

Evaluation of the Physician Global Assessment and Body Surface Area Composite Tool for Assessing Psoriasis Response to Apremilast Therapy: Results from ESTEEM 1 and ESTEEM 2

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ABSTRACT

Background: The Physician Global Assessment and Body Surface Area (PGAxBSA) composite tool is a simple, effective alternative for measuring psoriasis severity.

Objective: To evaluate the product of PGAxBSA as a sensitive alternative to the Psoriasis Area and Severity Index (PASI) for assessing disease severity and therapeutic response with data collected from the phase 3 ESTEEM 1 and 2 trials.

Methods: This post hoc analysis included 836 patients randomized to apremilast 30 mg BID at baseline (ESTEEM 1, n=562; ESTEEM 2, n=274). Spearman correlation coefficients were used to compare PGAxBSA, PASI, and the Dermatology Life Quality Index (DLQI). Concordance between PGAxBSA and PASI was evaluated for 50%/75%/90% improvement from baseline at week 16.

Results: In ESTEEM 1 and 2, PGAxBSA and PASI exhibited significant positive correlations for measuring disease severity at baseline ($r \geq 0.757$) and week 16 ($r \geq 0.807$). At week 16, ≥79% concordance was observed between PGAxBSA and PASI for 75% and 90% improvement from baseline; greater concordance (>88.0%) was observed using 50% improvement from baseline. At week 16, PGAxBSA and PASI were moderately correlated with DLQI.

Limitations: Analysis was limited to patients with baseline BSA ≥10% and static PGA ≥3.

Conclusions: In patients with moderate to severe psoriasis, PGAxBSA is correlated with PASI and sensitive to therapeutic response.

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INTRODUCTION

The assessment of psoriasis disease activity in a consistent and clinically meaningful way is critically important for clinicians and clinical research. The Psoriasis Area and Severity Index (PASI), the Physician Global Assessment (PGA), and the percentage of body surface area (BSA) involvement are commonly used to assess psoriasis disease activity in clinical trials.[1,2] The PASI is a composite tool that combines the assessment of disease severity and BSA involvement into a single score ranging from 0 (no disease) to 72 (maximum disease).[3] The PASI score is derived from a complex multistep formula that is weighted based on the total BSA of each region. Static PGA rating scales assess erythema, desquamation, and induration characteristics of psoriatic plaques using 5- to 8-point scales that are less complex than PASI[4]; however, most PGA tools do not account for BSA involvement and thus do not include a key aspect of disease severity (Table 1).[1,2] For example, a patient with severe disease characterized by 32% BSA and sPGA of 4 at baseline may resolve with treatment to a single scaly red raised lesion that covers 0.25% of body area (Figure 1). The PGA score would remain unchanged based on the nature of the plaque characteristics alone, suggesting no clinical improvement in disease severity. Similarly, the percentage of BSA involvement is easily estimated, but does not evaluate the intensity of the psoriatic lesion and is subject to high inter observer variability.[1,4] Thus, as stand-alone instruments, the static PGA and BSA do not consistently provide global assessment of psoriasis disease activity (Table 1).[4]

A psoriasis severity measurement tool using the product of the static PGA and the percentage of BSA involvement, the Physician Global Assessment and Body Surface Area (PGAxBSA composite tool; also known as s-MAPA), accounting for both extent and severity of psoriasis disease activity, has been developed to provide a simple global assessment of psoriasis disease activity and has been examined as an alternative to the PASI.[5] When the PGA is multiplied by the BSA, the resulting score provides an accurate global assessment of disease severity that can be done relatively quickly (Figure 2). In a study using data

TABLE 1.

