Use of Outcome Measures of Minimal Disease Activity (MDA) in Psoriasis

Alice Bendix Gottlieb MD, PhD
Professor of Dermatology
New York Medical College
Valhalla, NY
DISCLOSURE OF RELEVANT
RELATIONSHIPS WITH INDUSTRY

Current Consulting/Advisory Board Agreements:

Amgen Inc.; Astellas, Akros, Centocor (Janssen), Inc.; Celgene Corp., Bristol Myers Squibb Co., Beiersdorf, Inc., Abbott Labs. (Abbvie), TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd., Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Karyopharm, CSL Behring Biotherapies for Life, Glaxo Smith Kline, Xenoport, Catabasis, Meiji Seika Pharma Co., Ltd, Takeda, Mitsubishi, Tanabe Pharma Development America, Inc, Genentech, Baxalta, Kineta One, KPI Therapeutics, Crescendo Bioscience, Aclaris, Amicus, Reddy Labs, Valeant, Dermira

Research/Educational Grants (paid to Tufts Medical Center) until 5/11/16 Then None:

Centocor (Janssen), Amgen, Abbott (Abbvie), Novartis, Celgene, Pfizer, Lilly, Levia, Merck, Xenoport, Dermira, Baxalta
Reasons for Measuring MDA in the Clinic

- Psoriasis is an undertreated condition*
- We need to improve, in both the community and in academia, clinical outcomes and patient satisfaction*
- Clinically useful outcome measures are essential for Treat-to-Target strategies for psoriasis management
  - NPF published BSA ≤ 1% within 12 weeks as the Treatment Target*.
  - The payers would like to see a measure which “would look like a diagnostic test” so that a solid connection between using the outcome measure and making a therapeutic decision can be made**
- We need to improve communication with our patients
- Entries are needed for outcomes sections in registries (DataDerm)
- Demonstration of excellent clinical outcomes may be a defense against physician tiering and tight networks
- Clinically useful outcome measures facilitate clinical research in the real world

* Armstrong et al J Am Acad Dermatol [http://dx.doi.org/10.1016/j.jaad.2016.10.017](http://dx.doi.org/10.1016/j.jaad.2016.10.017)
Measuring outcomes in clinic is essential for Treating-to-Target strategies for psoriasis management

Lessons Learned from Treating to Target in PsA
Minimal Disease Activity Criteria (MDA) (GRAPPA)

• A patient is classified as in MDA when they meet 5 of 7 of the following criteria:
  – tender joint count ≤1
  – swollen joint count ≤1
  – PASI ≤1 or BSA ≤3
  – patient pain VAS ≤15
  – patient global activity VAS ≤20
  – HAQ ≤0.5
  – tender entheseseal points ≤1

The TICOPA Study

Aim
• Does treat to target using MDA criteria improve outcome in psoriatic arthritis?

Primary Outcome
• ACR20 at 48 weeks

Sample Size Calculation
• 50% ACR20 response with standard care
• 70% ACR20 response with tight control
• Sample size = 186, alpha = 0.05, beta = 0.8

TICOPA Trial Design

Registered trial EudraCT No 2007-004757-28

WEEK  -4  0  4  8  12  16  20  24  28  32  36  40  44  48  52

DMARD naïve early PsA n=206

Tight Control n=101

Randomisation 1:1

Standard Care n=105

BLINDED ASSESSMENT of Clinical and PROs

Primary Outcome – Complete Case Analysis

- ACR20: 62% (N=172) vs. 45% (N=172), p=0.02
- ACR50: 51% (N=170) vs. 25% (N=170), p=0.0004
- ACR70: 38% (N=172) vs. 17% (N=172), p=0.002

## PASI outcomes

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>OR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI75</td>
<td>1.51</td>
<td>5.65</td>
<td></td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Prescribed therapy at 48 weeks

## Serious Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Tight Control</th>
<th>Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>SAE related to drug</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Blood/lymph system</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GI</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Immune system</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infection/infestation</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Injury/poisoning</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MSK and CTD</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Renal/urinary</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive/breast</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory and thoracic</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Treating to Target in PSA results in better efficacy, increased biologic use and modestly increased serious adverse safety events.

