Exploration of the Product of the 5-Point Investigator's Global Assessment and Body Surface Area (IGA × BSA) as a Practical Minimal Disease Activity Goal in Patients with Moderate-to-Severe Psoriasis

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Keywords

Psoriasis · Investigator's Global Assessment · Physician's Global Assessment · Affected body surface area · Minimal disease activity

Abstract

Background/Aims: In the treat-to-target era, psoriasis disease activity measures that can be easily performed in routine clinical practice are needed. This retrospective pooled analysis explored cutoff values of the product of the 5-point Investigator's Global Assessment and percentage of affected body surface area (IGA × BSA) correlating with achievement of minimal disease activity (MDA). **Methods:** Post hoc analysis of the phase 3 clinical trials ERASURE, FIXTURE, FEATURE, and JUNCTURE was conducted to determine associations between IGA × BSA and 2 MDA definitions (Psoriasis Area and Severity Index [PASI] 90 and Dermatology Life Quality Index [DLQI] 0/1, or PASI score ≤1 or BSA <3%) in patients with moderate-to-severe psoriasis receiving secukinumab 300 mg. For each definition of MDA, a range of possible cutoff values of IGA × BSA was examined at each time point. The optimal cutoff value was determined using Youden index (YI), calculated as (sensitivity + specificity – 1). **Results:** For MDA defined as PASI 90 and DLQI 0/1, optimal IGA × BSA

cutoffs were 2.10 at week 12 (YI, 0.60; sensitivity, 0.78; specificity, 0.82), 1.02 at week 24 (YI, 0.55; sensitivity, 0.73; specificity, 0.82), and 1.00 at week 52 (YI, 0.65; sensitivity, 0.79; specificity, 0.86). For MDA defined as PASI score ≤1 or BSA <3%, optimal IGA × BSA cutoffs were 2.98 at week 12 (YI, 0.91; sensitivity, 0.99; specificity, 0.92), 2.80 at week 24 (YI, 0.94; sensitivity, 0.99; specificity, 0.95), and 3.00 at week 52 (YI, 0.96; sensitivity, 1.00; specificity, 0.96). **Conclusion:** IGA × BSA could be a valid measure highly associated with achievement of MDA.

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Introduction

Psoriasis is a common, systemic, chronic immune-mediated disease that manifests mainly as plaque, but other manifestations include guttate, flexural, erythrodermic, pustular, palmoplantar, and/or nail psoriasis [1, 2]. The goal of treatment in patients with psoriasis is to clear skin and normalize health-related quality of life, with the target of achieving minimal disease activity (MDA). Physicians and payers want a treatment target that will be used to make decisions regarding continuing, stopping, or changing treatment [3]. Currently, a variety of treat-

Fig. 1. Flowchart of Materials and Methods.

ments, including topical agents, phototherapy, systemic therapies, and/or biologic therapies are used clinically for psoriasis [4]. The National Psoriasis Foundation guidelines for management of psoriasis recommend a treat-to-target strategy for clinicians and patients to work together to improve treatment decisions, reduce disease burden, and improve clinical outcomes [5].

The Psoriasis Area and Severity Index (PASI) is typically used as a measure of psoriasis disease activity in clinical trials but may not be practical for use in clinical practice. Limitations of the PASI include (1) the need for complex calculations; (2) time-consuming documentation; (3) complex scoring that may not be understood by most clinicians; and (4) non-reader-friendly format due to nonlinearity, with poor sensitivity to change and poor discrimination at lower score ranges [6, 7]. Alternatively, the 5-point Investigator's Global Assessment (IGA) and percentage of affected body surface area (BSA) are measures of psoriasis disease activity that are easily performed in routine clinical practice. Valid but simple, highly feasible measures, such as the product of the 5-point IGA or Physician's Global Assessment (PGA) and percentage of affected BSA (IGA $\times$ BSA or PGA $\times$ BSA, respectively), are easily captured by health-care providers and understood by providers, regulators, and payers.

PGA $\times$ BSA has been validated and used in several studies [7–12]; most notably, PGA $\times$ BSA was highly cor-

related with PASI [7]. Furthermore, correlations between static PGA $\times$ BSA and PASI were stronger than that between BSA and PASI [13]. PGA $\times$ BSA also provided a clinically relevant assessment of MDA in patients with psoriasis, using PASI and Dermatology Life Quality Index (DLQI) response categories as anchors [14, 15].