Comparison of Common Tools for the Assessment of Psoriasis Disease Severity

	Erythema	Desquamation	Induration	BSA	Ease of Use
PASI	+	+	+	+	++
BSA	-	-	-	+	+++
PGA	+	+	+	-	+++

BSA=body surface area; PASI=Psoriasis Area and Severity Index; PGA=Physician Global Assessment.

from a clinical trial registry, the PGAxBSA assessment of disease severity correlated well with that of PASI, and demonstrated sensitivity to changes from baseline in a cohort of patients with mild to moderate psoriasis. A subgroup analysis demonstrated that PGAxBSA performed well in the subset of participants with severe disease (ie, participants with BSA ≥10%).[5] These findings suggest that PGAxBSA is a simple and effective alternative for measuring psoriasis severity compared with PASI.

Apremilast (Otezla, Celgene Corporation, Summit, NJ) is an oral small-molecule phosphodiesterase 4 inhibitor that works to elevate cyclic adenosine monophosphate in immune cells, which in turn regulates the production of pro-inflammatory mediators, including tumor necrosis factor-α, interleukin-23 and interleukin-17, and anti-inflammatory mediators implicated in the pathogenesis of psoriasis.[6,7] Apremilast was approved by the US Food and Drug Administration in 2014 and by the European Commission in 2015 for the treatment of adult patients with moderate to severe plaque psoriasis and adult patients with active psoriatic arthritis who are candidates for phototherapy or systemic therapy.[8,9] The approval for patients with moderate to severe plaque psoriasis is based on the findings of the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) phase 3 clinical trial program comprising 2 randomized, placebo-controlled studies that evaluated the efficacy, safety, and tolerability of apremilast 30 mg BID for the treatment of moderate to severe plaque psoriasis for up to 52 weeks, with a long-term extension to 5 years.[10,11] In these studies, apremilast was well tolerated and demonstrated statistically significant and clinically meaningful improvements as measured by PASI-75 response at 16 weeks (primary end point), which was generally maintained in patients continuing apremilast for 52 weeks.[10,11]

The present post hoc analysis evaluated the PGAxBSA and PASI tools as measures of (1) psoriasis severity and (2) therapeutic response in patients receiving apremilast treatment in the phase 3 ESTEEM 1 and ESTEEM 2 clinical trials.

METHODS

Study Design and Participants

ESTEEM 1 (NCT01194219) and ESTEEM 2 (NCT01232283) were similarly designed, phase 3, multicenter, randomized, double-blind, placebo-controlled studies of apremilast 30 mg BID

FIGURE 1. Clinical example of disease severity assessment using PASI, BSA, and PGA.

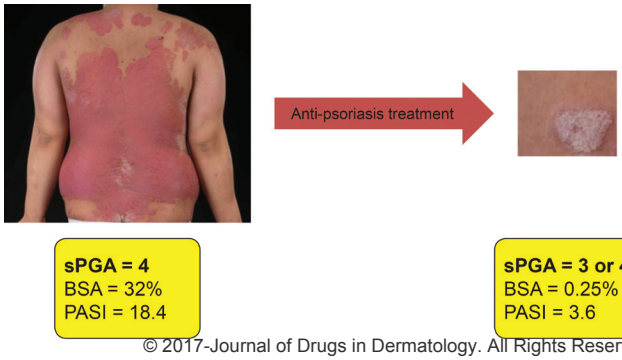
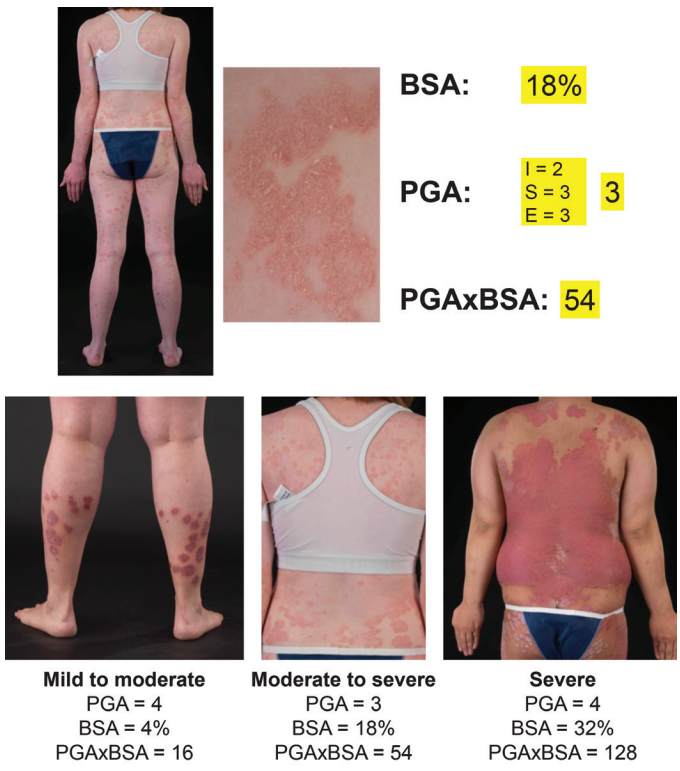


