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Original Article

Factors Associated With Achieving Complete Skin Clearance Compared to Almost Complete Skin Clearance in Patients With Moderate to Severe Psoriasis Treated With Biologics: A Retrospective Chart Review

Eun Ji Hong [1], **Hee Jung Yoon** [1], **Min Jung Kwon** [1], **Jae Yun Kim** [2], **Jung Eun Kim** [2], **Young Lip Park** [1], **SangHoon Lee** [1], **Youin Bae** [3], **Sul Hee Lee** [1]

[1]Department of Dermatology, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Korea
[2]Department of Dermatology, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan, Korea
[3]Department of Dermatology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea

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Corresponding Authors:
Youin Bae
Department of Dermatology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, 59 Daesagwan-ro, Yongsan-gu, Seoul 04401, Korea.
Email: tempugene@naver.com

Sul Hee Lee
Department of Dermatology, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, 170 Jomaru-ro, Bucheon 14584, Korea.
Email: dermalsh@schmc.ac.kr

ABSTRACT

Background: Biologics have demonstrated high efficacy in achieving 'almost complete' skin clearance in patients with moderate to severe psoriasis. Nonetheless, achieving 'complete' skin clearance remains a treatment goal for some highly biologics-resistant patients, as residual lesions impact their quality of life.
Objective: The risk factors for failure to achieve a Psoriasis Area and Severity Index (PASI) 100 response in patients with good response to biologics remain unknown.
Methods: This retrospective study evaluated the risk factors by comparing patients who achieved complete skin clearance (PASI100) with those who achieved almost complete skin clearance (PASI90). A database of 131 psoriasis patients treated with biologics, who achieved a PASI90 or PASI100 response, was reviewed from a tertiary referral hospital in South Korea. The patients were classified into PASI90 and PASI100 groups according to their PASI response.
Results: The PASI100 group had a lower prevalence of smoking history (adjusted odds ratio [OR], 0.34; 95% confidence interval [CI], 0.14–0.85; p=0.021) and psoriasis on the anterior lower legs at baseline (adjusted OR, 0.18; 95% CI, 0.03–0.99; p=0.049) than patients in the PASI90 group.
Conclusion: This study suggested that smoking history and psoriatic skin lesions on the anterior lower legs are considered as the risk factors for the failure to achieve a PASI100 response in psoriasis patients treated with biologics.

Keywords: Biologics; Psoriasis; Risk factors

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that affects approximately 2% of adult population in Western countries[1,2]. It is characterized by well-demarcated red, scaly papules and plaques, which have a significant negative impact on patients' quality of life (QoL). Research has shown a strong correlation between the severity of the disease, as measured by the Psoriasis Area and Severity Index (PASI), and the Dermatology Life Quality Index score in patients with moderate to severe psoriasis[3,4]. Biologics, which inhibit key cytokines such as interleukin-12/23, -17, and -23, have demonstrated remarkable efficacy and favorable safety profiles in these patients. Recently, a 90% improvement in the PASI score from baseline, known as PASI90, has become a standard treatment goal for biologics[5]. Consequently, the use of biologics has significantly reduced the social burden caused by psoriasis and greatly improved overall QoL[5-7].

Nonetheless, achieving 'complete' skin clearance (PASI100) with biologics still remains a challenge for some treatment-resistant patients[8,9]. Recent studies have shown significant differences in health-related QoL between patients with 'complete' skin clearance and those with 'almost complete' skin clearance demonstrating that even small residual lesions can be important for patients treated with biologics[10-15]. Although risk factors for treatment failure (<PASI75) have been investigated[16-21], the differences between patients who achieved PASI90 and those who achieved PASI100 have yet to be determined. Therefore, this study aims to identify potential risk factors that make it difficult to achieve PASI100 among patients with moderate to severe psoriasis who have already achieved PASI90 with biologics.

MATERIALS AND METHODS

In this retrospective study, data from 131 patients with moderate to severe psoriasis who underwent ongoing biologics therapy and achieved an improvement of more than 90% in their PASI scores were reviewed. The data were collected over 10 years, from January 2011 to August 2021, at a tertiary referral hospital, specifically the Department of Dermatology at Soonchunhyang University Hospital in Bucheon, South Korea. The severity and extent of psoriasis were assessed using PASI and body surface area (BSA).

