Report of the Skin Research Working Groups from the GRAPPA 2017 Annual Meeting

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ABSTRACT. At the 2017 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), the International Dermatology Outcome Measures (IDEOM) psoriasis working group presented an overview of its cutaneous domain of psoriatic arthritis (PsA) projects. First, the group presented an overview of IDEOM's work to establish psoriasis outcome measures that satisfy the needs of all those involved. Second, the group discussed replacements for the Psoriasis Area and Severity Index (PASI) that can be used in clinical practice, including data that support the use of the physician's global assessment × body surface area measurement score as a PASI surrogate. Third, the group discussed the contribution of skin disease to composite measures of PsA. Last, the group summarized the National Psoriasis Foundation's efforts to establish treat-to-target strategies for psoriasis care. (J Rheumatol Suppl. 2018 June;94:40–3; doi:10.3899/jrheum.180137)

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IDEOM | PSORIASIS OUTCOMES | MINIMAL DISEASE ACTIVITY

International Dermatology Outcomes Measures Group

The International Dermatology Outcome Measures (IDEOM) group is a nonprofit organization whose mission is to establish patient-centered measurements to enhance research and treatment for those with dermatologic disease[1,2,3,4,5]. From the onset in 2013, IDEOM's efforts have included perspectives of patients, health economists, payers, physicians, and regulatory agencies. The dermatology division of the US Food and Drug Administration has also been involved in these efforts and regularly attends IDEOM's annual meetings. IDEOM's goal is to establish validated and standardized outcome measures that satisfy all needs and that can be applied to clinical research and practice.

At the 2017 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) annual meeting in Amsterdam, the Netherlands, selected deliverables to date were discussed[5]. The domains for psoriasis clinical trials were presented. These had been selected by a process akin to that used by Outcome Measures in Rheumatology for rheumatologic outcomes. The core domains were skin manifestations [primary: body surface area (BSA)/erythema/induration/scale], location of skin lesions (palmar-plantar and scalp psoriasis), investigator's global assessment, psoriasis and psoriatic arthritis (PsA) symptoms, patient's global assessment, treatment satisfaction, and health-related quality of life. Important, but not required, were the skin manifestations of nail, inverse, genital, guttate psoriasis, and secondary symptoms. The research agenda included PsA signs (because it was felt that dermatologists would not be able to or desire to assess these), economic consequences, work productivity and participation, and cardiovascular disease. In collaboration with the Hidradentis Suppurativa Core Outcomes Set International Collaboration (HISTORIC), an international consortium of hidradenitis suppurativa (HS) healthcare providers and patients, HS clinical trial domains that were selected through an iterative Delphi process were briefly mentioned, because HS has been associated with seronegative spondyloarthopathies[6].

Because PsA symptoms and psoriasis treatment satis-

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faction were selected to be in the core set of domains to be measured in all psoriasis clinical trials, and because these domains have not routinely been studied in psoriasis clinical trials, 2 working groups were formed to select or develop outcome measures for these domains[3]. Results from these 2 working groups are anticipated by the next annual GRAPPA meeting in 2018.

IDEOM is proceeding to develop psoriasis outcome measures that are useful for clinical practice. The need is urgent because, at least in the United States, payers are making judgments on physicians and making access decisions that do not have disease clearance as a major criterion. Additionally, treat-to-target (T2T) strategies and registries for clinical practice require practical and brief outcome measures that are compatible with major electronic medical record systems. In the United States, payers want universally accepted, published outcome measures that are useful in clinical practice and mandated to be performed by published guidelines that are issued by major professional societies. They want clinically meaningful outcome measures, i.e., it is not enough to be better than placebo. Outcomes should justify the cost given the benefit and risk aspects of a given drug. They would like outcomes that measure how the overall cost of care decreases by treatment intervention and how work productivity increases by treatment intervention. Outcomes should be applied universally in clinical practice to reduce variability in practice and make costs more predictable. Last, they would like to see a measure that looks like a diagnostic test (e.g., HbA1c or blood pressure measurement) so that a solid connection can be made between the clinical outcome and a therapeutic decision[7].