FIGURE 2. Clinical examples of disease severity assessment using PGAxBSA.



in patients with chronic moderate to severe plaque psoriasis (PASI ≥12; BSA ≥10%; static PGA ≥3) who were candidates for phototherapy and/or systemic therapy. Full details of the study design, inclusion and exclusion criteria, patient population, and primary safety and efficacy results for ESTEEM 1 and ESTEEM 2 have been described previously.[10,11]

Analysis End Points and Assessments

Assessments in the present post hoc analysis included PASI, static PGA, BSA, and Dermatology Life Quality Index (DLQI) scores as determined according to the ESTEEM 1 and 2 clinical trial protocols at scheduled visits among patients receiving apremilast. The PASI score consisted of the sum of the erythema, induration, and desquamation for each body region, multiplied by weighted area scores, with higher scores (range: 0 to 72) indicating greater severity.[3] The static PGA used in the ESTEEM 1 and 2 trials consisted of a 5-point rating scale ranging from 0 (clear) to 4 (severe) that reflects the severity of erythema, induration, and scaling across all psoriatic lesions (Table 2).[10,11] Assessment of overall severity was made by factoring in areas that have already been cleared (ie, scores of 0) and remaining lesions for severity (ie, the severity of each sign is averaged across all areas of involvement, including cleared lesions). In the event of different severities across disease signs, the sign that is the predominant feature of the disease was used to help determine the static PGA score. Average erythema, induration, and scaling were scored separately over the whole body and the severity scores were summed and averaged including cleared lesions. The total average was rounded to the nearest whole number score to determine the PGA score and category. BSA was defined as the percentage of total body surface area involvement, with each 1% estimated based on the entire palmar surface of the patient's hand. The PGAxBSA score was calculated by multiplying the static PGA score by the BSA (range: 0 to 400 [eg, maximum static PGA = 4 and maximum BSA = 100]).[5] The DLQI, a 10-item patient-reported questionnaire commonly used to assess health-related quality of life in clinical trials of patients with chronic plaque psoriasis, was used to assess the impact of skin disease on quality of life and daily activities, with higher scores (range: 0 to 30) indicating worse quality of life.[12]

Statistical Analysis

Patients initially randomized to receive apremilast at baseline were included in the current post hoc analysis; at each time point, data as observed and sufficient for evaluation were used for analysis, with no imputation for missing values. Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

Correlation Between PGAxBSA and PASI

Spearman correlation coefficients were calculated to evaluate the relationship between PGAxBSA and PASI scores at baseline and at week 16 of apremilast treatment.

Agreement between PGAxBSA and PASI scores was further assessed based on intra-class correlation coefficients and response concordance rates, using improvements from baseline of 50%, 75%, and 90% as the response thresholds in both scales. Specifically, at week 16, concordance was calculated as: (number of patients without PASI response and without PGAxBSA response) + (number of patients with PASI response and with PGAxBSA response) / the total number of patients with sufficient data for evaluation. Patients were considered overrated if response was achieved based on PGAxBSA, but not achieved based on PASI. Patients were considered underrated if response was achieved based on PASI, but not achieved based on PGAxBSA. PGAxBSA, and PASI responsiveness to therapeutic change was assessed based on effect sizes (vs placebo) at week 16.