Inclusion and exclusion criteria

We included patients aged ≥19 years who were diagnosed with plaque psoriasis through a skin biopsy and had been treated with biologics for more than one year, exhibiting a PASI90 or PASI100 response. These patients had moderate to severe psoriasis with both PASI ≥10 and BSA ≥10 despite receiving phototherapy or other conventional systemic drug therapy (such as cyclosporine or methotrexate) for more than 3 months before starting biologics. Patients who failed to achieve a PASI100 response despite more than one year of ongoing biologics therapy were assigned to the PASI90 group, while those who achieved a PASI100 response during the study period were assigned to the PASI100 group. The biologics administered to the patients included guselkumab, ixekizumab, risankizumab, secukinumab, and ustekinumab.

Patients who were pregnant or lactating, had hypersensitivity to biologics, had a history or current signs of an uncontrolled medical condition (including malignancy and active tuberculosis), and failed to achieve a PASI90 response were excluded from the study. The study was approved by the relevant Institutional Review Board (IRB; IRB No. SCHBC 2022-01-010) and was conducted in accordance with the principles of the Helsinki Declaration of 1964 and its subsequent amendments.

Data extraction and analysis

The following data were extracted: age, sex, duration of psoriasis, duration of biologics treatment, body mass index (BMI), smoking status, history of psoriatic arthritis (PsA) or ankylosing spondylitis (AS), type of currently used biologics, and history of previous biologics treatment. The history of PsA or AS was documented through a self-report questionnaire regarding symptoms, and radiographic examinations were not performed. The baseline PASI of each patient and the time taken to achieve PASI90 or PASI100 were also collected. Lastly, it was determined whether the patients' skin lesions were located in difficult-to-treat areas at baseline and the time of PASI90 achievement, including the scalp, nails, lower legs, palms, and soles.

Statistical analysis

The demographic and clinical characteristics of the patients were presented as proportions and numbers for categorical variables and as means and standard deviations for continuous variables. The patients were divided into 2 groups based on treatment outcomes: the almost complete skin clearance (PASI90) group and the complete skin clearance (PASI100) group. Age, sex, duration of psoriasis, baseline PASI, BMI, smoking status, history of PsA or AS, presence of difficult-to-treat areas at baseline, history of previous biologics use, and the time taken to achieve PASI90 were considered as potential risk factors for failure to achieve a PASI100 response. Differences between the groups were compared using the 2-sample t-test for continuous variables and Pearson's χ^2 test for categorical variables. The linear relationship between risk factors and the failure to achieve a PASI100 response was evaluated through univariable and multivariable logistic regression analyses. The multivariable analysis included variables from the univariable analysis that showed a significant association with PASI100.

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A *p*-value less than 0.05 was considered statistically significant. All statistical analyses were conducted using Rex software (version 1.0; RexSoft Inc., Seoul, Korea).

RESULTS

Demographics and clinical characteristics

Among the 131 patients treated for moderate to severe psoriasis, 80 were included in the PASI90 group and 51 were included in the PASI100 group. The demographic and clinical characteristics of the 2 groups are summarized in **Table 1**. The PASI90 group consisted of 56 males (70%) and 24 females (30%), while the PASI100 group consisted of 25 males (49%) and 26 females (51%). The mean age of all patients was 43.85±11.49 years (range, 20–69 years), with the PASI90 group having a mean age of 42.94±11.48 years and the PASI100 group having a mean age of 45.29±11.59 years (p≥0.05). The duration of biologics treatment was over 1 year for all patients, with a mean duration of 194.86±144.35 weeks (range, 52–540 weeks) for the entire patient group. The mean time to achieve PASI90 was 26.90±33.40 weeks for all patients, with the PASI90 group taking 30.14±40.51 weeks and the PASI100 group taking 21.82±16.25 weeks (p≥0.05). The mean time required to achieve PASI100 in the PASI100 group was 71.71±42.27 weeks. Among the total patients, 27 (20.6%) experienced biologics switching, with 19 (23.8%) in the PASI90 group and 8 (15.7%) in the PASI100 group (p≥0.05). There was no significant difference in the currently used biologics types between the PASI90 and PASI100 groups (p≥0.05). All patients had skin lesions in difficult-to-treat areas at baseline, with the lower extremities being the most common area. After achieving a PASI90 response, 63 patients (78.8%) in the PASI90 group and 25 patients (49%) in the PASI100 group still had difficult-to-treat areas.

