# Composite Measures in Psoriatic Arthritis: GRAPPA 2008

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***ABSTRACT.*** At the 2008 annual meeting of GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) in Leeds, UK, members discussed the value and current status of composite measures for the assessment of psoriatic arthritis (PsA). In plenary presentations, examples of composite measures developed for rheumatoid arthritis (RA) and ankylosing spondylitis (AS) were reviewed, followed by a presentation of the assessment of disease activity in systemic lupus erythematosus. Three recently devised composite methods of assessing activity or response in PsA also were presented. Considerable discussion followed in breakout groups, and members agreed that a new composite measure specifically for PsA is necessary. The composite measure should include components that encompass the spectrum of psoriatic disease, i.e., in addition to assessment of peripheral joints, it should include assessment of sacroiliitis, spondylitis, enthesitis, and dactylitis, as well as skin and nail disease. (J Rheumatol 2010;37:453–61; doi:10.3899/jrheum.090956)

*Key Indexing Terms:*
PSORIATIC ARTHRITIS PSORIASIS DISEASE ACTIVITY

At the 2008 annual meeting of GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) in Leeds, United Kingdom, the purpose of the plenary session on composite measures was to consider whether there was an available measure for the assessment of psoriatic arthritis (PsA), or whether a new measure would need to be developed specifically for this disease. In order to properly inform discussion on the topic, plenary talks on composite disease measures for rheumatoid arthritis (RA), ankylosing spondylitis (AS), and systemic lupus erythematosus (SLE) were reviewed. Three recently devised composite methods of assessing activity or response in PsA also were presented.

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**Disease Activity Score for rheumatoid arthritis and ankylosing spondylitis: Robert Landewé**

The Disease Activity Score (DAS) for RA was developed from a prospective cohort of 113 patients with early RA seen in clinical practice[1]. In this cohort, treatment decisions were made by each individual patient's rheumatologist. All information was collected in a systematic way. A construct was defined from high disease activity based on start of new disease-modifying antirheumatic drug (DMARD) or stop of DMARD for lack of efficacy. Low disease activity was considered when there was no change in DMARD and no start of DMARD for one year. There were 138 instances of high disease activity and 39 of low disease activity. Factor analysis was used to reduce the number of variables, discrimination analysis was used to distinguish between high and low disease activity states, and regression analysis was used to define individual variables that explain the discrimination formula. The resultant formula defines the DAS:

$$0.54 * \sqrt{(RAI)} + 0.065 * (SJC) + 0.33 * Ln(ESR) + 0.0072 \text{ (general health)}$$

where RAI is Ritchie Activity Index, SJC is swollen joint count, ESR is erythrocyte sedimentation rate

DAS was further refined based on 28 joints[2]. Different formulae were defined for ESR or C-reactive protein (CRP).

The assessment of disease activity in AS has been difficult. Single-item variables such as pain, and indices such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) measure only part of disease activity. Available disease activity measures do not show a relation with structural damage. Moreover, patients and physicians have different perspectives of the disease. Whereas patients complain of pain and fatigue, physicians are primarily concerned with range of movement and CRP.

The Ankylosing Spondylitis Assessment (ASAS) group set out to develop a composite measure for disease activity in AS that was based on selection of single-item variables and construct for discrimination. The measure was based on a Delphi process of ASAS members through which domains and variables describing disease activity in AS were identified (Table 1). This construct was then tested in a cohort of AS patients in an international study using anti-tumor necrosis factor (TNF) agents in AS [International Study of Starting anti-TNF agents in AS (ISSAS)][3], in which rheumatologists determined which patients should start a TNF-blocking agent after a regular clinical visit (Table 2). Information was collected on demographics, previous treatment, work status, core set measures, BASDAI, and Bath Ankylosing Spondylitis Functional Index (BASFI) at the same visit. Analysis with 11 principal components was done, followed by discriminant function analysis on factor loadings to determine the best composition of factors[4]. Based on these analyses, the following items were selected: back pain, morning stiffness, patient global assessment, ESR, and CRP with 3 alternatives — ESR excluded, CRP excluded, or patient global excluded. Thus, 4 possible candidates for an ASAS-endorsed DAS (ASDAS) were proposed:

