ORIGINAL ARTICLE

PGAxBSA composite versus PASI: Comparison across disease severities and as therapeutic response measure for Cal/BD foam in plaque psoriasis

Linda Stein Gold, MD,[a] Jes B. Hansen, PhD,[b,c] Dharm Patel, PhD,[b,c] Karen A. Veverka, PhD,[b,c] and Bruce Strober, MD, PhD[d,e]

Detroit, Michigan; Madison, New Jersey; Ballerup, Denmark; and New Haven and Cromwell, Connecticut

Background: The product of the Physician Global Assessment and body surface area (PGA×BSA) is simpler to use than the Psoriasis Area and Severity Index (PASI), which lacks sensitivity in patients with mild psoriasis.

Objective: To compare the PGA×BSA versus the modified PASI (mPASI) for assessing disease severity and therapeutic response to calcipotriol/betamethasone dipropionate (Cal/BD) foam.

Methods: This post hoc analysis evaluated the efficacy of Cal/BD foam in mild, moderate, and severe psoriasis, as assessed by the PGA×BSA and mPASI, using data from 3 randomized controlled trials (NCT01536886, NCT01866163, NCT02132936). Spearman correlation and Bland-Altman plots were used to compare the PGA×BSA with the mPASI.

Results: Proportions of patients receiving Cal/BD foam achieving 75% response for PGA×BSA and mPASI at weeks 1, 2, and 4 were similar and significantly greater than with vehicle ($P \leq .002$ at all timepoints); at week 4, mean improvements were 51.0% and 50.7%, respectively. Spearman correlations for mild, moderate, and severe psoriasis were moderate to high between PGA×BSA and mPASI at baseline ($r = .51$, .72, and .86, respectively; n = 126, 465, and 58, respectively) and high at week 4 ($r = .80$, .81, and .89, respectively; n = 121, 452, and 58, respectively) ($P < .001$).

Limitations: Pooled data from different trials were not prespecified for post hoc analysis. Interrater reliability was not assessed.

Conclusion: Pooled data analysis showed that the PGA×BSA and mPASI correlation was higher with increasing psoriasis severity. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2020.02.077.)

Key words: body surface area; Cal/BD; extent of disease activity; mPASI; psoriasis; PGA×BSA; Physician Global Assessment; severity.

From the Henry Ford Hospital, Detroit[a]; LEO Pharma Inc, Madison[b] and Ballerup[c]; Yale University, New Haven[d]; and Central Connecticut Dermatology Research, Cromwell.[e]

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Correspondence to: Linda Stein Gold, MD, Henry Ford Health System, 6530 Farmington Rd, West Bloomfield, Michigan 48322. E-mail: lstein1@hfhs.org.

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In the evaluation of patients with psoriatic disease in clinical practice and trials, there is a need for an assessment tool that is simple, comprehensive, and accurate. Unfortunately, many tools are complex or fail to account for all aspects of the condition,[1-3] and their variability can make measurement of disease severity inconsistent across studies.[4,5]

One of the most widely used evaluation tools is the Psoriasis Area and Severity Index (PASI). For PASI, an investigator must individually score and then tally several components: body surface area (BSA) involvement (face/scalp, trunk, lower and upper extremities), erythema, induration, and scaling.[1] The final PASI score (range, 0-72) measures overall severity and extent of psoriasis.[1,6] Considered the criterion standard in clinical trials,[1,7] it is complex, rarely used in clinical practice, and insensitive in individuals with mild psoriasis.[1,2] Therefore, in clinical trials that enroll large populations of patients with mild disease, it may not be the most appropriate instrument. Mild disease is important to study because 80% of patients with psoriasis have mild to moderate disease.[8] One alternative to the PASI is the Physician Global Assessment (PGA),[1] which is simpler, based on plaque characteristics, and sensitive in patients with mild disease.[1,5,9] PGA limitations are that its subjective variability may affect interpretation of results across studies,[5] and it does not quantify BSA.[5]

A newer, simpler tool that may overcome some of the challenges of the PASI uses the product of the PGA and BSA (PGA×BSA).[7,10] The PGA is determined by an average of erythema, induration, and desquamation scores.[7] Thus, for a PGA of 4 and BSA of 30%, the PGA×BSA is 120.[7] The final PGA×BSA score (range, 0-400 in our study) accounts for both the severity and extent of disease activity in plaque psoriasis.[7] To date, studies assessing the PGA×BSA as an alternative to the PASI have been confined to limited data sets or analyses, although some information about its utility has accrued.

