years[4].

The psoriasis area severity index (PASI) is the standard measurement most often used to determine treatment efficacy in many clinical trials. The PASI evaluates four body regions (the head/neck, upper limbs, trunk, and lower limbs) and three plaque characteristics (erythema, induration/thickness, and scaling). The total PASI score is calculated by summing the regional scores weighted by surface area of the skin[5]. PASI scores are typically reported as a composite measurement that does not account for results for each individual body region. The purpose of this study was to assess and compare the characteristics of and clinical responses to ustekinumab across the four PASI body regions independent of weighting by surface area of each body region. Further, clinical responses across body regions may differentially affect patients' quality of life (QoL) and impact communication with patients for formulating their treatment plans.

MATERIALS AND METHODS

Study design

This was a post-hoc analysis of a postmarketing surveillance study for ustekinumab conducted in Korea[6]. The study enrolled patients aged 18 years or higher to whom ustekinumab was administered for the treatment of psoriasis. Demographic variables (age, sex, body mass index [BMI], and smoking/drinking history), disease-related variables (disease duration, age at diagnosis, comorbidity, and medication history), and disease severity variables (body surface area [BSA], PASI, and physician's global assessment [PGA]) were collected. Data on PASI, as a measure of effectiveness, were collected at baseline and each patient visit. The Institutional Review Board of each participating site reviewed and approved the study protocol (IRB number of the corresponding author's hospital [Seoul National University Bundang Hospital]: B-1112/141-201). Written informed consent was obtained from all participating patients.

Statistical analysis

Descriptive statistics for continuous variables were presented as means with standard deviation (SD), and dichotomous variables were presented as frequencies with percentages in parentheses. Only patients who adhered to treatment based on criteria per local label and reimbursement guidelines were included in the effectiveness assessment. For example, local practice guidelines for ustekinumab stipulate that patients should have a PASI ≥10 and BSA ≥10% at baseline and that treatment after the initial injection should be according to the following dosing intervals; visit 2: 1 month (or 4 weeks)±2 weeks after baseline, and visits 3~6: 3 months (or 12 weeks)±2 weeks after the previous visit. Scores for each of the four PASI body regions were extracted for comparison between the body regions. Pearson's correlation coefficient was used to determine the linear relationship between the baseline PASI subscore for each body region.

To compare effectiveness across the four body regions, a linear mixed-effects model was used with subject-specific intercepts as random effects, an unstructured covariance structure for continuous outcomes, generalized estimating equation with logit link, and compound symmetry correlation for binary outcomes (recommended for analyzing longitudinal or correlated data). The confounding covariates of age and sex were included as fixed effects in all models.

For comparisons of effectiveness between the four body regions at each post-baseline visit, the assessment of PASI response (PASI75, 90, and 100) included only patients with PASI sub-scores of ≥1 for the body regions at baseline. Furthermore, determination of the proportion of patients achieving a score of 0 for each of the clinical signs (erythema [redness], infiltration [thickness], and desquamation [scaliness]) assessed in the PASI included only patients with a baseline score of ≥2 (moderate to very marked) for each respective body region. Severity at baseline (reflected by body region PASI or clinical signs scores) was used as a covariate. All statistical tests were performed using two-sided tests, and p-values <0.05 were considered statistically significant. All analyses were performed using the statistical software package SAS 9.4 (Statistical Analysis System; SAS Institute, Cary, NC, USA).

RESULTS

Baseline characteristics

In all, 581 patients with psoriasis who adhered to ustekinumab treatment based on criteria per local label and reimbursement guidelines were included in the analysis. The mean (±SD) age of the patients was 44.2±13.29 years, and 391 patients

(67.3%) were male. The mean BMI, disease duration, and age at diagnosis were 24.3±3.58 kg/m^2, 11.3±9.65 years, and 32.9±15.07 years, respectively. Regarding psoriasis-associated comorbidities, 60 (10.3%), 37 (6.4%), 31 (5.3%), 27 (4.6%), and 20 (3.4%) patients had hypertension, type 2 diabetes mellitus, obesity, psoriatic arthropathy, and dyslipidemia, respectively. Furthermore, 60.6% (n=352) of the patients did not have a smoking history, and 39.1% (n=227) had no history of drinking at baseline. The mean BSA (%) and PASI were 27.8±17.83 and 18.9±9.69, respectively. Regarding prior treatment, 83.8% (n=487) of the patients had been treated with phototherapy, 84.7% (n=492) had received oral agents, and 9.6% (n=56) had previously used biologics (Table 1).