$$\text{ASDAS A} = 0.122 * \text{back pain} + 0.061 * \text{morning stiffness} + 0.119 * \text{patient global} + 0.210 * \sqrt{(\text{ESR})} + 0.383 * \text{Ln}(\text{CRP} + 1)$$

$$\text{ASDAS B} = 0.079 * \text{back pain} + 0.069 * \text{morning stiffness} + 0.113 * \text{patient global} + 0.086 * \text{pain/swelling peripheral} + 0.293 * \sqrt{(\text{ESR})}$$

$$\text{ASDAS C} = 0.121 * \text{back pain} + 0.058 * \text{morning stiffness} + 0.110 * \text{patient global} + 0.073 * \text{pain/swelling peripheral} + 0.579 * \text{Ln}(\text{CRP} + 1)$$

$$\text{ASDAS D} = 0.152 * \text{back pain} + 0.069 * \text{morning stiffness} + 0.078 * \text{fatigue} + 0.224 * \sqrt{(\text{ESR})} + 0.400 * \text{Ln}(\text{CRP} + 1)$$

Using these 4 formula options in the ISSAS dataset (from which they were developed), standardized differences showed that each of the 4 options performed similarly and all better than the BASDAI (Table 3). Further validations were carried out using the Outcome in Ankylosing Spondylitis International Study (OASIS) cohort, the Norwegian DMARD (NORDMARD) registry, and data from 4 randomized clinical trials in AS using TNF blockers[4]. In the OASIS cohort, the discriminator was patient global disease activity (high > 6 vs low < 4). NORDMARD was compared using the condition-satisfactory descriptor, and again the ASDAS performed well: physician global at baseline was better than BASDAI and remains so after 3 months and 6 months. Effect size of ASDAS is better than BASDAI. ASDAS worked in patients who do not have elevations of CRP. These studies demonstrate that it is possible to statistically construct and validate a weighted disease activity index for AS based on items obtained by consensus, provided there is a large database of patients to derive the instrument and separate cohorts for cross-validation.

*Table 1*. Domains and variables for disease activity in ankylosing spondylitis.

| Domains | Variables |
|---|---|
| Pain | 1. Global pain |
| | 2. Total back pain |
| | 3. Peripheral pain (BASDAI, Question 3) |
| Inflammation | 4. Back pain at night |
| | 5. Duration of morning stiffness (BASDAI, Question 6) |
| Function | 6. Bath Ankylosing Spondylitis Functional Index |
| Laboratory | 7. C-reactive protein |
| | 8. Erythrocyte sedimentation rate |
| Global | 9. Global disease activity (patient) |
| Peripheral | 10. Swollen joint count |
| | 11. Tender enthesitis count |
| Fatigue | 12. Fatigue (BASDAI, Question 1) |

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

*Table 2*. Results from International Study on Starting Tumour Necrosis Factor Blocking Agents in Ankylosing Spondylitis (ISSAS) cohort.

| Variables | Candidates, n = 595* | No Candidates, n = 612 | p |
|---|---|---|---|
| Sex, % male | 73 | 74 | 0.6 |
| Age, yrs | 43 | 45 | 0.08 |
| Age < 40, % | 39 | 37 | 0.5 |
| Hip involvement, % | 40 | 25 | < 0.001 |
| IBD, % | 11 | 9 | 0.3 |
| Paid job, % | 64 | 62 | 0.5 |
| Current sick leave, % | 29 | 17 | < 0.001 |
| BASDAI, mean score | 5.5 | 4.8 | < 0.001 |
| BASFI, mean score | 5.3 | 3.3 | < 0.001 |
| Cervical rotation, mean | 49 | 57 | < 0.001 |
| Swollen joint count, mean | 1.9 | 0.7 | < 0.001 |
| Tender entheses, mean count | 5.3 | 2.8 | < 0.001 |
| CRP, mean, mg/dl | 20 | 10 | < 0.001 |
| ESR, mean, mm/h | 34 | 19 | < 0.001 |

* For 77 patients (6%), no decisions regarding candidacy were made. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IBD: inflammatory bowel disease.