TABLE 2.

Static PGA Scale Used in the ESTEEM Studies

Score	Category	Description
0	Clear	• Plaque elevation=0 (no elevation over normal skin) • Scaling = 0 (no evidence of scaling) • Erythema = 0 (except for residual hyperpigmentation/hypopigmentation)
1	Almost clear	• Plaque elevation=± (possible but difficult to ascertain whether there is a slight elevation above normal skin) • Scaling = ± (surface dryness with some desquamation) • Erythema = ± (faint, diffuse pink or slight red coloration)
2	Mild	• Plaque elevation=slight (slight but definite elevation, typically edges are indistinct or sloped) • Scaling = fine (fine scale partially or mostly covering lesions) • Erythema = mild (light red coloration)
3	Moderate	• Plaque elevation=marked (marked definite elevation with rough or sloped edges) • Scaling = coarser (coarser scale covering most or all of the lesions) • Erythema = moderate (definite red coloration)
4	Severe	• Plaque elevation=marked (marked elevation typically with hard or sharp edges) • Scaling = coarser (coarse, non-tenacious scale predominates, covering most or all of the lesions) • Erythema = severe (very bright red coloration)

TABLE 3.

Patient Demographics and Baseline Characteristics in ESTEEM 1 and ESTEEM 2

Characteristics	ESTEEM 1	ESTEEM 2
	Apremilast 30 mg BID n=562	Apremilast 30 mg BID n=274
Age, mean (SD), y	45.8 (13.1)	45.3 (13.1)
Male, n (%)	379 (67.4)	176 (64.2)
Duration of plaque psoriasis, mean (SD), y	19.8 (13.0)	17.9 (11.4)
PASI score (0-72), mean (SD)	18.7 (7.2)	18.9 (7.1)
PASI score >20, n (%)	158 (28.1)	81 (29.6)
BSA, mean (SD), %	24.4 (14.7)	25.5 (15.4)
BSA >20%, n (%)	266 (47.3)	143 (52.2)
Static PGA score of 3 (moderate), n (%)	401 (71.4)	198 (72.3)
Static PGA score of 4 (severe), n (%)	161 (28.6)	75 (27.4)
DLQI (0-30), mean (SD)	12.7 (7.1)	12.6 (7.2)

The n reflects the number of randomized patients; actual number of patients available for each parameter may vary.
BSA=body surface area; DLQI=Dermatology Life Quality Index; ESTEEM=Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; PASI=Psoriasis Area and Severity Index; SD=standard deviation; PGA=Physician Global Assessment.

The relationships between PGAxBSA and PASI and other measures of psoriasis severity, such as static PGA and DLQI, were assessed at baseline and week 16. Responsiveness to change was evaluated by Spearman correlation analyses correlating changes in PGAxBSA and PASI scores to changes in static PGA and DLQI scores.

RESULTS

Patients

The current post hoc analysis included a total of 836 patients who were randomized to receive apremilast at baseline in ESTEEM 1 (apremilast 30 mg BID: n=562) and ESTEEM 2 (apremilast 30 mg BID: n=274). Demographic and baseline disease characteristics of the included patients are summarized in Table 3.

Correlation analysis: PGAxBSA and PASI

Among patients receiving apremilast in both ESTEEM 1 and ESTEEM 2, statistically significant (P<0.0001) positive correlation coefficients were demonstrated between PGAxBSA and PASI in measuring disease severity at baseline (r≥0.757) and week 16 (r≥0.807; Table 4). Intra-class correlation coefficients values also demonstrated significant, positive agreement between PGAxBSA and PASI values among patients in both studies who received apremilast (Table 4). Both the PGAxBSA and PASI were associated with the Cohen's effect sizes >0.8, indicating that PGAxBSA and PASI had similar measurement of treatment effect at week 16 (Table 4).