Table 1. Baseline characteristics*

Category	No. of available patients	Value†
Age (yr)	581	44.2±13.29
Sex	581	
Male		391 (67.3)
Female		190 (32.7)
Body mass index (kg/m^2)	578	24.3±3.58
Disease duration (yr)	566	11.3±9.65
Age at diagnosis (yr)	566	32.9±15.07
Comorbidity‡	581	
Hypertension		60 (10.3)
Type 2 diabetes mellitus		37 (6.4)
Obesity		31 (5.3)
Psoriatic arthropathy		27 (4.6)
Dyslipidemia		20 (3.4)
Hepatic steatosis		10 (1.7)
Tinea pedis		9 (1.5)
Liver function test abnormal		7 (1.2)
Osteoporosis		6 (1.0)
Smoking history	581	
Never		352 (60.6)
Current		132 (22.7)
Former		97 (16.7)
Drinking history	581	
Never		227 (39.1)
Current		257 (44.2)
Former		97 (16.7)
Disease-specific variables		
BSA (%)	581	27.8±17.83
PASI	581	18.9±9.69
PGA≥'moderate'	581	508 (87.4)
Prior treatment	581	
Phototherapy		487 (83.8)
Oral agent		492 (84.7)
Biologics		56 (9.6)

Values are presented as mean±standard deviation or number (%). BSA: body surface area, PASI: psoriasis area severity index, PGA: physician's global assessment. *Total number of patients in the analysis set was 581. †Percentages are based on the number of available patients per variable. ‡Comorbidity includes lists with a frequency of 1% or higher.

Correlations between the four PASI body regions (the head and neck, trunk, upper extremities, and lower extremities) at baseline are presented in Table 2. The head and neck showed fair or moderate correlation, in the range of 0.323~0.447, with the other body regions. However, the correlation between the trunk and upper extremities or the trunk and lower extremities showed a positive linear relationship (r=0.638 and 0.606, respectively), and the correlation between the upper and lower extremities was the highest (r=0.680). Comparison of the mean baseline PASI sub-scores revealed significant differences between the body regions, with the highest being for the lower extremities. Furthermore, the mean PASI sub-score for the lower extremities was also the highest in each of the five stratified total PASI score groups (Table 3). In addition, there were significant differences in the proportions of patients with involvement of each clinical sign between body regions, with the highest proportions showing involvement of the lower extremities for each sign (Table 3).

Effectiveness over time between the body regions

With regard to the PASI75 response, the head and neck scores generally indicated the lowest response rates through visit 6 among the four body regions (Fig. 1A). In addition, signifi-

Table 2. Correlation between body regions (n=581)

Pearson's correlation coefficient (r)	PASI (H)	PASI (T)	PASI (U)	PASI (L)
PASI (H)	1.000			
PASI (T)	0.406	1.000		
PASI (U)	0.447	0.638	1.000	
PASI (L)	0.323	0.606	0.680	1.000

PASI: psoriasis area severity index, H: head and neck, T: trunk, U: upper extremities, L: lower extremities. All *p*-values are <0.0001.