In a longitudinal registry study, the PGA×BSA correlated well with PASI scores, particularly in patients with mild disease.[7] However, the tool's ability to assess therapeutic response could not be determined because the patients were not evaluated at predefined therapy intervals and were receiving many different therapies.[7] Moreover, its utility in severe disease was unclear, because most of the patients had mild to moderate disease.[7] In 3 different post hoc analyses of pooled data, the PGA×BSA correlated well with the PASI and was considered a sensitive tool for assessing therapeutic response.[3,6,11] Nonetheless, all 3 studies lacked patient populations with mild psoriasis (baseline PASI scores ranged from ≥12 to 22.7).[3,6,11] Although the PGA×BSA can detect the achievement of minimal disease activity in moderate to severe psoriasis, the absence of minimal disease activity data across disease severities has been a recognized limitation.[11]

To guide physicians in effectively using the PGA×BSA as an alternative to the PASI,[3,6,7,9,11-14] especially in patients with mild psoriasis, clinical evidence for its utility derived from a large and comprehensive data set of patients with psoriasis is needed. Such evidence should indicate the tool's sensitivity in measuring therapeutic response to drugs, including topical agents, which are a mainstay of treatment for patients with mild psoriasis.[8]

This post hoc analysis evaluated and compared the PGA×BSA composite score with the modified (excluding head) PASI (mPASI) score in the assessment of disease severity and therapeutic response to calcipotriol plus betamethasone (Cal/BD) foam treatment, a topical treatment for psoriasis.

CAPSULE SUMMARY

- A newer tool, the product of the Physician Global Assessment and body surface area, is simpler to use than the Psoriasis Area and Severity Index, which lacks sensitivity for mild psoriasis.
- Correlation between these tools was higher with increasing psoriasis severity.
- This analysis will help clinicians make informed psoriasis assessment decisions.

METHODS

Study design and participants

Data were pooled from 3 randomized controlled trials conducted in patients with mild to severe psoriasis: 1 phase 2 trial[15] and 2 phase 3 trials, PSO-FAST (Cal/BD Foam in Psoriasis Vulgaris, a Four-Week, Vehicle-Controlled, Efficacy and Safety Trial; NCT01866163)[16] and PSO-ABLE (Psoriasis—The Effect of Prolonged Use of Calcipotriol and Betamethasone Dipropionate Combination Therapy, a Randomized, Active- and Vehicle-Controlled 12-Week Trial; NCT02132936).[17] The post hoc analysis included 848 patients randomly assigned to receive once-daily treatment with topical Cal/BD foam (n = 649) or foam vehicle (n = 199) at baseline. The study design and primary outcomes of all 3 clinical trials have been described in detail.[15-17] Eligible patients were aged 18 years or

Abbreviations used:

BSA:	body surface area
Cal/BD:	calcipotriol/betamethasone dipropionate
CI:	confidence interval
mPASI:	modified Psoriasis Area and Severity Index
mPASI-75:	75% or greater improvement on the modified Psoriasis Area and Severity Index
PASI:	Psoriasis Area and Severity Index
PGA:	Physician Global Assessment
PGA×BSA:	product of Physician Global Assessment and body surface area
PGA×BSA-75:	75% or greater improvement on product of Physician Global Assessment and body surface area
SD:	standard deviation

older and had a PGA score indicating at least mild disease, an mPASI score of 2 or greater, and 2% to 30% BSA (trunk and/or limbs) affected by psoriasis.[15-17] PGA scores for classification of psoriasis severity were 2, mild; 3, moderate; and 4, severe.

Objectives and assessments

The primary objective was to evaluate and compare the PGA×BSA composite to the mPASI for assessing disease severity and therapeutic response to Cal/BD foam. The retrospective efficacy analysis used pooled data from the Cal/BD foam and vehicle groups in the intention-to-treat population at baseline and at weeks 1, 2, and 4. The efficacy endpoints in the clinical studies before pooling were the PGA, BSA, and the mPASI.

Statistical analysis

Nonresponder imputation analysis was done for binary endpoints, and last-observation-carried-forward analysis was used for continuous endpoints, in the efficacy analysis when comparing Cal/BD foam to vehicle; however, only observed values were used when analyzing mPASI versus PGA×BSA and when both values were present. Efficacy endpoints of the mPASI and the proportion of patients with at least 75% reduction in mPASI (mPASI-75), and corresponding measures of PGA×BSA (PGA×BSA-75), were resummarized for the pooled data set.