*Table 3.* Ankylosing spondylitis disease activity score (ASDAS) versions in International Study of Starting anti-TNF agents in AS (ISSAS) cohort.

| ASDAS | Actual Mean (SD) Scores | | Standardized Mean Differences |
|---|---|---|---|
| | Anti-TNF Yes, n = 358 | Anti-TNF No, n = 350 | |
| Back pain, morning stiffness, patient global, ESR, CRP | 3.9 (1.0) | 2.7 (1.0) | 1.18 |
| Back pain, morning stiffness, patient global, pain/swelling peripheral, ESR | 3.5 (1.0) | 2.4 (1.0) | 1.14 |
| Back pain, morning stiffness, patient global, pain/swelling peripheral, CRP | 3.5 (1.0) | 2.4 (1.0) | 1.07 |
| Back pain, morning stiffness, fatigue, ESR, CRP | 3.9 (1.0) | 2.8 (1.0) | 1.14 |
| BASDAI | 5.5 (2.1) | 3.8 (2.2) | 0.81 |

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate.

**Lessons from the British Isles Lupus Activity Group measure of disease activity in SLE: Neil McHugh**

A different type of composite measure for disease activity was developed by the British Isles Lupus Activity Group (BILAG)[5]. BILAG divides lupus activity into 9 different systems or organs: general/constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardio-respiratory, gastrointestinal, vasculitis, renal, and hematological. It is based on the "physician's intention-to-treat" principle such that each system may be scored as: A (action): if a significant change of treatment is required such as increasing prednisone or adding immunosuppressive therapy; B (beware): where a change in therapy may be necessary but not to the same extent as in A; C (contentment): mild activity but no need to change therapy; D: previous involvement but no current activity; or E: no evidence for involvement of the system. A computer algorithm calculates the BILAG score based on information collected at each visit. Disease flares also have been defined on the basis of BILAG, and there is evidence in the literature for the reliability and sensitivity to change for the BILAG, as well as for a revised version, BILAG-2004. There was concern that a recent drug trial that used the BILAG as an outcome measure was not able to demonstrate differences between treatment arms[6]. Nonetheless, a similar approach to devising activity in the relevant domains of psoriatic disease (i.e., peripheral joint, axial disease, enthesis, skin, and nails) may learn from the BILAG model.

**Psoriatic arthritis joint activity index (PsAJAI): Dafna Gladman**

Instruments used in clinical trials in PsA to date include those borrowed from clinical trials in RA such as the American College of Rheumatology (ACR) improvement/response criteria and the Disease Activity Score (DAS and DAS28). The Psoriatic Arthritis Response Criteria (PsARC) is a composite instrument originally developed for a sulfasalazine study in PsA. None of these instruments had been validated for PsA prior to their use in clinical trials. Nonetheless, the ACR20 (20% improvement from baseline in tender and swollen joint counts as well as in 3 of 5 other features) and the PsARC demonstrated efficacy of biologic therapies including anti-TNF agents and leflunomide in patients with PsA. Moreover, an investigation based on the results of phase II trials with etanercept and infliximab concluded that while all the instruments were useful in the assessment of arthritis response in PsA, the ACR20 was better than PsARC[7].