The simplicity of IGA $\times$ BSA or PGA $\times$ BSA may allow for their potential use in a number of novel applications, such as defining a useful minimal disease criterion for treat-to-target strategies. The focus of this study is on the 5-point IGA and its product with BSA [16–18] that correlates with defined MDA, using data from four phase 3 clinical trials of secukinumab in patients with moderate-to-severe psoriasis.

Materials and Methods

For further details, see the online supplementary material (see www.karger.com/doi/10.1159/000499925 for all online suppl. material) (Fig. 1).

Results

Pooled Baseline Characteristics

A total of 691 patients randomized to receive secukinumab 300 mg were included in the pooled pa-

Table 1. Pooled baseline demographics, clinical characteristics, and treatment history of patients treated with secukinumab 300 mg ($n = 691$)^a

Age, years	44.9 (13.3)
Male, n (%)	477 (69.0)
Body weight, kg	86.6 (23.2)
Body mass index, kg/m ²	29.4 (6.9)
Race, n (%)	
White	505 (73.1)
Asian	129 (18.7)
Native American	29 (4.2)
Black	9 (1.3)
Pacific Islander	4 (0.6)
Other	13 (1.9)
Unknown	2 (0.3)
IGA score, n (%)	
0 = clear	0
1 = almost clear	0
2 = mild	0
3 = moderate	436 (63.1)
4 = severe	255 (36.9)
BSA, % involvement ($n = 690$)	33.0 (18.8)
PASI score	22.7 (9.4)
DLQI score ($n = 676$)	13.5 (7.3)
Severity of psoriasis, n (%)	
Moderate	202 (29.2)
Severe	489 (70.8)
Time since first diagnosis of psoriasis, years	17.0 (12.0)
Psoriatic arthritis present, n (%)	126 (18.2)
Time since first diagnosis of psoriatic arthritis, years	8.1 (8.3)
Previous exposure to psoriasis therapy, n (%)	
Systemic therapy	438 (63.4)
Biologic systemic therapy	146 (21.1)
Nonbiologic systemic therapy	373 (54.0)

All values were calculated on the basis of available data and are presented as means (SD) unless otherwise stated. BSA, body surface area; DLQI, Dermatology Life Quality Index; IGA, 5-point Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index. ^a Patients with moderate-to-severe psoriasis randomized to secukinumab 300 mg in the ERASURE, FIXTURE, FEATURE, and JUNCTURE clinical trials.

tient population from the ERASURE, FIXTURE, FEATURE, and JUNCTURE clinical trials (Table 1). Patients were mostly male (69.0%) and white (73.1%), with a mean (SD) age of 44.9 (13.3) years and a mean (SD) disease duration of 17.0 (12.0) years. All patients had IGA scores of 3 (63.1%) or 4 (36.9%), indicating moderate or severe psoriatic arthritis, respectively. In addition, patients had a mean (SD) percentage of affected BSA of 33.0% (18.8%), a mean (SD) PASI score of 22.7 (9.4), and

Table 2. Optimal IGA $\times$ BSA cutoffs for predictability of PASI 90 and DLQI 0/1 MDA definition (pooled secukinumab 300 mg treatment group)

Week	IGA $\times$ BSA	Sensitivity	Specificity	Youden index ^a
4	8.90	0.8440	0.9000	0.74398
8	3.20	0.8034	0.8261	0.62949
12	2.10	0.7790	0.8191	0.59815
24	1.02	0.7317	0.8190	0.55073
36	0.62	0.8030	0.8333	0.63636
52	1.00	0.7857	0.8605	0.64626

BSA, body surface area; DLQI, Dermatology Life Quality Index; IGA, 5-point Investigator's Global Assessment; MDA, minimal disease activity; PASI, Psoriasis Area and Severity Index. ^a Youden index = sensitivity + specificity – 1.

a mean (SD) DLQI score of 13.5 (7.3), further indicating moderate-to-severe disease activity. Approximately one-fifth of patients (21.1%) had previous exposure to biologic therapy.