Correlation between the PGA×BSA and the mPASI was evaluated according to the Spearman correlation coefficient (r) separately for each study and combined using the Fisher z transformation; correlation was stratified by baseline disease severity, visit, and treatment group. Spearman correlations range from −1 to 1, with values of 0 reflecting no correlation, and 1 indicating a perfect positive correlation (and −1 indicating a perfect negative correlation). For visual assessment, scatterplots of mPASI scores versus PGA×BSA values (Supplemental Fig 1; available via Mendeley at http://dx.doi.org/10.17632/5xht9343nc.2#file-9193dea0-08af-4366-ae4b-b51aff29d890) and Bland-Altman plots of differences between mPASI and PGA×BSA values versus the averages of these 2 assessments were used. In the Bland-Altman plots, 95% limits of agreement (defined as the mean difference ± 2 standard deviations) are included, and, assuming normality, 95% of differences are expected to lie within these limits. Furthermore, good agreement between the 2 measures would be indicated by a mean difference close to zero without obvious trends in the plotted points between the difference and average of these 2 assessments. In view of evident trends in the distribution of differences across severities, regression analyses were performed to explore the relationship between the differences and the severity and, thereafter, between the corresponding absolute residuals and the severity. The analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patients

All 848 randomized patients (intention-to-treat population) were included in the pooled analysis and represented mild (19%), moderate (71%), and severe (9%) disease. The mean age of all randomized patients was 51 years; the majority of patients were white and male (Table I). At baseline, the mean BSA involvement was 7.5%, and the mean mPASI score was 7.3. For the 649 patients treated with Cal/BD foam included in the baseline analysis, the mean mPASI score was 7.2, mean PGA was 2.9, and mean duration of psoriasis was 17.1 years. Treatment groups were generally well balanced in terms of demographic and baseline factors (Table I).

Efficacy: PGA×BSA and mPASI results

The proportions of patients achieving 75% response for PGA×BSA and mPASI at weeks 1, 2, and 4 were similar to each other and significantly greater than with vehicle ($P \leq .002$ at all timepoints) (Fig 1). For example, mPASI-75 was achieved by significantly more patients treated with Cal/BD foam (50.7%) at week 4 than by patients treated with foam vehicle (5.5%) (95% confidence interval [CI], 10.53-42.11; $P < .001$). Similarly, at week 4, PGA×BSA-75 was achieved by significantly more patients treated with Cal/BD foam (51.0%) than

Table I. Baseline demographic and disease characteristics*

Characteristic	Cal/BD foam (n = 649)		Foam vehicle (n = 199)		All randomized patients (N = 848)	
Age, y, mean (SD)	52.0	(13.9)	48.0	(14)	51.0	(14.0)
Male, n (%)	417.0	(64.3)	108.0	(54.3)	525.0	(61.9)
Body mass index, kg/m^2, mean (SD)	31.3	(7.3)	31.2	(7.9)	31.2	(7.4)
Race, n (%)						
Black or African American	38.0	(5.9)	10.0	(5.0)	48.0	(5.7)
White	577.0	(89.0)	180.0	(90.5)	757.0	(89.4)
Other†	33.0	(5.1)	9.0	(4.5)	42.0	(5.0)
Duration of psoriasis, y, mean (SD)	17.1	(14.0)	15.8	(12.5)	16.8	(13.7)
BSA, %, mean (SD) at baseline	7.4	(6.3)	7.9	(6.8)	7.5	(6.4)
BSA, %, median (min, max)	5.0	(2, 30)	5.0	(2, 30)	5.0	(2, 30)
mPASI, mean (SD)	7.2	(4.6)	7.5	(5.5)	7.3	(4.8)
PGA, mean (SD)	2.9	(0.5)	2.9	(0.5)	2.9	(0.5)
PGA×BSA, mean (SD)	22.2	(21.2)	24.1	(24.3)	22.6	(22.0)

BSA, Body surface area; *Cal/BD*, calcipotriol/betamethasone dipropionate; *max*, maximum; *min*, minimum; *mPASI*, modified Psoriasis Area and Severity Index; *PGA×BSA*, product of Physician Global Assessment and body surface area; *SD*, standard deviation.
*Values are observed.
†*Other* includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Guatemalan, mixed race, Réunion.

by those treated with foam vehicle (6.5%) (95% CI, 10.1-36.25; $P < .001$) (Fig 1).