Table 3. PASI score and clinical sign by body regions at baseline

Category	No. of available patients	Body region*				*p*-value
		Head and neck	Trunk	Upper extremities	Lower extremities	
PASI						
Body region score at baseline	581	12.9±11.38	19.0±11.78	17.5±11.16	21.1±11.70	<0.0001
Body region score at baseline by the total PASI group						
10≤total PASI <15	269	9.0±8.22	12.3±5.32	11.1±5.11	13.5±4.62	<0.0001
15≤total PASI <20	134	12.2±8.78	16.6±5.79	15.8±6.22	19.3±4.67	<0.0001
20≤total PASI <25	61	12.8±9.38	21.8±7.89	19.7±6.13	26.1±7.46	<0.0001
25≤total PASI <30	48	17.5±11.53	28.5±8.02	25.6±7.19	29.1±6.35	<0.0001
30≤total PASI	69	26.3±16.16	41.2±12.00	38.4±12.41	44.2±10.82	<0.0001
Points for clinical sign ≥2 points (moderate)						
Erythema (redness)	581	395 (68.0)	535 (92.1)	521 (89.7)	556 (95.7)	<0.0001
Infiltration (thickness)	581	298 (51.3)	450 (77.5)	461 (79.3)	487 (83.8)	<0.0001
Desquamation (scaliness)	581	288 (49.6)	425 (73.1)	423 (72.8)	477 (82.1)	<0.0001
Point of area ≥2 points (10%~29%)	581	400 (68.8)	520 (89.5)	505 (86.9)	558 (96.0)	<0.0001

Values are presented as mean±standard deviation or number (%). PASI: psoriasis area severity index. PASI score's *p*-values pertain to the 'body region' effect from the linear mixed-effects model with 'age', 'sex', and 'body region' as fixed effects; 'intercept (i.e., subject-specific)' as a random effect; and unstructured covariance as covariance structure. Clinical sign's *p*-values pertain to the 'body region' effect from the generalized estimating equation with 'age', 'sex', and 'body region' as covariates; 'body region' as a repeated measure; and compound symmetry correlation as working correlation. *Percentages are based on the number of available patients per variable.

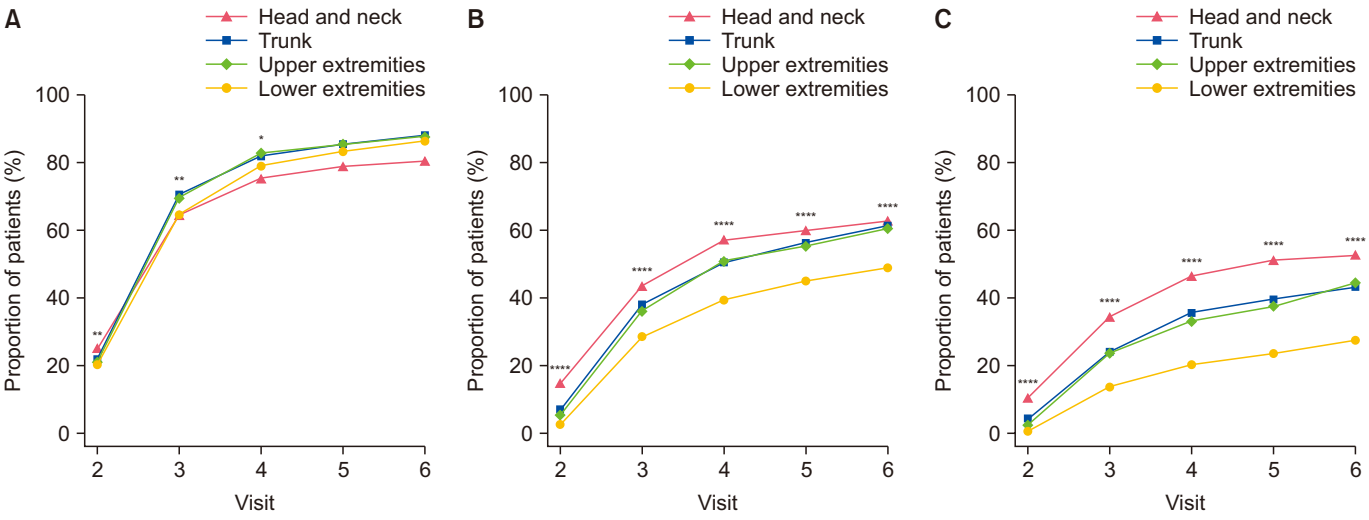

Fig. 1. Psoriasis area severity index (PASI) response by body region. (A) PASI75 response; (B) PASI90 response; and (C) PASI100 response. Overall *p*-value of 'body region' *$p<0.05$, **$p<0.01$, ****$p<0.0001$.