Summarizing IDEOM's ongoing motivation, drug regulatory agency approval and publications are only the beginning. The true finish line is when patients get to the right doctors and treatments, and their disease has minimal to no effect on their quality of life.

PGA×BSA as a PASI Proxy

There is an unmet need for practical psoriasis outcome measures. While the Psoriasis Area and Severity Index (PASI) has been a gold standard assessment, it is not practical in the clinical setting and involves complex nonlinear scoring. In addition, its absolute values are poorly understood by clinicians and patients, and there is poor sensitivity to change with poor discrimination at lower score ranges. The product of the physician's global assessment (PGA) and body surface area measurement (BSA %) represents a highly feasible measure that identifies both the severity and extent of psoriasis, has demonstrated sensitivity to change, correlates with PASI, and has the potential for use both in the clinical trials' setting, as well as the clinical practice setting[8,9]. Further, the PGA×BSA measure can be easily understood by providers, patients, regulators, and payers. It has multiple potential uses beyond clinical documentation, including Physician Quality Reporting System use, registry use, and prior authorization documentation. In addition to the PGA×BSA product, each number individually offers a quick glance into the characteristics of the disease from the perspective of plaque severity, as well as area of involvement.

The clinical response and correlation with a minimal disease activity (MDA) target was reported at the 2017 GRAPPA annual meeting based upon data analysis from the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) phase III trials of apremilast in psoriasis[9,10]. In the ESTEEM data, subjects had moderate to severe plaque psoriasis with PASI ≥ 12, BSA ≥ 10%, static PGA (sPGA) ≥ 3. Primary endpoints were measured at Week 16 with a maintenance phase to Week 32 and a week 32–52 randomized withdrawal phase. A 5-point PGA was used, and other relevant outcomes including Dermatology Life Quality Index (DLQI), BSA, and PASI were collected. Specific baseline demographics and other results are outside the scope of this report and will be reported separately in a future publication[9]. A few highlights of the data presented included PGA×BSA scores as they correlated with PASI response categories at Week 16, as well as correlation with a proposed MDA criterion definition of PASI90 + DLQI = 0 or 1. The percent of patients achieving response at Week 16 by PASI or PGA×BSA in 2 ESTEEM trials (ESTEEM1 and 2) were presented and demonstrated best correlation of > PASI 90 with PGA×BSA scores of 0 to 1 and 0 to 1.5[9,10].

One current limitation is that several versions of the sPGA/Investigator's Global Assessment of psoriasis exist. IDEOM is actively addressing this gap with a planned consensus project to drive the use of a single sPGA in clinical trials and practice.

PGA×BSA has been shown to be a feasible measure that is sensitive to change in disease severity in apremilast-treated patients with moderate to severe psoriasis. Also, PGA×BSA bands can aid measurement and interpretation of meaningful clinical response, including MDA in patients with psoriasis. Ongoing work includes looking at PsA data in a population of low PASI baseline subjects to compare with PASI outcome data. The potential for a PGA×BSA cutoff as a potential T2T goal with validation in a real-world clinical trial is also being considered[10].

Composite Scores for PsA: The Role of Cutaneous Disease in Composite PsA Measures

There is increasing interest in treating to an objective target in PsA as discussed in the European League Against Rheumatism treatment recommendations[11] and the National Psoriasis Foundation (NPF) published guidance on T2T in PsA and psoriasis[12]. The new T2T recommendations for spondyloarthritis state that either the Disease Activity in PsA (DAPSA) remission/low disease activity, or very low disease

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activity (VLDA)/MDA criteria are recommended[13]. DAPSA focuses on articular disease incorporating joint counts, patient assessment of pain and disease activity, and C-reactive protein[14]. VLDA/MDA are composite measures that incorporate more PsA domains with 7 different cutpoints: tender joint count ≤ 1; swollen joint count ≤ 1; PASI ≤ 1; patient's pain visual analog scale (VAS) ≤ 15 mm; patient's global VAS ≤ 20 mm; Health Assessment Questionnaire ≤ 0.5; and tender entheseal points ≤ 1[15]. To be in VLDA, patients must meet all 7 cutpoints, while to achieve MDA, patients must meet 5 of 7 cutpoints[16].