The PGA×BSA was a sensitive measure of treatment efficacy for Cal/BD foam. Reductions in the PGA×BSA from baseline at weeks 1 and 4, respectively, were −6.28 and −14.38 for the Cal/BD foam group ($P < .001$) (data not shown), compared with −2.93 and −5.12 for the foam vehicle group ($P < .001$). Reductions in the mPASI from baseline were −2.72 and −5.12, respectively ($P < .001$), for Cal/BD foam (data not shown) and −1.41 and −2.31 for foam vehicle at these timepoints. The percent reduction from baseline for Cal/BD foam using PGA×BSA and mPASI showed the similarity of both tools in demonstrating a change in disease severity. Percent reduction (±standard deviation [SD]) from baseline at week 4 was −64.22% (±42.65) for the PGA×BSA versus −70.24% (±26.37) for the mPASI (data not shown).

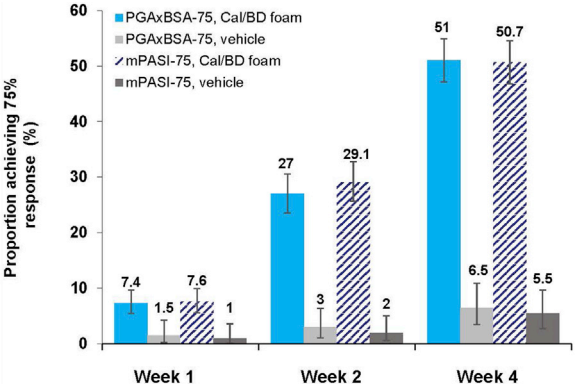

Fig 1. Proportion of patients achieving 75% response for the PGA×BSA or mPASI at weeks 1, 2, and 4. Cal/BD foam, n = 649; foam vehicle, n = 199. Values were calculated using nonresponder imputation. *Cal/BD*, Calcipotriol/betamethasone dipropionate; *mPASI*, modified Psoriasis Area and Severity Index; *PGA×BSA*, product of Physician Global Assessment and body surface area.

Correlation analysis of the mPASI and PGA×BSA

The Spearman correlation coefficient summarizes the strength of the relationship between 2 sets of data. The strength of correlation between the PGA×BSA and mPASI depended on the timing of the study visit and disease severity (Table II). The Spearman correlation between the PGA×BSA and mPASI was moderate to high at baseline and week 1 and was high at weeks 2 and 4. The strongest correlation between the 2 measures was observed at week 4 (Table II). At week 4, the Spearman coefficients for the mPASI versus the PGA×BSA in the Cal/BD foam−treated group were 0.80, 0.81, and 0.89 for patients with mild, moderate, and severe disease at baseline, respectively, and were statistically significant ($P < .001$). Although the Spearman correlation coefficients exhibited moderate to high correlations for the PGA×BSA versus the mPASI, they indicated low correlations for the Dermatology Life Quality Index versus the PGA×BSA and mPASI (data not shown).

By scatterplot analysis, the mPASI measured psoriasis as more severe than did the PGA×BSA in patients treated with Cal/BD foam (Supplemental Fig 1). The Bland-Altman plot was used to visually identify differences and trends between the mPASI and PGA×BSA. The plots further measured the amount of agreement between the 2 instruments at

Table II. Mean PGA×BSA and mPASI by severity and correlation coefficients for the PGA×BSA versus mPASI in patients treated with Cal/BD*

Severity†	mPASI, mean ± SD	PGA×BSA, mean ± SD	Spearman correlation‡: mPASI vs PGA×BSA
Baseline			
Mild (n = 126)	4.57 ± 2.27	9.75 ± 7.43	0.51
Moderate (n = 465)	7.35 ± 4.09	22.56 ± 18.48	0.72
Severe (n = 58)	12.00 ± 7.26	46.03 ± 36.04	0.86
Week 1			
Mild (n = 125)	2.94 ± 1.88	7.76 ± 7.53	0.67
Moderate (n = 455)	4.44 ± 2.94	15.71 ± 13.99	0.74
Severe (n = 57)	7.94 ± 6.38	32.02 ± 31.40	0.86
Week 2			
Mild (n = 123)	1.86 ± 1.49	5.25 ± 5.35	0.73
Moderate (n = 456)	3.09 ± 2.57	11.27 ± 12.34	0.75
Severe (n = 58)	5.47 ± 4.89	24.59 ± 27.65	0.86
Week 4			
Mild (n = 121)	1.27 ± 1.50	3.37 ± 4.66	0.80
Moderate (n = 452)	2.11 ± 2.20	7.69 ± 10.73	0.81
Severe (n = 58)	3.49 ± 3.73	16.84 ± 22.49	0.89