In summary, the 2 groups showed significant differences in terms of sex (p=0.026), baseline PASI (p=0.005), BMI (p=0.012), the number of patients with BMI ≥25 (p=0.002), smoking history (p=0.003), the presence of lesions on the anterior lower legs at baseline (p=0.015), the presence of difficult-to-treat lesions at PASI90 achievement (p=0.001), and the presence of scalp lesions at PASI90 achievement (p=0.029).

Table 1. Demographic and clinical characteristics of patients with moderate to severe psoriasis treated with biologics

Characteristics	PASI90 group (n=80)	PASI100 group (n=51)	*p*-value
Sex†			0.026*
Male	56 (70.0)	25 (49.0)	
Female	24 (30.0)	26 (51.0)	
Age (yr)‡	42.94±11.48	45.29±11.59	0.256
Duration of psoriasis history (yr)‡	16.96±9.65	16.00±10.31	0.589
Baseline PASI‡,§	20.16±10.30	16.28±5.27	0.005*
BMI (kg/m²)‡	26.04±4.58	23.87±4.98	0.012*
BMI ≥25 kg/m²†	45 (56.3)	14 (27.5)	0.002*
Ever-smoker†	41 (51.3)	12 (23.5)	0.003*
PsA or AS†	16 (20.0)	5 (9.8)	0.191
Difficult-to-treat areas at baseline§	80 (100.0)	51 (100.0)	-
Scalp†	55 (68.8)	31 (60.8)	0.455
Palm and sole†	7 (8.8)	1 (2.0)	0.227
Anterior lower legs†	78 (97.5)	43 (84.3)	0.015*
Posterior lower legs†	74 (92.5)	43 (84.3)	0.235
Nails†	25 (31.3)	11 (21.6)	0.313
Biologics switching†	19 (23.8)	8 (15.7)	0.373
Current biologic agents			
Guselkumab†	27 (33.8)	18 (35.3)	1.000
Ixekizumab†	11 (13.8)	7 (13.7)	1.000
Risankizumab†	7 (8.8)	5 (9.8)	1.000
Secukinumab†	19 (23.8)	8 (15.7)	0.373
Ustekinumab†	16 (20.0)	13 (25.5)	0.601
Duration of biologics treatment (wk)‡	188.74±144.80	204.47±145.45	0.529
Time needed to achieve PASI90 (wk)‡	30.14±40.51	21.82±16.25	0.104
Time needed to achieve PASI100 (wk)	-	71.71±42.27	-
Difficult-to-treat areas at the time of PASI90 achievement†	63 (78.8)	25 (49.0)	0.001*
Scalp†	33 (52.4)	6 (24.0)	0.029*
Palm and sole†	4 (6.3)	1 (4.0)	1.000
Anterior lower legs†	50 (79.4)	19 (76.0)	0.953
Posterior lower legs†	36 (57.1)	11 (44.0)	0.380
Nails†	16 (25.4)	3 (12.0)	0.276

Values are presented as number (%) or mean ± standard deviation.
PASI: psoriasis area and severity index, BMI: body mass index, PsA: psoriatic arthritis, AS: ankylosing spondylitis.
*p<0.05.
†Pearson's χ^2 test was used to analyze categorical variables.
‡A 2-sample t-test was used to analyze continuous variables.
§Patients had received phototherapy or systemic cyclosporine/methotrexate treatment for more than 3 months prior to the initiation of biologics.

Factors associated with complete skin clearance in patients on biologics with moderate to severe psoriasis

Univariable and multivariable logistic regression analyses were performed to estimate the probability of failure to achieve a PASI100 response based on potential risk factors. The odds ratios (ORs) of the risk factors are summarized in **Table 2**.

In the univariable logistic regression analysis, the PASI100 group exhibited a significantly lower proportion of men (OR, 0.41; 95% confidence interval [CI], 0.20–0.85; p=0.017). Additionally, the proportion of ever-smokers was significantly lower (OR, 0.29; 95% CI, 0.13–0.64; p=0.002), as well as the number of patients with skin lesions on the anterior lower legs at baseline (OR, 0.14; 95% CI, 0.03–0.68; p=0.015). The likelihood of achieving a PASI100 response decreased with each 0.01-unit increase in BMI (OR, 0.90; 95% CI, 0.82–0.98; p=0.015), and with 0.1-unit increase in baseline PASI (OR, 0.94; 95% CI, 0.88–0.99; p=0.022). However, no significant associations were observed between other factors, including age, and a PASI100 response.