cant differences in PASI90 and PASI100 responses were noted between the body regions at all visits. Ironically, the head and neck region showed the highest PASI90 and PASI100 response rates, while those for the lower extremities were markedly lower at all visits (Fig. 1B, C). Comparison of improvements in clinical signs indicated significant differences in erythema and infiltration between the body regions at all visits. Additionally, the lower extremities showed the lowest rates of achieving a score of 0 at all visits for all clinical signs (Fig. 2), and erythema (redness) showed the lowest response rates across clinical signs in all body regions at all visits (Fig. 3)

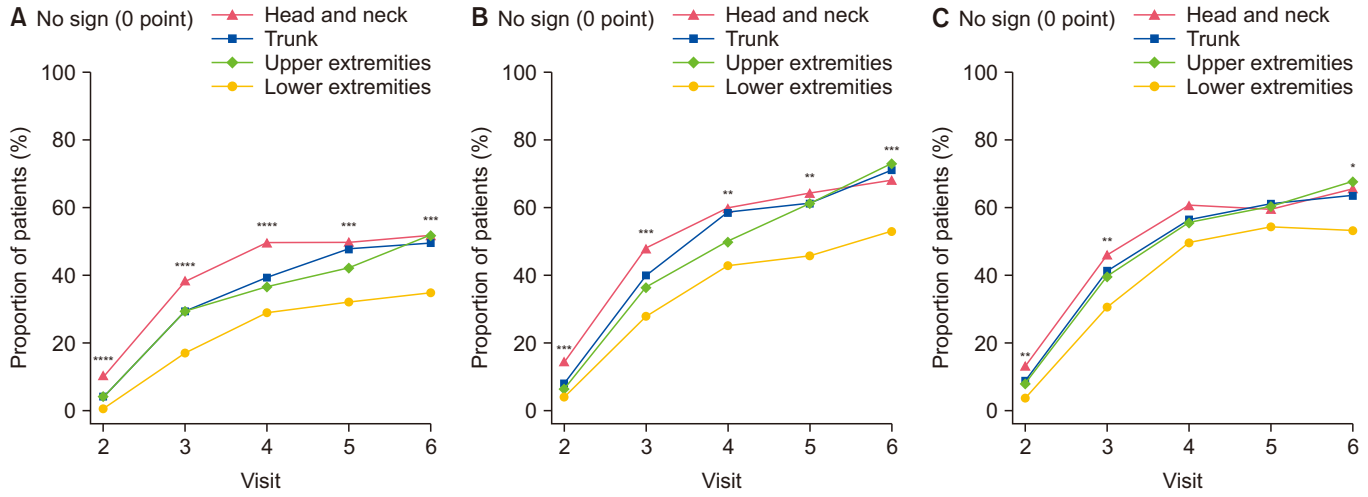

Fig. 2. Clinical sign response by body region; (A) erythema (redness), (B) infiltration (thickness), and (C) desquamation (scaliness). Overall *p*-value of 'body region' *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$.