DAPSA does not include a measure of skin disease. VLDA requires a PASI of ≤ 1; MDA only requires that 5 cutpoints be met, with only 1 cutpoint measuring psoriasis. Thus it is possible for a patient to meet MDA, but have psoriasis activity. Therefore, different modifications of MDA have been tested that mandate joint counts, skin criteria, or both. Data were presented from 2 posthoc analyses that investigated these criteria. The first analysis was from the Psoriasis Randomized Etanercept Study in Subjects with PsA, a large randomized controlled trial in patients with severe psoriasis (mean baseline PASI 20) and PsA[17,18]. The second analysis was from a clinical cohort of 250 patients[19,20]. These studies showed good control of disease activity with all definitions, but highlighted potential issues, particularly with psoriasis. In VLDA or MDA with skin mandated, the PASI needed to be ≤ 1 so that skin control was assured. However, in MDA without skin mandated, residual skin disease could be present despite meeting 5 cutpoints, which is particularly common in cohorts with severe skin disease. In DAPSA, because skin disease is not measured at all, residual skin disease could be present to a significant extent. Even in the clinic, with more modest skin disease (baseline median PASI 0.3), people meeting DAPSA remission with a PASI ≥ 2 had a significantly poorer quality of life.

Reassuringly, the T2T recommendations state that "validated measures of musculoskeletal disease activity and assessment of cutaneous […] manifestations should be used in clinical practice to define the target and to guide treatment decisions"[13]. If physicians are aiming for a target of VLDA, then skin would be assessed and treatment escalated in cases with active psoriasis. Caution should be exercised when using MDA, and domains with residual disease activity including skin should be addressed even if the minimum 5 domain cutpoints are met. If rheumatologists use a peripheral joint-focused measure such as DAPSA, it is imperative that additional measures of other important domains in PsA (e.g., skin and enthesitis) be assessed within a target of treatment.

US Treatment Targets for Patients with Psoriasis

At the GRAPPA 2017 annual meeting, Dr. April W. Armstrong (Los Angeles, California, USA) discussed a pivotal effort to establish treatment targets for patients with psoriasis in the United States[12]. This effort, which was organized by the NPF, was the first to establish treatment goals for those with plaque psoriasis. NPF is a US-based nonprofit organization whose mission is to drive efforts to cure psoriatic disease and improve the lives of those affected.

There is a critical need in the United States to establish treatment goals for patients with psoriasis. NPF used a rigorous process to arrive at consensus for treatment goals. The NPF process consisted of literature review, elicitation of patient input in the creation of the Delphi survey, and a multiround Delphi consensus-building procedure involving experts in providing psoriasis care. The key principles of the Delphi consensus-building process are anonymity and transparency. In this process, the anonymity of individual responses prevents a participant's authority, personality, and reputation from dominating others. This also minimizes "bandwagon effect" and fosters self-critique.

The consensus-building process results showed that the most preferred instrument to assess treatment goals was the BSA, and 3 months was the most preferred time for evaluating patient response after starting new therapies. Two levels of response, acceptable response and target response, were defined at 3 months after treatment initiation. Acceptable response was either BSA 3% or less or BSA improvement 75% or more from baseline. The target response was BSA 1% or less. During the maintenance period, the target response should be BSA 1% or less at every 6-month evaluation interval.

The NPF treatment target publication explicitly states that the treatment targets are to be used to increase access to therapies and never to limit treatment options[12]. The treatment targets provide the start point from which clinicians and patients can evaluate their current regimen and determine whether changes are necessary to achieve treatment goals. Specifically, the treatment targets encourage clinicians and patients to monitor disease progression and evaluate patient treatment response.

Discussion at the 2017 GRAPPA annual meeting centered on the clinical application of these treatment targets and what would be recommended if treatment targets are not met. If treatment goals are not met, providers and patients have an opportunity to reevaluate the patient's disease state, comorbidities, and current treatments. Any therapeutic decision making would need to be based on a patient's comorbidities, which is part of a thorough benefit-risk assessment. Ways to help patients achieve treatment targets include, but are not limited to, current therapy dose escalation, combination therapy, or switching the primary treatment. It is also important to ensure that the primary therapy has had enough time to achieve its optimal therapeutic effect before changing treatments.

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