Cal/BD, Calcipotriol/betamethasone dipropionate; *mPASI*, modified Psoriasis Area and Severity Index; *PGA*, Physician Global Assessment; *PGA×BSA*, product of Physician Global Assessment and body surface area; *SD*, standard deviation.
*Values are as observed.
†Mild (PGA, 2); moderate (PGA, 3); severe (PGA, 4). Severity determinations were made at baseline.
‡Interpret Spearmen correlation values using 0.30-0.50 (low), 0.50-0.70 (moderate), 0.70-0.90 (high), and ≥90 (very high) for positive correlations.[3]

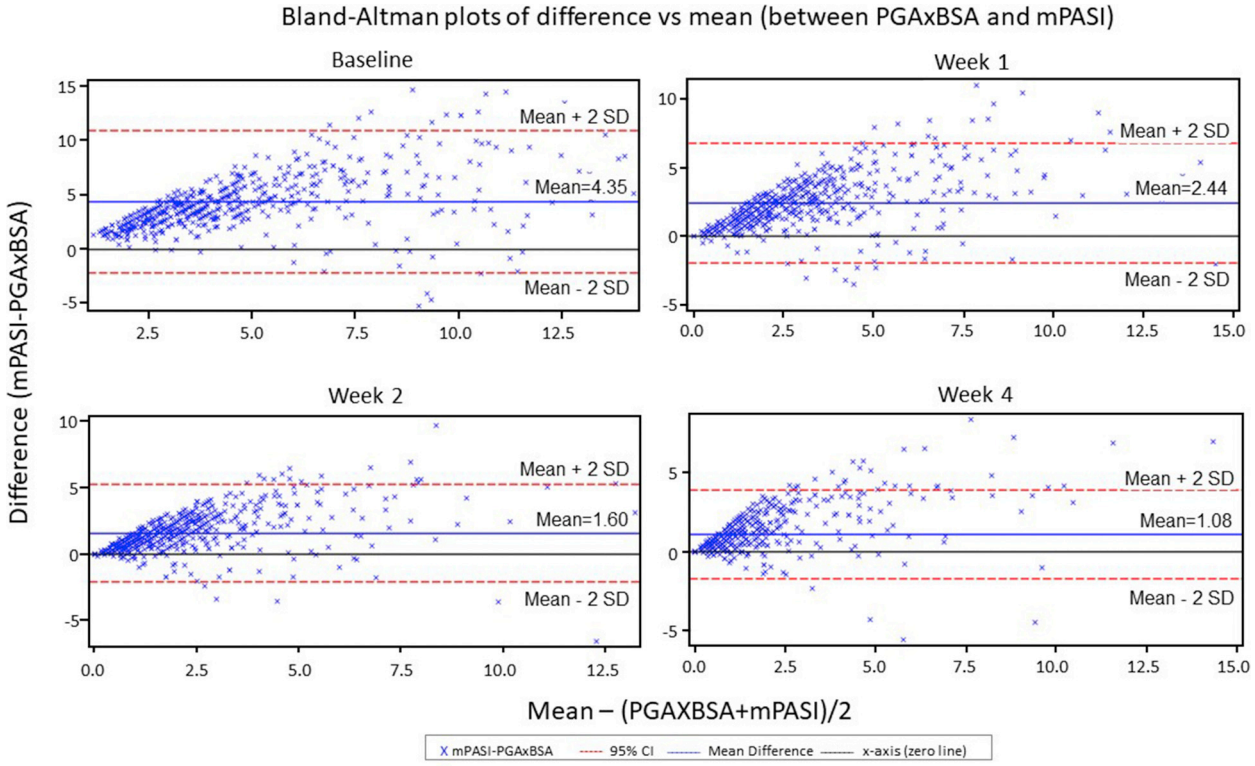

Fig 2. Bland-Altman plots by visit. Values are as observed. Horizontal lines are drawn at the mean difference (blue) and at the 95% confidence interval of limits of agreement (red) between the 2 measurements. *CI*, Confidence interval; *mPASI*, modified Psoriasis Area and Severity Index; *PGA×BSA*, product of Physician Global Assessment and body surface area; *SD*, standard deviation.