Gladman, *et al*[8,9] aimed to develop statistical models to define arthritis response measures for clinical trials in PsA. Using the data from the infliximab, adalimumab, and etanercept phase III trials in PsA, they divided the data into a training set that included baseline and 24-week data from 2 trials to derive the models, and a testing set based on baseline and interim data from the third trial and baseline and interim data from the first 2 trials, on which the models were then tested. Randomization was used as a surrogate for response in this study. Initial comparisons on the responsiveness of various change measures were done by mean and standard deviation (SD) for the groups of patients randomized to the placebo and drug arms of the training dataset, using effect size (ES, mean change from baseline within group/SD baseline), group effect size (GES, mean change between groups in difference measure/pooled standard deviation for difference measure), standardized response mean (SRM, mean change from baseline/SD change from baseline), T-tests, and univariate logistic regression models to the treatment responsiveness indicator, with and without adjusting or stratifying for trial.

The results of these analyses demonstrated that all items except the mental health component score of the Medical Outcomes Study Short-Form 36 (SF-36) distinguished between patients randomized to drug or placebo. Further analyses were used to eliminate variables not statistically important for discrimination in the logistic regressions and to arrive at candidate models. Testing for internal validity of the candidates was performed by cross-validation, with 10% random removal of subjects in the training set. Joint counts, which were included in all models built, were required to remain statistically significant in the final models. Factor analysis with varimax rotation was performed on the training dataset to identify domains based on the factor loadings and receiver operating characteristic (ROC) curves. Responsiveness indices were developed from logistic mod-

els and the area under the ROC curve (AUC) calculated to assess performance in the training dataset. Validation of models was done using the testing sets. The logistic regression models and factor analysis identified the same variables to be included in the response measure. Based on these analyses, 2 models were derived: Model 1 was based on differences between baseline and last visit values (and including baseline measures); and Model 2 was based on percentage change from baseline (Table 4).

Model 1 provided an AUC ROC of 0.846 for the training set, and 0.821, 0.892, and 0.826 for the testing sets. Further analyses suggested that adding the Psoriasis Area and Severity Index (PASI) score (when it was available) reduced the discriminating effect size of the index from the model based on domains, suggesting that the anti-TNF agents have a huge influence on skin psoriasis, and therefore skin should be considered separately from arthritis.

Model 2 provided similarly high AUC of 0.820 for the training data, and 0.831, 0.836, and 0.851 for the testing sets. Analyzing the currently used ACR response criteria and PsARC in these datasets confirmed their good performance in discriminating active drug from placebo (based on z-values).

However, it was thought that a weighted combination of the various items may be more efficient than the original construct. "Responsiveness" indices were derived from the linear predictors of the logistic regression models. It was shown that a measure of 30% improvement was better able to discriminate than the 20% improvement. The resultant psoriatic arthritis joint activity measure (PsAJAI) was defined as:

$$2 \times 30\%\downarrow\text{JNT} + 2 \times 30\%\downarrow\text{CRP} + 2 \times 30\%\downarrow\text{MDGDA} + 1 \times 30\%\downarrow\text{PTGDA} + 1 \times 30\%\downarrow \text{PAIN} + 1 \times 30\%\downarrow\text{HAQ}$$

where MDGDA is physician global disease assessment, PTGDA is patient global disease assessment, HAQ is Health Assessment Questionnaire

The AUC for the PsAJAI score was 0.83. With a cutpoint of ≥ 5 to define belonging to the active drug group, the sensitivity and specificity of the PsAJAI are 0.74 and 0.84, respectively, better than the sensitivity and specificity of the ACR or PsARC criteria. An illustrative example is a patient who had 20 tender joints, CRP of 14, physician global assessment (MDGDA) of 7, patient global assessment (PTGDA) of 8, pain score of 5, and HAQ of 1.2 at baseline. Following 12 weeks of new treatment, the numbers were 5 tender joints, CRP of 7, MDGDA of 3, PTGDA of 4, pain score of 2, and HAQ of 0.6. The PsAJAI for this patient would be 6 + 6 + 6 + 1 + 1 + 1 = 21, clearly a responder. Compared to the ACR20 response in the dataset, more patients would be considered responders with the PsAJAI indicator (using cutpoint of 5) than with the ACR20, with the majority being in the active drug group. Thus, the PsAJAI is proposed as an outcome measure for the assessment of joint disease in PsA.