We need a clinically useful measure of MDA for PSO so that we can demonstrate that treating to target results in better outcomes.
PASI is not useful in clinical practice

• Too time consuming
• Cumbersome entry into EMRs
• Not responsive to change at low BSAs
• Not well understood by community dermatologists, i.e., most of us
PGAxBSA (static Physician Global Assessment x Body Surface Area)

A clinically useful, validated outcome measure which measures both the extent of psoriasis and the severity (redness, thickness and scaling) of the predominant lesions
PGA x BSA: Validating Studies

- Kristina Duffin MD MS, a Kim A. Papp MD PhD, b Jerry Bagel MD, c Eugenia Levi PharmD BCPS, d Rongdean Chen PhD, a and Alice B. Gottlieb MD PhD. 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, J. Drugs. Dermatol., 2017, in press.
Evaluation of the Physician’s Global Assessment and Body Surface Area Composite Tool for Assessing Psoriasis Response to Apremilast Therapy: Results From the ESTEEM 1 Study

Kristina Callis Duffin, MD¹; Alice B. Gottlieb, MD, PhD²; Kim Papp, MD³; Eugenia Levi, PharmD, BCPS⁴; Rongdean Chen, PhD⁴; Jerry Bagel, MD⁵

¹University of Utah, Salt Lake City, UT, USA; ²New York Medical College, Valhalla, NY USA; ³Probit Medical Research, Waterloo, ON, Canada; ⁴Celgene Corporation, Warren, NJ, USA; ⁵Psoriasis Treatment Center of Central New Jersey, East Windsor, NJ, USA

Kristina Duffin MD MS, Kim A. Papp MD PhD, Jerry Bagel MD, Eugenia Levi PharmD BCPS, Rongdean Chen PhD, and Alice B. Gottlieb MD PhD. 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, J. Drugs. Dermatol., 2017, in press.
Introduction

The static Physician Global Assessment and Body Surface Area (PGAxBSA) tool has been shown to be a simple instrument for measuring psoriasis severity.1,2

Currently, the Psoriasis Area and Severity Index (PASI) tool is widely accepted as the gold standard for assessing psoriasis severity in clinical trials, but its use in the clinical practice setting is limited by its complexity and insensitivity in mild to moderate psoriasis.2,3

Objective

To evaluate the PGAxBSA and PASI tools as measures of (1) psoriasis severity, and (2) response in patients receiving apremilast treatment, in the phase 3 ESTEEM 1 clinical trial.

Methods

Data were collected from 562 patients with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy, were enrolled in the phase 3, double-blind, placebo-controlled ESTEEM 1 trial, and were randomly assigned to receive apremilast 30 mg BID at baseline.

Agreement between PASI and PGAxBSA was evaluated using the Spearman correlation, intra-class correlation coefficients (ICC), and concordance rates.

Responsiveness to change during treatment was also evaluated based on effect size estimates.

Patients

The apremilast 30 mg BID group comprised 562 patients with a mean age of 45.8 years, psoriasis duration 19.8 years, PASI score 18.7, and BSA 24.4% at baseline.

Spearman and ICC Correlations and Effect Sizes: PASI and PGAxBSA

- A high correlation coefficient ($r=0.742$ to $0.807$) was demonstrated between PASI and PGAxBSA in measuring disease severity at baseline, Week 16, and Week 32.
  - ICC values also indicated a high level of agreement between standardized PASI scores and PGAxBSA scores at all time points evaluated.
- Based on effect size analysis, PGAxBSA was less sensitive than PASI with respect to mean change from baseline at both Week 16 and Week 32.

<table>
<thead>
<tr>
<th></th>
<th>PASI Mean (SD)</th>
<th>PGAxBSA Mean (SD)</th>
<th>Spearman Correlation: PASI vs. PGAxBSA</th>
<th>ICC (95% CI): Standardized PASI vs. PGAxBSA</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline N=562</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$18.7$ (7.2)</td>
<td>$81.8$ (54.9)</td>
<td>$0.757^*$</td>
<td>$0.886$ (0.87, 0.90)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>$NA$</td>
<td>$NA$</td>
</tr>
<tr>
<td><strong>Change from baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 16 n=499‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$-10.2$ (7.3)</td>
<td>$-46.5$ (45.8)</td>
<td>$0.807^*$</td>
<td>$0.834$ (0.81, 0.86)</td>
<td>$-1.41$</td>
</tr>
<tr>
<td></td>
<td>$-1.57$</td>
<td>$-0.97$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 32 n=424‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$-11.3$ (6.8)</td>
<td>$-53.3$ (45.7)</td>
<td>$0.742^*$</td>
<td>$0.805$ (0.77, 0.84)</td>
<td>$-1.57$</td>
</tr>
</tbody>
</table>

* $P<0.0001$.  ‡ $n=501$ for change from baseline in mean PASI score; $n=499$ for change from baseline in mean PGAxBSA.
‡ $n=425$ for change from baseline in mean PASI score; $n=424$ for change from baseline in mean PGAxBSA.
Effect size=$\frac{(mean\ change\ at\ time\ point)}{SD_{baseline}}$.  $N=$ patients with value at the time point indicated; $NA=$ not applicable.