In the multivariable logistic regression analysis, after adjusting for confounding factors, sex, BMI, and baseline PASI did not

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Table 2. Univariable and multivariable logistic regression analyses of variables associated with complete skin clearance in patients with moderate to severe psoriasis treated with biologics

Characteristics	Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sex				
Male	0.41 (0.20–0.85)	0.017*	0.84 (0.36–1.98)	0.696
Female	1.00			
Age (1 yr older)	1.02 (0.99–1.05)	0.254	-	-
Duration of psoriasis history (1 yr longer)	0.99 (0.96–1.03)	0.586	-	-
Baseline PASI (0.1-unit increase)†	0.94 (0.88–0.99)	0.022*	0.97 (0.92–1.02)	0.254
BMI (0.01-unit increase)	0.90 (0.82–0.98)	0.015*	0.94 (0.86–1.03)	0.191
Ever-smoker	0.29 (0.13–0.64)	0.002*	0.34 (0.14–0.85)	0.021*
PsA or AS	0.43 (0.15–1.27)	0.128	-	-
Difficult-to-treat areas at baseline†				
Scalp	0.70 (0.34–1.47)	0.350	-	-
Palms and soles	0.21 (0.02–1.75)	0.148	-	-
Anterior lower legs	0.14 (0.03–0.68)	0.015*	0.18 (0.03–0.99)	0.049*
Posterior lower legs	0.44 (0.14–1.34)	0.147	-	-
Nails	0.61 (0.27–1.37)	0.228	-	-
Biologics switching	0.60 (0.24–1.49)	0.269	-	-
Time needed to achieve PASI90 (1 week longer)	0.99 (0.97–1.01)	0.186	-	-

ORs are for potential risk factors according to the PASI100 vs. PASI90 group comparison.
OR: odds ratio, CI: confidence interval, BMI: body mass index, PsA: psoriatic arthritis, AS: ankylosing spondylitis, PASI: psoriasis area and severity index.
*$p<0.05$.
†Patients had received phototherapy or systemic cyclosporine/methotrexate treatment for more than 3 months prior to the initiation of biologics.

show statistically significant associations. However, the likelihood of achieving a PASI100 response was significantly lower among ever-smokers (adjusted OR, 0.34; 95% CI, 0.14–0.85; p=0.021). Additionally, patients with psoriatic skin lesions on the anterior lower legs at baseline also had a significantly lower likelihood of achieving a PASI100 response (adjusted OR, 0.18; 95% CI, 0.03–0.99; p=0.049).

DISCUSSION

Psoriasis is a chronic inflammatory skin disease characterized by erythematous plaques and silvery scales accompanied by pain and itching. The prevalence of psoriasis is gradually increasing worldwide, leading to a greater social burden associated with the condition[22]. Fortunately, the introduction of new biologics in recent years has made PASI90 a realistic goal for even moderate to severe psoriasis patients[5]. The severity of psoriatic skin lesions and patient-reported outcomes, which reflect QoL, are generally correlated[3,4]. However, studies have shown differences in patient-reported outcomes between those who achieve 'almost complete' skin clearance and those who achieve 'complete' skin clearance[11,12,14,23]. Nevertheless, research on the characteristics of patients who achieve PASI100 (complete skin clearance) after biologics therapy is still lacking. In this study, we aimed to investigate the characteristics of patients who did not achieve PASI100 despite showing a stable PASI90 response and the potential risk factors associated with achieving PASI100 response.

Table 3 presents a literature review on the clinical characteristics of psoriasis patients with limited efficacy of biologics. Sex, obesity, biologics switching, smoking history, comorbid PsA, and genetic variations have been suggested to be associated with poor response to biologics[23,25,29-34]. Among them, obesity, defined as a BMI of 30 kg/m^2 or higher, has consistently been reported as significantly related to treatment failure in biologics[16,25]. However, these BMI cutoffs may underestimate the risk in the Asian population, leading to the guidelines defining obesity as a BMI of 25 kg/m^2 or higher for Asian populations[35]. In addition, Mastorino et al.[25] demonstrated negative correlations between smoking history and comorbid PsA with PASI100 response in a study involving patients treated with risankizumab.

To our knowledge, the majority of previous investigations have predominantly focused on the treatment failure of biologics, defined as a response below PASI75, and research on the characteristics of patients achieving PASI100 response has been extremely limited. This can be attributed to the relatively short history and narrow indications of biologics, resulting in small sample sizes, short follow-up periods, and the inclusion of heterogeneous types of biologics in each study. None of the previous investigations identified distinguishing characteristics between patients with PASI90 and PASI100 responses, possibly because PASI90 response has generally been considered an excellent response to biologics treatment and has not received much attention from researchers.