Correlations between IGA $\times$ BSA and PASI Score

IGA $\times$ BSA and PASI scores were significantly correlated at week 12 (Pearson correlation coefficient, 0.92), week 24 (0.94), and week 52 (0.90; $p < 0.001$ for all). IGA $\times$ BSA and PASI score improvements between ≥ 75 and $< 90\%$ from baseline were significantly correlated at week 12 (Pearson correlation coefficient, 0.64), week 24 (0.75), and week 52 (0.75; $p < 0.001$ for all).

Correlations between IGA $\times$ BSA and Achievement of Defined MDA

With the MDA definition of PASI 90 and DLQI 0/1, the IGA $\times$ BSA cutoff with the best sensitivity and specificity was 2.10 at week 12 (Youden index [YI], 0.60; sensitivity, 0.78; specificity, 0.82), 1.02 at week 24 (YI, 0.55; sensitivity, 0.73; specificity, 0.82), and 1.00 at week 52 (YI, 0.65; sensitivity, 0.79; specificity, 0.86) (Table 2; online suppl. Fig. 1).

Furthermore, with the MDA definition of PASI score ≤ 1 or BSA $< 3\%$, the IGA $\times$ BSA cutoff with the best sensitivity and specificity was 2.98 at week 12 (YI, 0.91; sensitivity, 0.99; specificity, 0.92), 2.80 at week 24 (YI, 0.94; sensitivity, 0.99; specificity, 0.95), and 3.00 at week 52 (YI, 0.96; sensitivity, 1.00; specificity, 0.96) (Table 3; online suppl. Fig. 2).

Table 3. Optimal IGA $\times$ BSA cutoffs for predictability of PASI score ≤ 1 or BSA $< 3\%$ MDA definition (pooled secukinumab 300 mg treatment group)

Week	IGA $\times$ BSA	Sensitivity	Specificity	Youden index ^a
2	3.50	0.9985	1.0000	0.99850
3	4.50	0.9849	1.0000	0.98487
4	5.20	0.9637	0.9583	0.92203
8	2.99	0.9906	0.8972	0.88782
12	2.98	0.9897	0.9167	0.90636
13	3.00	0.9851	0.9419	0.92701
14	3.10	0.9677	0.9269	0.89464
15	3.00	0.9832	0.9511	0.93439
16	3.00	0.9750	0.9551	0.93015
20	3.00	0.9937	0.9503	0.94393
24	2.80	0.9928	0.9470	0.93978
28	2.80	1.0000	0.9360	0.93596
32	2.65	1.0000	0.9521	0.95214
36	3.00	1.0000	0.9645	0.96447
40	3.00	0.9915	0.9617	0.95326
44	3.00	0.9836	0.9485	0.93206
48	3.00	1.0000	0.9490	0.94898
52	3.00	1.0000	0.9631	0.96306

BSA, body surface area; IGA, 5-point Investigator's Global Assessment; MDA, minimal disease activity; PASI, Psoriasis Area and Severity Index. ^a Youden index = sensitivity + specificity – 1.

Discussion

This post hoc analysis of four phase 3 clinical trials in patients with moderate-to-severe psoriasis receiving secukinumab 300 mg showed that an IGA $\times$ BSA cutoff of 2.10–2.98 at week 12 could be a valid measure highly associated with achievement of MDA. A lower cutoff value may be needed for evaluations up to week 52 (range, 1.00–3.00), but values were mostly within the ranges reported for week 12. These results are comparable to the PGA $\times$ BSA banding of 0.0–3.0 that correlated with achievement of MDA defined as PASI ≥ 90 and DLQI 0/1 [14]. This further indicates the validity of IGA $\times$ BSA as a composite tool for assessing clinical response to treatment.

The treat-to-target approach has become the recommended strategy for the treatment of patients with psoriasis. New National Psoriasis Foundation guidelines for the treatment of psoriasis state that the initial treatment goal should be to reduce BSA to $\leq 1\%$ after 3 months; however, a reduction in BSA to $\leq 3\%$ is considered an acceptable response [5]. Calculating the optimal IGA $\times$ BSA cutoff (2.98) at week 12 on the basis of BSA $< 3\%$ aligns

with the treat-to-target goal. Nevertheless, a more meaningful assessment of MDA that coincides with clinical trial endpoints in patients with moderate-to-severe psoriasis is needed in routine clinical practice and could also be a clinically relevant measure for database analyses. IGA $\times$ BSA is strongly correlated with absolute PASI score, providing further support that IGA $\times$ BSA captures disease severity and could be used to evaluate treatment response in place of the PASI. Furthermore, IGA $\times$ BSA cutoff values associated with MDA measures of PASI 90 and DLQI 0/1 include health-care provider- and patient-reported outcomes that allow patients and providers to be partners in their treat-to-target strategies, while also providing insight into patient quality of life as affected by skin clarity.