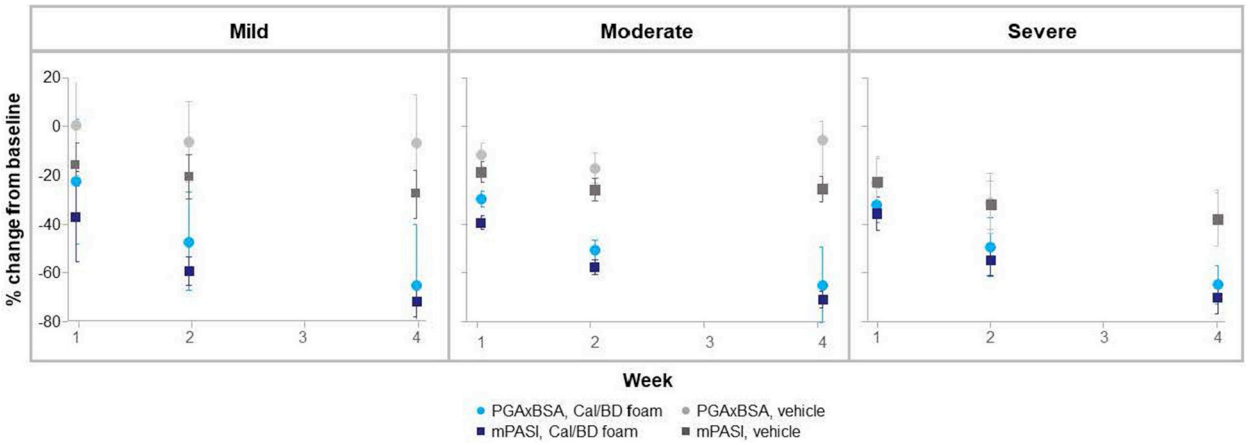

Fig 3. Mean percent change in PGA×BSA versus mPASI from baseline by severity, visit, and treatment. The adjusted mean for each data point is graphed. The adjusted mean was calculated from analysis of variance using last-observation-carried-forward values and adjusted for study and pooled center (random effects) and baseline score (fixed effects). *Cal/BD*, Calcipotriol/betamethasone dipropionate; *mPASI*, modified Psoriasis Area and Severity Index; *PGA×BSA*, product of Physician Global Assessment and body surface area.

baseline and at weeks 1, 2, and 4 (Fig 2). There was a statistically significant association between the difference in the mPASI and PGA×BSA and the severity and, similarly, between the variation in the differences and the severity (by regression analysis). The mean differences between the instruments decreased by visit, with values of 4.35, 2.44, 1.60, and 1.08 from baseline to week 4, respectively. A similar, but weaker, agreement between the instruments was observed in the patients treated with foam vehicle (data not shown).

Percent changes from baseline over time for each outcome measure, stratified by disease severity

The mean percent changes from baseline over time for the PGA×BSA versus the mPASI were stratified by disease severity (Fig 3). In patients with mild disease treated with Cal/BD foam, the mean percent changes (±SD) for weeks 1, 2, and 4 for the PGA×BSA were −19.69 (±35.04), −44.81 (±37.95), and −61.91 (±40.78), respectively, compared with the PASI at −36.02 (±25.54), −58.42 (±27.55), and −71.36 (±29.08), respectively. In contrast, for patients treated with foam vehicle, the mean percent changes (±SD) for the PGA×BSA were 2.88 (±33.60), −3.74 (±35.13), and −3.94 (±43.92), respectively, and for mPASI, they were −14.43 (±21.87), −19.64 (±30.63), and −26.27 (±35.64) respectively. In patients with moderate and severe disease treated with Cal/BD foam, at week 4, the respective mean percent changes (±SD) for the PGA×BSA were −64.67 (±44.83) and −65.66 (±25.62), versus −69.93 (±26.07) and −70.21 (±22.73) for the mPASI.