Our study suggests that even patients who show an excellent response to biologics may struggle to achieve PASI100 in cases with a history of smoking and anterior lower leg lesions prior to biologics treatment. Smoking produces harmful free radicals and stimulates the secretion of inflammatory cytokines such as tumor necrosis factor-α and interferon-γ[36]. These factors activate immune cells and keratinocytes, thereby worsening psoriasis. Therefore, smoking cessation may be crucial in achieving complete skin clearance and enhancing QoL in these patients.

In the past, the scalp, nails, palms, soles, and intertriginous areas were recognized as classic difficult-to-treat areas rather than the anterior lower legs. However, the lower extremities, especially the anterior lower legs, have recently been demonstrated as difficult-to-treat areas in several investigations as shown in the **Table 4**. Since a significant difference in the prevalence of psoriatic skin lesion on anterior lower legs between patients achieving PASI90 and PASI100 has also been observed in our study, we assume that psoriasis on the anterior lower legs can be considered as one of the possible indicators predicting incomplete response to biological

Table 3. Literature review of the clinical characteristics associated with poor treatment response for biologics

References	Year	Type	No. of patients/ Included studies	Type of biologics	Definition of poor response	Country	Factors
Loft et al.[16]	2022	Cohort study (retrospective)	3,280 patients	Adalimumab, etanercept, infliximab, ustekinumab, guselkumab, brodalumab, ixekizumab, secukinumab, others	Treatment failure to at least 3 different biologics working on at least 2 different pathways	Denmark	High bodyweight (compared with the other patients in study), high BMI (BMI >30)
Warren et al.[24]	2019	Cohort study (prospective)	5,885 patients	Adalimumab, etanercept, ustekinumab	Failure of PASI90 up to 1 yr	UK	Female, non-white ethnicity, smoking (current or ever), high bodyweight (>70 kg), unemployment, psoriasis on the palms and/or soles
Zhou et al.[17]	2020	Meta-analysis	5 studies	Adalimumab, etanercept, ustekinumab, secukinumab, certolizumab, golimumab	Less efficacy of biologics treatment at 6 mo	China	Ever-smoker
Edson-Heredia et al.[21]	2014	Review	15 studies	Adalimumab, alefacept, etanercept, infliximab, ustekinumab	NA	USA	High BMI and bodyweight
Karczewski et al.[18]	2014	Review	NA	NA	NA	Poland	High BMI and bodyweight, severe psoriasis, PsA
Mourad et al.[20]	2019	Meta-analysis	32,194 patients (16 studies)	Adalimumab, etanercept, infliximab, ustekinumab, golimumab, guselkumab	Biologics discontinuation	Canada	Obesity, female
Mastorino et al.[25]	2022	Cohort study (retrospective)	166 patients	Risankizumab	Lower achievement of PASI75, 90, 100 at 16, 28, 40 wk	Italy	Previous biologics failure, obesity (BMI ≥30), smoking (current or ever), PsA
Xie et al.[26]	2018	Cohort study (retrospective)	146 patients	Adalimumab, etanercept, infliximab, ustekinumab	Lower achievement of PASI75 at 12, 24 wk	Australia	High BMI
Schwarz et al.[27]	2021	Cohort study (retrospective)	2,384 patients	Adalimumab, etanercept, infliximab, secukinumab, ustekinumab	Lower achievement of PASI ≤2 at 6 mo	Denmark	High bodyweight (>90 kg, compared with below 70 kg), ever-smoker
Zweegers et al.[28]	2017	Cohort study (prospective)	326 patients	Adalimumab, etanercept, infliximab, ustekinumab	Lower achievement of PASI90 at 24 wk	Netherlands	Baseline PASI <10

BMI: body mass index, PASI: psoriasis area and severity index, NA: not applicable, PsA: psoriatic arthritis.