**Composite disease activity measure for PsA:**
**Oliver FitzGerald**

The PsAJAI addresses only the response in terms of joint disease. However, in "real life," patients with PsA present with a mixture of features, including peripheral arthritis, axial arthritis, dactylitis, enthesitis, and skin and nail involvement. It is thus important to have a measure that includes these features and assesses disease activity in a composite way. The question that arises is, should treatment decisions be based on worst feature or some composite index? Additionally, we need to consider whether activity grading should be based on extent, potential to cause damage, or effect on function/quality of life. There is still no agreement on the instruments that should be used to measure the various disease features. Moreover, there is no agreement on a disease activity severity scale for each instrument. The systematic review of treatment modalities in PsA led to a construct of the various components of the disease and their treatment (Figure 1). More recently, a treatment grid has been suggested (Table 5).

Based on the work of GRAPPA, a composite activity measure for PsA has been proposed[10]. Using the recommendations in Table 5, numerical values were added to each of the states (Table 6). Based on these values, if a patient has a total score of 3, they would be considered mild, unless the score of 3 was derived from a single domain, in which case they would be considered at least moderate. For mild disease, symptomatic treatment may be sufficient. However, if the total score is 4–6, which would occur if more than one aspect of the disease was involved, then the disease activity

*Table 4*. Developing a response measure in PsA — models derived from logistic regression.

| Model 1 | Model 2 |
|---|---|
| Current tender joint count (of 68) | % Change in TJC 68 |
| Baseline and change in CRP | % Change in CRP |
| The measure with the highest difference among | % Change in physician global disease activity |
| Patient global assessment | % Change in patient assessment of pain |
| Physician global assessment | % Change in HAQ |
| Patient assessment of pain | |
| HAQ | |

CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; TJC: tender joint count.

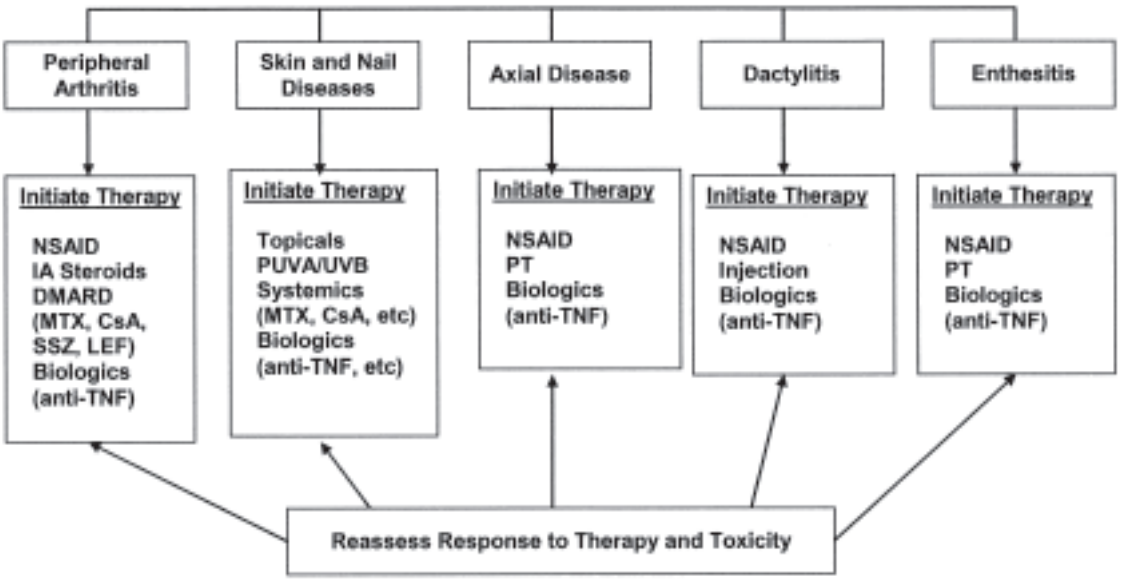


*Figure 1*. GRAPPA treatment guidelines for psoriatic arthritis, categorized by disease characteristics and distinct organ involvement[19]. Anti-TNF: tumor necrosis factor inhibitor; CsA: cyclosporin A; DMARD: disease-modifying antirheumatic drugs; IA: intraarticular; LEF: leflunomide; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drugs; PT: physiotherapy; PUVA: psoralen plus ultraviolet light A; SSZ: sulfasalazine; UVB: ultraviolet light B. From J Rheumatol 2006;33:1417-21.