The IGA/PGA is categorized into 2 distinct basic forms: a static form, which measures the physician's evaluation of the disease activity at a single point, and a dynamic form, in which the physician assesses the global improvement from the baseline disease activity [19]. The US Food and Drug Administration prefers static IGA/PGA; thus, clinical research generally uses static IGA/PGA instruments. However, multiple versions of the static IGA/PGA exist, ranging from a 4-point to an 11-point scale, with varying descriptions of each point value [20, 21]. The static 5-point IGA scale, which was modified from the 6-point IGA/PGA scale [22], has become the standard form used in many phase 3 clinical trials [16–18]. Notably, the IGA/PGA does not account for the extent of disease. Therefore, IGA $\times$ BSA can aid physicians in the evaluation of treatment responses and assessments of therapeutic options to optimize patient care.

Limitations

Despite several strengths, this study has a few limitations, mainly related to the nature of the analysis. This was a post hoc analysis using pooled trial data, the use of which was not prespecified in the protocol of the individual studies. Furthermore, no adjustments for any potential confounding variables were conducted using multivariate analyses. Currently, there is no agreed-upon standard IGA/PGA to be used for clinical assessment of disease activity; the 5- and 6-point forms commonly used in clinical trials have different definitions of each scale value, complicating the physician's ability to efficiently and consistently measure treat-to-target goals. Including patients treated with the highly effective biologic agent secukinumab in this study leaves the potential for underestimation of cutoff values when evaluating the efficacy of other therapies; this measure needs to be tested in studies that include other psoriasis treatments. As IGA $\times$ BSA

was validated as an indication of MDA achievement only for patients with moderate-to-severe psoriasis, further examination of the criteria is needed for patients with all levels of psoriasis severity.

Conclusion

This exploratory post hoc analysis identified IGA $\times$ BSA as a potential simple tool to assess achievement of MDA as a treat-to-target goal; however, additional observational studies with other psoriasis treatments are needed to further investigate this measure. For example, studies examining and comparing the cutoff values for other psoriasis treatments to identify treatment targets should be conducted to provide information that may be used by physicians for making proper formulary decisions. Findings from this study may provide physicians with a more practical way to capture disease activity in routine clinical practice beyond the traditional PASI.

Key Message

IGA $\times$ BSA may provide clinicians with a simple tool to measure treat-to-target goals.

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Statement of Ethics

This article is based on previously conducted studies and does not involve any new studies of humans or animal subjects performed by any of the authors. The previously conducted individual study protocols were approved by institutional review boards or ethics committees at all investigational sites. These studies were conducted in accordance with the ethical principles of the Declaration of Helsinki, and US sites maintained compliance with Health Insurance Portability and Accountability Act regulations. All study subjects were required to provide written consent prior to participating. Clinicaltrials.gov listings are as follows: NCT01365455, NCT01358578, NCT01555125, and NCT01636687.

Disclosure Statement

Dr. Gottlieb has served as an advisor, consultant, or speaker for Janssen, Celgene, Bristol-Myers Squibb, Beiersdorf, AbbVie, UCB, Novartis, Incyte, Eli Lilly and Company, Dr. Reddy's Laboratories, Valeant, Dermira, Allergan, and Sun Pharmaceutical Industries and has received research funding from Janssen, Incyte, UCB, Novartis, and Eli Lilly and Company. Drs. Germino, Herrera, and Meng are employees of Novartis. Dr. Merola has served as a consultant, advisor, or investigator for Biogen Idec, AbbVie, Eli Lilly and Company, Novartis, Pfizer, Janssen, UCB, Samumed, Celgene, Sanofi Regeneron, Merck, and GlaxoSmithKline.

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Author Contributions

All authors made substantial contributions to the conception and design, execution, or analysis and interpretation of the data; were involved in drafting and critically revising the manuscript; have given necessary attention to ensure the integrity of the work; have read and approved all versions of this manuscript.

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