DISCUSSION

The results of this post hoc analysis showed that the PGA×BSA exhibited significant positive correlations (Spearman) with the PASI for measuring psoriasis severity at baseline and also after 4 weeks of treatment with Cal/BD foam. The majority of patients achieved considerable improvements when treating plaque psoriasis with a once-daily regimen of Cal/BD foam, regardless of which tool was used to assess treatment outcome. Among this study population representing mild (19%), moderate (71%), and severe (9%) disease, the correlation was higher for the PGA×BSA versus the mPASI with increasing psoriasis severity.

Spearman correlations between the PGA×BSA and mPASI for patients with moderate to severe disease were high (r = 0.72-0.89) and consistent with those reported for such patients in several other post hoc analyses (r = 0.74-0.9).[3,6,18] However, some of the studies used in previous post hoc analyses did not assess therapeutic response[7] or did not include patients with plaque psoriasis[14] or with mild disease.[3,6,18] Similarly, a recent post hoc analysis of 4 clinical studies (ERASURE, FEATURE, FIXTURE, and JUNCTURE) was restricted to data from a patient population with moderate to severe disease, whose baseline mean BSA was 33.3% and PASI score was 22.7.[11]

To our knowledge, this current post hoc analysis is unique because it encompasses a comprehensive

data set of patients with mild, moderate, and severe plaque psoriasis, and it assessed therapeutic response. Eligibility required an mPASI of 2 or greater.[15-17] For the overall randomized population, the mean baseline mPASI score was 7.3, BSA was 7.5%, and PGA was 2.9; in contrast, patients with mild psoriasis had a lower mPASI (4.6). The Spearman correlation between the PGA×BSA and mPASI was moderate at baseline for the patients with mild psoriasis versus high in patients with severe psoriasis. By week 4, the population with mild disease treated with Cal/BD foam had high Spearman coefficient correlations between the PGA×BSA and mPASI. Therapeutically, patients treated with Cal/BD foam achieved similar results for PGA×BSA-75 and mPASI-75 responses at weeks 1, 2, and 4. This stands in good agreement with previous studies comparing PGA×BSA-75 and mPASI-75.[3,6,14] The mean percent change in the PGA×BSA from baseline readily detected improvement over time in patients treated with Cal/BD foam with lower baseline BSAs, and this improvement was comparable to the mPASI score.

Although the 2 outcome measures were in good agreement overall, both the timing of the study visit and disease severity affected the strength of the correlation. The Spearman correlation increased with increasing disease severity. This result was a consequence of increasing differences between measurements, rather than reflecting good agreement between the 2 methods.[19,20] We detected increasing differences between the PGA×BSA and mPASI with increasing disease severity. Although the Spearman correlation coefficients between the PGA×BSA and mPASI exhibited moderate to high correlations, they exhibited low correlations for the Dermatology Life Quality Index versus the PGA×BSA and mPASI (data not shown). These correlations between patient outcomes and psoriasis assessment methods are consistent with findings from other studies in which correlations were low to moderate.[3,6,10]

Although the PGA×BSA is a simple and valid tool, it is not an exact substitute for the PASI but, rather, a supplement. The PGA×BSA provides more detailed information at lower disease severities than the mPASI, which, for example, scores all BSAs of less than 10% as a 1 in the area domain. The PGA×BSA is likely an easier instrument to use in both clinical trials and real-world practice settings. Interest in real-world studies is rising, increasing the need for a simpler, easier-to-use tool.[21] Among the variety of data sources for real-world studies (eg, electronic health records), some types of psoriasis outcome measures may not be reported.[2,21,22] Therefore, the PGA×BSA may be useful in cases when PASI outcomes are not available.[2,23]

Limitations of this study were related to data analysis. First, data were pooled from phase 2 and phase 3 trials. However, the primary inclusion and exclusion criteria were the same. Second, there is no standard scale for PGA outcomes; scales vary across clinical trials and range from 4 points to 10 points.[5] Finally, interrater reliability was not assessed in this study. However, interrater reliability has been reported as moderate for the PASI and PGA and high for BSA.[24]

In conclusion, the PGA×BSA is an alternative tool to measure both psoriasis severity and response to therapy. With increasing disease severity, however, the difference between the mPASI and PGA×BSA also increases. Cal/BD is efficacious in psoriasis regardless of the assessment tool used, mPASI or PGA×BSA, and both measures are well correlated. In clinical practice, and after the standardization of the PGA tool is employed, dermatologists might consider the PGA×BSA not only easy to use but also accurate in its measurement of psoriasis severity. Importantly, the calculation of the PGA×BSA takes minimal training and would involve very little additional time during a typical patient encounter.

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