*Table 5*. Treatment grid for disease components of psoriatic arthritis.

| | Mild | Moderate | Severe |
|---|---|---|---|
| Peripheral arthritis | > 5 joints; no damage on radiograph; no LOF; QOL—minimal impact; patient evaluation mild | ≥ 5 joints (S or T); damage on radiograph; IR to mild treatment; moderate LOF; moderate impact on QOL; patient evaluation moderate | ≥ 5 joints (S or T); severe damage on radiograph; IR to mild-moderate treatment; severe LOF; severe impact on QOL; patient evaluation severe |
| Skin disease | BSA > 5, PASI > 5; asymptomatic | Nonresponse to topicals; DLQI, PASI > 10 | BSA > 10, DLQI > 1, PASI > 10 |
| Enthesitis | 1–2 sites; no LOF | > 2 sites or LOF | LOF or > 2 sites and failure of response |
| Dactylitis | Pain absent to mild; normal function | Erosive disease or functional loss | Failure of response |

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BSA: body surface area; DLQI: Dermatology Life Quality Index; IR: inadequate response; LOF: loss of physical function; PASI: Psoriasis Area and Severity Index; QOL: quality of life; S: swollen; T: tender.

*Table 6*. Proposed composite measure for disease activity for psoriatic arthritis.

| | None (0) | Mild (1) | Moderate (2) | Severe (3) |
|---|---|---|---|---|
| Peripheral arthritis | Nil | ≤ 4 joints; normal function (HAQ > 0.5) | ≤ 4 joints but function impaired; or > 4 joints, normal function | > 4 joints *and* function impaired |
| Skin disease | Nil | PASI ≤ 10 and DLQI ≤ 10 | PASI ≤ 10 but DLQI > 10; or PASI > 10 but DLQI ≤ 10 | PASI > 10 *and* DLQI > 10 |
| Enthesitis | Nil | ≤ 3 sites; normal function (HAQ > 0.5) | ≤ 3 sites but function impaired; or > 3 sites but normal function | > 3 sites *and* function impaired |
| Dactylitis | Nil | ≤ 3 digits; normal function (HAQ > 0.5) | ≤ 3 digits but function impaired; or > 3 digits but normal function | > 3 digits *and* function impaired |
| Spinal disease | Nil | BASDAI > 4; normal function (AS QOL > 6) | BASDAI > 4 but normal function; BASDAI > 4 but function impaired | BASDAI > 4 *and* function impaired |

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DLQI: Dermatology Life Quality Index; HAQ: Health Assessment Questionnaire; PASI: Psoriasis Area and Severity Index; AS QOL: ankylosing spondylitis quality of life.

becomes moderate, and a DMARD should be instituted. A total score of 7 or more would constitute severely active disease and would warrant an anti-TNF agent. Failure to respond moves a patient to the next grade, and the most severely active item directs treatment. An illustrative case for the composite index is that of a 55-year-old female with polyarticular PsA of less than 2 years' duration who has widespread scalp and trunk psoriasis and who has 26 tender and 20 swollen joints, as well as lymphedema of the left upper limb. She has been taking methotrexate 20 mg weekly, with secondary failure. She scored 3 (severe) for peripheral arthritis, 3 for psoriasis, with both PASI and Dermatology Life Quality Index (DLQI) scores above 10. She thus has severe disease and qualifies for an anti-TNF agent. As she improves, the composite score would be expected to decline, thus allowing this measure to be used to assess response to therapy.