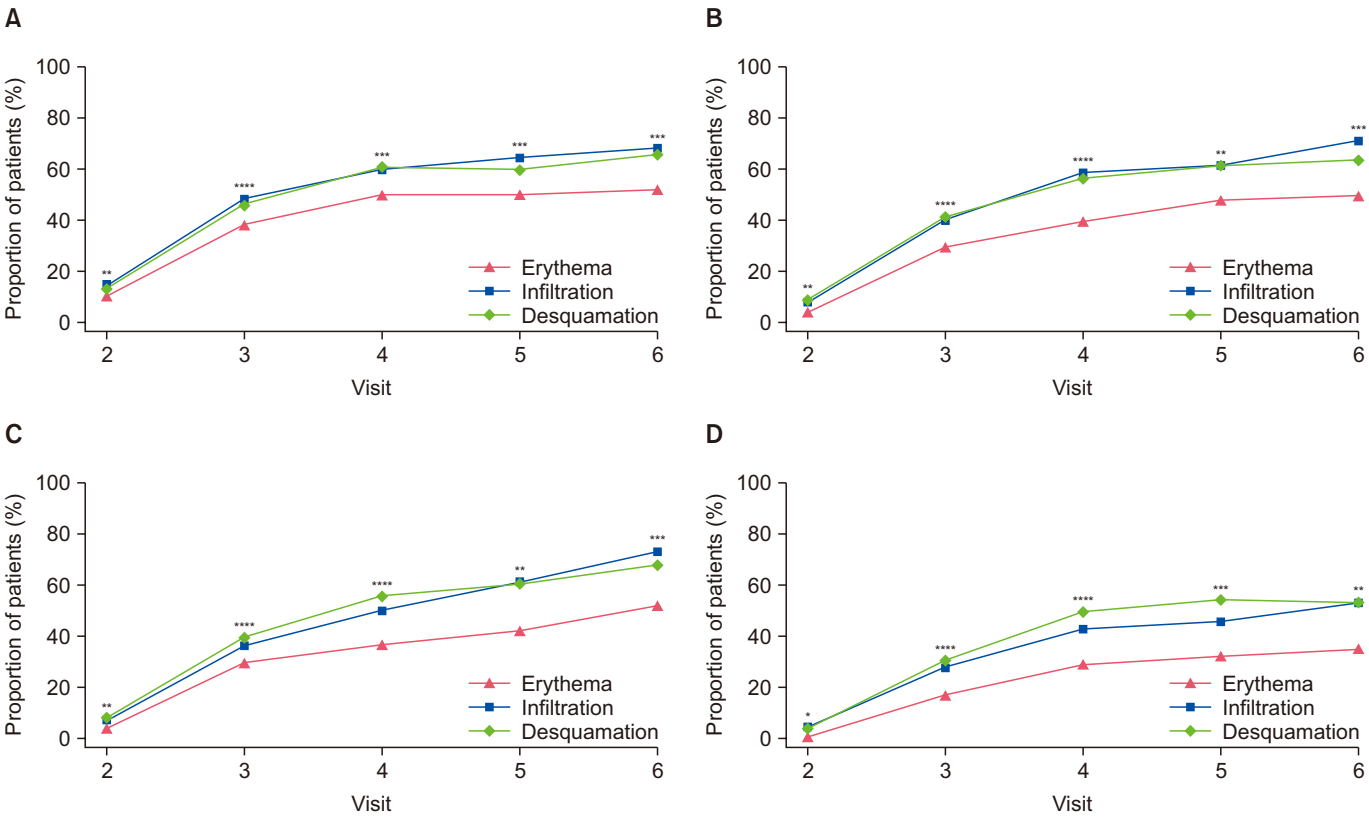

Fig. 3. Response in body regions by clinical sign. No signs (0 point) in head and neck (A), trunk (B), upper extremities (C), and lower extremities (D). Overall *p*-value of 'body region' *$p<0.05$, **$p<0.01$, ***$p<0.001$, ****$p<0.0001$.

DISCUSSION

Patients who achieve a PASI75 or even a PASI90 response using biologics show persistent residual psoriatic lesions in certain areas. If patterns in areas in which lesions persist despite biological treatment can be identified, patient expectations may be set more accurately during the course of care. Overall, 581 patients who adhered to local label and reimbursement

guidelines for ustekinumab treatment from among 977 patients with psoriasis who were enrolled in this postmarketing surveillance study in Korea were included in the analysis to address regional differences in the extent of disease at baseline and response to ustekinumab treatment.

With regard to the degree and severity of psoriasis across the four body regions at baseline, correlation between the head and neck and the other body regions was low (r=0.323~0.447). In particular, correlation between the head and neck and the lower extremities was the lowest (r=0.323). Comparison of PASI sub-scores across the four body regions at baseline showed that those for the head and neck were the lowest (12.9±11.38) and those for the lower extremities were the highest (21.1±11.70). Similarly, comparison of the severity of clinical signs across the four body regions at baseline showed that the proportions of patients with moderate to very marked (score of ≥2) erythema (redness), infiltration (thickness), and desquamation (scaliness) were the lowest for the head and neck region and highest for the lower extremities (68.0% vs 95.7% for erythema; 51.3% vs 83.8% for infiltration; and 49.6% vs 82.1% in desquamation, respectively). Therefore, differences in disease burden by region should be considered when evaluating the overall degree of severity of psoriasis in individual patients.