Concordance of PGAxBSA and PASI Response Thresholds (improvement from baseline, 50%, 75%, 90%)

At week 16 in ESTEEM 1 and ESTEEM 2, ≥79% concordance was observed between PGAxBSA and PASI (which included the total number of patients with agreement on both scales [response achievement and non-achievement]) at thresholds of 75% and 90% improvement from baseline; greater concordance (>88%) was observed using a threshold of 50% improvement from baseline (Figure 3). Most cases of non-concordance included patients who achieved the PGAxBSA response threshold, but did not achieve the same relative improvement from baseline on the PASI, indicating that PGAxBSA overrated their improvement relative to PASI (Figure 3). Similar patterns of concordance were observed for PGAxBSA and PASI using these response thresholds at week 32 in ESTEEM 1 and 2 (data not shown).

Responsiveness to Change Analyses

In ESTEEM 1 and ESTEEM 2, changes in PGAxBSA and PASI demonstrated statistically significant positive correlations with changes in static PGA at week 16, with all correlations of a generally similar magnitude (Table 5). Moderate positive correlations that were generally similar in magnitude were also observed between changes in DLQI and changes in PGAxBSA and PASI at week 16 in ESTEEM 1 and ESTEEM 2 (Table 5).

DISCUSSION

The findings from the post hoc analysis of ESTEEM 1 and 2 are consistent with and extend those of previous reports investigating the validity of the PGAxBSA as a measure of disease severity and therapeutic response.[5,13,14] Initial retrospective analyses using data from the Utah Psoriasis Initiative, a registry with more than 1,200 consecutively enrolled psoriasis patients, found that PGAxBSA correlated well with PASI for the assessment of

TABLE 4.

PASI and PGAxBSA Correlations and Effect Sizes						
	PASI Mean (SD)	PGAxBSA Mean (SD)	Spearman Correlation: PASI vs PGAxBSA	ICC (95% CI): Standardized PASI vs PGAxBSA	Effect Size	
					PASI	PGAxBSA
Baseline						
ESTEEM 1 n=562	18.7 (7.2)	81.8 (54.9)	0.757*	0.886 (0.87, 0.90)	NA	NA
ESTEEM 2 n=274	18.9 (7.1)	85.1 (57.5)	0.830*	0.923 (0.90, 0.94)	NA	NA
Change from baseline						
Week 16						
ESTEEM 1 n=499	-10.2 (7.3)	-46.5 (45.8)	0.807*	0.834 (0.81, 0.86)	-1.41	-0.85
ESTEEM 2 n=237	-10.3 (6.9)	-50.0 (48.6)	0.841*	0.859 (0.82, 0.90)	-1.46	-0.87
Week 32						
ESTEEM 1 n=424	-11.3 (6.8)	-53.3 (45.7)	0.742*	0.805 (0.77, 0.84)	-1.57	-0.97
ESTEEM 2 n=191	-10.6 (6.1)	-51.4 (42.2)	0.737*	0.8 (0.74, 0.85)	-1.5	-0.89

*$P<0.0001$.
Note: n values represent the number of patients with sufficient data for PGAxBSA score at time point; actual number of patients with sufficient data for each parameter may vary.
Effect size = (mean change at time point)/SDBaseline; n=patients with value at the time point indicated; standardized = (score – mean)/SD.
CI=confidence interval; ESTEEM=Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; ICC=intra-class correlation coefficients; NA=not applicable; PASI=Psoriasis Area and Severity Index; PGAxBSA=Physician Global Assessment and Body Surface Area composite tool; SD=standard deviation.

psoriasis disease severity in patients with mild to moderate disease (ie, median BSA involvement of 3.0%).[5] A responsiveness to change analysis indicated that PGAxBSA and PASI had similar abilities to capture changes in disease severity. However, response to therapy could not be determined in this study due to the different treatments used in the registry. Similar findings were reported in a retrospective multicenter study using data from the Dermatology Clinical Effectiveness Research Network (DCERN), a consortium of private and academic centers of dermatologists in the United States, that included patients with

FIGURE 3. Concordance between PGAxBSA and PASI categorical response thresholds at week 16 in ESTEEM 1 and ESTEEM 2.