Table 4. Literature review of difficult-to-treat areas in patients with moderate to severe psoriasis treated with biologics

References	Year	Type	No. of patients	Type of biologics	Country	Difficult-to-treat area
Bardazzi et al.[37]	2022	Observational (retrospective)	240	TNF-α inhibitor, IL-17 inhibitor, IL-12/23 inhibitor, IL-23 inhibitor	Italy	Nails, lower extremities, scalp, feet, hands
Muslimani et al.[38]	2020	Observational (retrospective)	75	Adalimumab, etanercept, infliximab, ustekinumab, guselkumab, secukinumab, ixekizumab	Italy	Elbow, anterior lower legs, forearm
Hjuler et al.[39]	2019	Observational (NA)	146	Adalimumab, etanercept, infliximab, ixekizumab, secukinumab, ustekinumab	Denmark	Anterior lower legs, elbow, posterior lower legs
Won et al.[40]	2023	Observational (NA)	50	Adalimumab, guselkumab, ixekizuamb, secukinumab, ustekinumab	Korea	Anterior lower legs, knee, posterior lower legs, scalp, back
Son et al.[41]	2022	Observational (prospective)	581	Ustekinumab	Korea	Lower extremities

NA: not applicable, TNF: tumor necrosis factor, IL: interleukin.

agents. Previous investigations have revealed a tendency for psoriasis on the lower legs and elbows not to improve significantly even in patients achieving PASI90 or higher[38,41]. These areas are known to be common sites for the Koebner phenomenon due to repetitive friction induced by factors such as up-regulation of abnormal cytokines, autoantigen unmasking, and resident memory T cells[38,42,43]. Furthermore, in addition to the Koebner phenomenon, the lower legs are also a potential site of venous stasis and hydrostatic pressure[37]. One study has demonstrated that histologically, psoriasis on the lower legs has characteristics resembling chronic venous stasis dermatitis, such as spongiosis and vessel proliferation, which differ from typical psoriasis[44]. Further research is needed to understand the exact mechanisms behind the relationship between anterior lower leg involvement and resistance to biologics.

Additionally, it is important to note that all patients included in this study, despite achieving a stable PASI90 response with biologics, had at least one difficult-to-treat area. This emphasizes the need for additional research focused on these challenging areas, not only the anterior lower legs, to get a better understanding of the response to biologics treatment in the future.

This study has several limitations. Due to the small sample

size, we couldn't analyze the factors associated with PASI100 response for each specific class of biologics. Nevertheless, our study holds significance for its unique perspective, demonstrating factors associated with achieving completes skin clearance among a group previously classified as good responders. Secondly, in the PASI90 group, some individuals may have achieved PASI100 later through extended treatment beyond the study period. However, based on the literature, PASI100 response rates typically increase rapidly within the first 6 months and show no significant additional increase after 12 months, with stable outcomes observed for 3 to 5 years[9,32,45]. Given that we included patients over a relatively long median follow-up period of 195 weeks and defined patients who failed to achieve a PASI100 response despite more than one year of ongoing biologic therapy as belonging to the PASI90 group, we believe that we may have minimized those possibilities. Finally, since we aimed to focus on the previously known treatment-resistant area, and some patients included in this study refused to have photographs taken of sensitive areas such as the genital area, we couldn't analyze the difference in the prevalence of every part of the body between these groups.

Nevertheless, this study has the following strengths. It is the first study to statistically analyze patients who achieved a stable PASI90 response but not PASI100, in comparison to those achieving PASI100 in Korea. Given the widespread achievement of PASI90 in psoriasis patients treated with biologics, this study holds significant importance. In addition, our study identified smoking and psoriatic skin lesions on anterior lower legs as obstacles to achieving complete skin clearance in patients with stable and excellent responses. We also suggest that they can be considered as the potential indicators of incomplete response to biological agents in moderate to severe psoriasis. Therefore, detailed localization of skin lesions and an assessment of smoking habits would be helpful in predicting and enhancing the therapeutic response to biologics when treating patients with moderate to severe psoriasis and cessation of smoking would be recommended for achieving complete skin clearance even in the patients with PASI90 response. We believe that our study provides insights into the optimal treatment of biologics for patients in real-world settings, contributing to the development of improved treatment strategies and enhancing patients' QoL.

ORCID iDs

Eun Ji Hong
https://orcid.org/0000-0002-6393-0534
Hee Jung Yoon
https://orcid.org/0000-0002-3992-5313
Min Jung Kwon
https://orcid.org/0000-0003-1751-7092
Jae Yun Kim
https://orcid.org/0000-0002-5023-8880
Jung Eun Kim
https://orcid.org/0000-0002-8399-8456
Young Lip Park
https://orcid.org/0000-0002-6532-3156
SangHoon Lee
https://orcid.org/0000-0002-7146-3702
Youin Bae
https://orcid.org/0000-0003-3184-7960
Sul Hee Lee
https://orcid.org/0000-0002-2990-9774

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

DATA SHARING STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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