The disease burden of facial psoriasis is significant[7]; scalp psoriasis has also been reported to have a negative impact on patients' QoL and affect patient health physically and psychologically regardless of psoriasis severity[8,9]. Previous reports indicate that the body region with the greatest negative impact of psoriasis on QoL and highest disease burden is the head and neck. However, our results show that the most severely affected body region based on objective PASI assessments is the lower extremities rather than the head and neck, which implies that QoL and disease severity are not necessarily related and their relationship may be affected by the body regions involved. Plaque-type psoriasis is known to develop commonly at the elbows, knees, and scalp; however, it can affect other parts of the body as well[10]. Larko[11] reported that the scalp, nail, sole, and intertriginous area were particularly difficult areas to treat[12]. Patients with psoriatic lesions at such sites may experience a psychological burden because of their visibility[13] and the negative impact on work productivity[14].

Our results showed that PASI90 and PASI100 responses were the highest for the head and neck, the body region with the greatest impact of psoriasis on patients' QoL. To our knowledge, these findings are the first to suggest that the head and neck region may tend to show greater improvements in psoriasis compared to other body regions, although head and neck psoriasis may be resistant to biologic treatment in some patients. This may be reflected by our finding that the head and neck region generally showed numerically lower PASI75 response rates relative to those associated with other body regions. This means, in other words, although head and neck region is difficult part to achieve PASI75 response among 4 body regions, however, most of the patients are expected to show high responses (PASI90 & 100 response) if the patients meet clinically meaningful response cut-off (PASI75 response). In addition, with regard to the three clinical signs assessed in the PASI, the lower extremities consistently showed the least improvement at each visit through visit 6 (53.7±2.1, weeks), which also supports that the lower extremities were the most difficult body region to treat. This is consistent with recent findings that the most common sites of recalcitrant psoriasis are on the lower legs[15]. Therefore, in addition to treating psoriatic lesions on exposed body regions including the head and neck, which affect patients' QoL, attention should be paid to the treatment of the most difficult to treat body region, the lower extremities. Besides, as one of the limitations as well as further study concepts, other specific sites beyond comprehensive 4 body regions should be further investigated. For example, nails, scalp, palms, and soles are known as a part difficult to treat[16]. However, we didn't specify those parts in our study and couldn't see treatment outcomes in those specific sites.

CONFLICTS OF INTEREST

Dr. Sang Wook Son has no conflict of interest to declare. Dae Young Yu, Youngdoe Kim, and Dr. YoungJa Lee are employees of Janssen Korea Ltd. Dr. Hyo Hyun Ahn performed phase II clinical trial sponsored by Regeneron, and phase III trial by Novartis, Pfizer, and Galderma. Dr. Yong Hyun Jang served as a speaker or consultant for AbbVie, Eli Lilly, GlaxoSmithKline, LEO Pharma, Janssen, Sanofi Genzyme, and Novartis also performed phase III clinical trials sponsored by Pfizer and Eli Lilly. Dr. Joo Young Roh served as a adviser or investigator for clinical trials for Novratis, Eli-Lilly, Janssen, Abbvie, BMS and Regeneron and Sanofi. Dr. Young Bok Lee served as a speaker for AbbVie, Janssen, Novartis and has engaged or been work-

ing as a principal investigator or sub-investigator in number of clinical trials sponsored by Janssen, Novartis, and Sanofi. Dr. Ji Yeoun Lee served as a speaker for Novartis. Dr. Myung Hwa Kim served as a speaker for Novartis and has engaged or been working as a principal investigator or sub-investigator in number of clinical trials sponsored by Eli- Lilly, Janssen, LEO Pharma, Novartis, Abbvie, and Sanofi. Dr. Gyeong-Hun Park and Dr. Hyun-Sun Yoon have no conflict of interest to declare. Dr. Sang Woong Youn served as a speaker for AbbVie, Eli Lilly, Janssen, and Novartis and also performed phase III clinical trials sponsored by AbbVie, BMS, Eli Lilly, Janssen, Novartis and UCB.