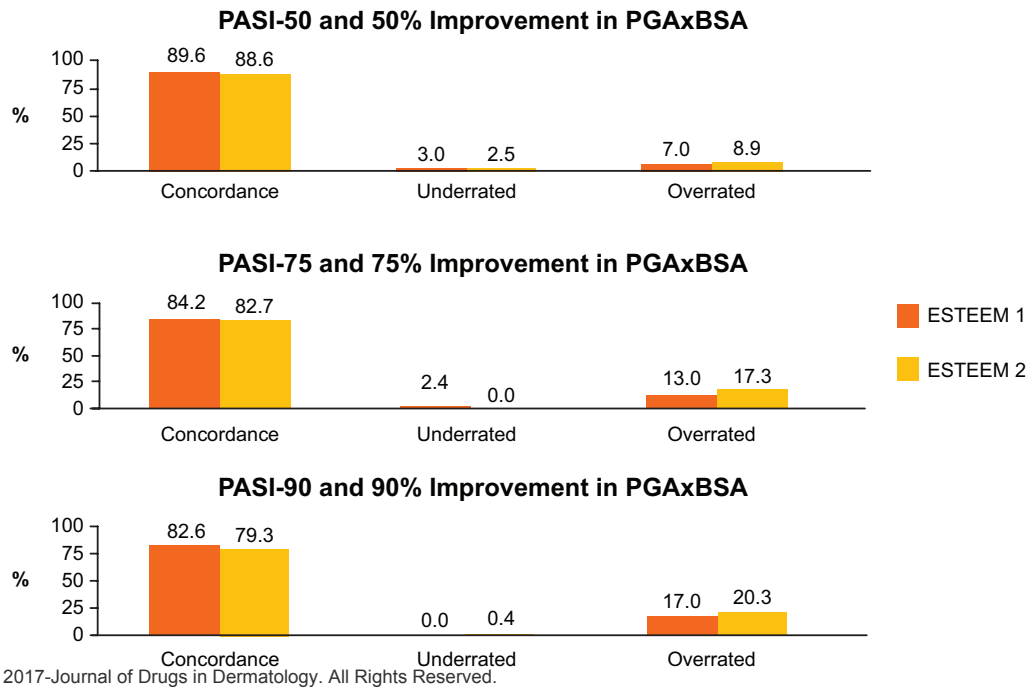


TABLE 5.

Correlations Between PGAxBSA, PASI, and Other Psoriasis Severity Measures

	Static PGA R	DLQI R
Baseline		
PGAxBSA		
ESTEEM 1, n=562	0.441*	0.164*
ESTEEM 2, n=274	0.462*	0.161‡
PASI		
ESTEEM 1, n=562	0.435*	0.159§
ESTEEM 2, n=274	0.434*	0.187‡
Week 16		
ΔDPGAxBSA		
ESTEEM 1, n=499	0.645*	0.268*
ESTEEM 2, n=237	0.559*	0.345*
ΔDPASI		
ESTEEM 1, n=499	0.695*	0.338*
ESTEEM 2, n=237	0.615*	0.415*
Week 32		
ΔDPGAxBSA		
ESTEEM 1, n=424	0.567*	0.217*
ESTEEM 2, n=191	0.570*	0.243§
ΔDPASI		
ESTEEM 1, n=424	0.697*	0.318*
ESTEEM 2, n=191	0.626*	0.293*

*P<0.0001; §P≤0.0007; ‡P≤0.008. Note: n values represent the number of patients with sufficient data for PGAxBSA or PASI score (orΔ) at time point; actual number of patients with sufficient data for each parameter may vary. DLQI=Dermatology Life Quality Index; ESTEEM=Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis; PASI=Psoriasis Area and Severity Index; PGAxBSA=Physician Global Assessment and Body Surface Area composite tool; R=Spearman correlation; Δ=change.