Standardized $= (score - mean) / SD$.  

• A high correlation coefficient ($r=0.742$ to $0.807$) was demonstrated between PASI and PGAxBSA in measuring disease severity at baseline, Week 16, and Week 32.

• ICC values also indicated a high level of agreement between standardized PASI scores and PGAxBSA scores at all time points evaluated.

• Based on effect size analysis, PGAxBSA was less sensitive than PASI with respect to mean change from baseline at both Week 16 and Week 32.
Concordance Between PASI and PGAxBSA

Concordance, overrated=number of patients who did not achieve PASI-50/75/90, but achieved PGAxBSA-50/75/90/total number of patients with data sufficient for evaluation; underrated=number of patients who achieved PASI-50/75/90, but did not achieve PGAxBSA-50/75/90/total number of patients with data sufficient for evaluation.
Correlations Between PASI, PGAxBSA, and Other Psoriasis Severity Measures

- Correlations (r values) between PASI and PGAxBSA and other measures of psoriasis severity were similar at Weeks 16 and 32.

<table>
<thead>
<tr>
<th></th>
<th>sPGA</th>
<th>DLQI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>R</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGAxBSA</td>
<td>562</td>
<td>0.441*</td>
</tr>
<tr>
<td>PASI</td>
<td>562</td>
<td>0.435*</td>
</tr>
<tr>
<td>Week 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆PGAxBSA</td>
<td>499</td>
<td>0.645*</td>
</tr>
<tr>
<td>∆PASI</td>
<td>499</td>
<td>0.695*</td>
</tr>
<tr>
<td>Week 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆PGAxBSA</td>
<td>424</td>
<td>0.567*</td>
</tr>
<tr>
<td>∆PASI</td>
<td>424</td>
<td>0.697*</td>
</tr>
</tbody>
</table>

*P<0.0001. ‡P=0.0002. DLQI=Dermatology Life Quality Index; N= number of patients; r=Spearman correlation; sPGA=static Physician Global Assessment; ∆=change.
Conclusions

• In ESTEEM 1, a high correlation existed between PGAxBSA and PASI with respect to measuring psoriasis severity in patients with moderate to severe psoriasis.
  - In this study population, a larger effect size for PASI compared with PGAxBSA may indicate a PASI score is impacted by larger changes.
• At Weeks 16 and 32, a ≥70% concordance was observed between PASI and PGAxBSA at 75% and 90% improvement; lower concordance (≤66.0%) was observed for 50% improvement.
• PGAxBSA is an alternate instrument for measuring psoriasis severity; the sensitivity of PGAxBSA with respect to other measures of disease severity needs further research.
What are still missing from the clinic?

• A standardized, clinically useful PRO for PSO
• A standardized PGA for PSO
• Standardized outcome measures for PSO subtypes, e.g., genital, PPP, Scalp, etc.
• Clinically useful outcome measures for PSA, both HCP-assessed and Patient-reported
Alice Bendix Gottlieb MD, PhD
Professor of Dermatology
New York Medical College
Valhalla, NY
IDEOM: Mission

• “To establish patient-centered measurements to enhance research and treatment for those with dermatologic disease”

• Perspectives of patients, health economists, payers, physicians and regulatory agencies are included from the onset

• IDEOM’s goal is to establish validated and standardized outcome measures that satisfy the needs of all stakeholders and can be applied to clinical research and clinical practice
Selected Deliverables

• Domains for Psoriasis for Clinical Trials Selected
• Collaboration with HISTORIC, an international consortium of HCPs and patients, well on its way to provide domains for Hidradenitis Suppurativa
• Published results of a Stakeholders meeting with payers to get their perspective unmet issues*
• Early collaboration with the acne outcome group (ACORN)
• National Alopecia Areata Foundation approached to discuss future collaborations
• Next Meeting in Washington DC, May 5,6 2017