FUNDING SOURCE

This study was sponsored by Janssen Korea Ltd.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Sang Wook Son, https://orcid.org/0000-0002-3332-7056
Dae Young Yu, https://orcid.org/0000-0003-1091-5792
Youngdoe Kim, https://orcid.org/0000-0002-0772-6360
Hyo Hyun Ahn, https://orcid.org/0000-0002-1129-5305
Yong Hyun Jang, https://orcid.org/0000-0003-1706-007X
Joo Young Roh, https://orcid.org/0000-0002-9878-6691
Young Bok Lee, https://orcid.org/0000-0002-8642-2479
Ji Yeoun Lee, https://orcid.org/0000-0001-9269-6591
Myung Hwa Kim, https://orcid.org/0000-0002-9072-201X
YoungJa Lee, https://orcid.org/0000-0001-6740-0613
Gyeong-Hun Park, https://orcid.org/0000-0001-8890-8678
Hyun-Sun Yoon, https://orcid.org/0000-0003-1401-2670
Sang Woong Youn, https://orcid.org/0000-0002-5602-3530

REFERENCES

1. Song HJ, Park CJ, Kim TY, Choe YB, Lee SJ, Kim NI, et al. The clinical profile of patients with psoriasis in Korea: a nationwide cross-sectional study (EPI-PSODE). Ann Dermatol 2017;29:462-470.
2. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665-1674.
3. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675-1684.
4. Sawyer LM, Cornic L, Levin LÅ, Gibbons C, Møller AH, Jemec GB. Long-term efficacy of novel therapies in moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis of PASI response. J Eur Acad Dermatol Venereol 2019;33:355-366.
5. Fredriksson T, Pettersson U. Severe psoriasis: oral therapy with a new retinoid. Dermatologica 1978;157:238-244.
6. Youn SW, Yu DY, Kim BS, Kim Y, Kim KJ, Choi JH, et al. Clinical outcomes in adult patients with plaque psoriasis treated with ustekinumab under real-world practice in Korea: a prospective, observational, multi-center, postmarketing surveillance study. J Dermatol 2021;48:778-785.
7. Young Park J, Hyun Rim J, Beom Choe Y, Il Youn J. Facial psoriasis: comparison of patients with and without facial involvement. J Am Acad Dermatol 2004;50:582-584.
8. Sampogna F, Linder D, Piaserico S, Altomare G, Bortune M, Calzavara-Pinton P, et al. Quality of life assessment of patients with scalp dermatitis using the Italian version of the Scalpdex. Acta Derm Venereol 2014;94:411-414.
9. Zampieron A, Buja A, Fusco M, Linder D, Bortune M, Piaserico S, et al. Quality of life in patients with scalp psoriasis. G Ital Dermatol Venereol 2015;150:309-316.
10. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet 2007;370:263-271.
11. Larko O. Problem sites: scalp, palm and sole, and nail. Dermatol Clin 1995;13:771-777.
12. Wozel G. Psoriasis treatment in difficult locations: scalp, nails, and intertriginous areas. Clin Dermatol 2008;26:448-459.
13. Kimball AB, Jacobson C, Weiss S, Vreeland MG, Wu Y. The psychosocial burden of psoriasis. Am J Clin Dermatol 2005;6:383-392.
14. Youn SW, Lee JH, Yu DY, Kim Y, Kim BS, Seo SJ, et al. The relationship between clinical characteristics including presence of exposed lesions and health-related quality of life (HRQoL) in patients with psoriasis: analysis from the nationwide epidemiologic study for psoriasis in Korea (EPI-PSODE study). J Eur Acad Dermatol Venereol 2018;32:1499-1506.

15. Hjuler KF, Iversen L, Rasmussen MK, Kofoed K, Skov L, Zachariae C. Localization of treatment-resistant areas in patients with psoriasis on biologics. Br J Dermatol 2019;181:332-337.
16. Sánchez-Regaña M, Aldunce Soto MJ, Belinchón Romero I, Ribera Pibernat M, Lafuente-Urrez RF, Carrascosa Carrillo JM, et al. Evidence-based guidelines of the spanish psoriasis group on the use of biologic therapy in patients with psoriasis in difficult-to-treat sites (nails, scalp, palms, and soles). Actas Dermosifiliogr 2014;105:923-934.