psoriasis and a history of ≥5% BSA.[13,15] In this study, PGAxBSA and PASI were highly correlated with each other (r =0.92; 95% confidence interval [CI] 0.91-0.93), and both had similar moderate correlations with the DLQI (r =0.48; 95% CI 0.44-0.51 vs r =0.47; 95% CI 0.43-0.5).[13] Consistent with these findings from these 2 analyses of clinical registry data, we found that PGAxBSA and PASI exhibited similar high correlation at baseline and week 16 and moderate correlations with DLQI at week 16 in the ESTEEM patient population. PGAxBSA was shown to be well correlated with PASI with respect to assessing responsiveness to therapy in patients with moderate to severe plaque psoriasis.[14] In a large phase 3, randomized, placebo-controlled study comparing etancercept or tofacitinib, a high concordance was observed bewteen PGAxBSA and PASI for 50%, 75%, and 90% improvement from baseline.[14] Consistent with these findings, high levels of concordance between PGAxBSA and PASI were noted at the same response cutoff values for apremilast in the ESTEEM patient population.

It should be noted that different static PGA scales have been used in reported comparisons of PGAxBSA and PASI. Analyses conducted in the registry settings have used a 6-point (0 [clear] to 5 [severe]) PGA scale to assess erythema, induration, and desquamation.[5,13,15] The PGA used in the ESTEEM study consisted of a 5-point scale (Table 2). Similarly, a 5-point PGA scale was used in the analysis of responsiveness of PGAxBSA and PASI from the phase 3 study of etanercept or tofacitinib in patients with moderate to severe psoriasis.[14] Despite this difference in static PGA scales used, the PGAxBSA score has consistently been shown to correlate well with PASI.[5,13,14]

The ability of the PGAxBSA composite tool to provide a simple and consistent measure of global psoriasis disease severity has made it an attractive alternative to PASI. The PASI assessment does not account for incremental changes in disease severity. For example, when assessing disease severity using PASI, a BSA involvement of 1% to 9% will result in a score of 1 whereas a BSA involvement of 10% to 29% will be assigned a score of 2, which on the legs correspond to a BSA variability of 1% to 3% and 4% to 11%, respectively. One limitation of the PASI is its use of a non-linear scale for scoring for area of involvement. As a result, the PASI is insensitive to detecting changes in disease severity at the lower end of the scale, particularly when BSA involvement is <10% because a BSA of 1% to 9% is assigned a single value of 1.[4] Thus, any change within that category would not be reflected in the PASI score. The PGAxBSA overcomes the limitations of the PASI in detecting changes at the lower end of the scale and thus may be particularly useful in assessing response to therapy patients with milder disease (ie, BSA involvement <10%). Initial analysis of PGAxBSA and PASI in patients with low (0.1%-2.9%), moderate (3.0%-9.9%), and high (≥10%) BSA involvement found that PGAxBSA correlated well with PASI and was sensitive in patients with mild disease (BSA <10%).[5] The ease of calculating the PGAxBSA score may make this tool useful in the clinical practice as well as the clinical trial setting. Future studies should aim to validate the scale in clinical practice.

Limitations

This post hoc analysis was limited to patients enrolled in the ESTEEM 1 and ESTEEM 2 studies, which selected individuals with moderate to severe plaque psoriasis with static PGA ≥3 and BSA involvement ≥10%, and thus may not generalize to patients with milder psoriasis.

In conclusion, the findings of this post hoc analysis suggest that the PGAxBSA composite tool may be a simpler, alternative tool for the assessment of disease severity and response to therapy with apremilast, compared with the PASI. Based on

these findings, further research is warranted to evaluate this new assessment tool in prospective studies that include patients with more moderate disease, in whom PASI may be less sensitive to therapeutic change, and to understand the clinical relevance with respect to change in disease severity.

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