**Combining the skin assessments in a meaningful way: Diamant Thaci**

Psoriasis is a chronic disease that constitutes about 10% of dermatology practice. There are various forms of psoriasis including plaque psoriasis, guttate psoriasis, pustular psoriasis, and psoriasis affecting the folds only[11]. PsA is considered part of the spectrum of psoriasis. There are several methods for quantifying psoriasis. The PASI incorporates several aspects of the lesion[12]. One assesses the severity of clinical symptoms of psoriasis (erythema, induration, and scale) as well as the area involved to provide a composite score, which ranges between 0 and 72. PASI has been used for the past 30 years in therapeutic trials. It is not robust but has clinical relevance. Its reliability has been questioned, but several recent studies show that there is very good inter-observer agreement with the PASI score[13,14]. The major source of variation in the PASI score is in estimating the area involved. Since this is a major component of the score it may lead to variation. PASI 75 (75% improvement from baseline in PASI) has been used as the outcome measure in many clinical trials. However, with more powerful drugs the bar has been raised and now the PASI 90 (90% improvement) is often used.

The Lattice System Physician's Global Assessment (LS-PGA), a relatively new tool to quantify psoriasis severity, provides an 8-step scoring system from clear to very severe[13]. It is a complex score and more complicated than the PASI, but it can be used in clinical trials and is better than the physical global assessments. The LS-PGA takes a quantitative approach to global assessment by integrating ranges of the percentage of body surface area involved and the overall plaque morphology. The lattice portion of the LS-PGA is performed by computerized algorithm. The LS-PGA shows good correlation with both PASI and the MDGDA for psoriasis, and very good intrarater and interrater reliability[13-15].

**Defining minimal disease activity in PsA — a proposed objective target for treatment: Laura Coates**

Another approach to assessing response in PsA has recently been proposed by Coates, *et al*[16]. Since the available instruments such as the ACR response criteria and DAS are based primarily on the assessment of joint disease, it was felt that an instrument that would incorporate all aspects of the disease would be worthwhile. Minimal disease activity (MDA) was introduced as "a state which is deemed a useful target of treatment by both physician and patient, given current treatment possibilities and limitations."[17] Coates and colleagues retrieved 40 sample cases from the Leeds PsA database. Among those cases a wide variety of disease activity was found, supplemented with patients with lower disease activity (visual analog scale < 3). A Web-based questionnaire was sent out to GRAPPA members with GRAPPA executive committee approval. For each case scenario, the questionnaire provided an introductory description, a table with scores for the items thought to be important in assessing disease activity [tender joint count, swollen joint count, PASI, body surface area (BSA), painful enthesitis points, patient-reported pain, disease activity by visual analog scale (VAS), and HAQ]. For each case scenario, the responder was asked to indicate whether they considered the patient in a state of MDA or remission (yes/no). Profiles were classified as MDA if there was > 70% agreement among the responders. Differences between MDA and non-MDA cases were tested for differences using the Mann-Whitney U test, and a regression analysis was performed for each different variable. Summary statistics for each outcome measure were calculated including mean, rounded mean, upper limit of 95% confidence interval (CI), rounded upper limits of 95% CI, and maximum score.

Sixty GRAPPA members responded to the questionnaire: 82% were rheumatologists and 18% dermatologists. Thirteen cases were defined as MDA. Three possible cut-points were chosen for MDA criteria including the rounded mean, the upper limit of the 95% CI, and the maximum score. Significant differences ($p < 0.05$) were demonstrated between MDA and non-MDA cases for all variables except enthesitis ($p = 0.159$). With univariate regression analysis, all variables except enthesitis are predictors of MDA. It should be noted, however, that the majority of the cases had no enthesitis. There were too few cases for multivariate analysis. ROC curve analyses revealed AUC ≥ 0.94 with the various options of defining the criteria. Using 5/7 criteria based on the rounded mean to define MDA, the sensitivity and specificity were 0.92 and 0.89, respectively. With the rounded upper limit of the 95% CI, the sensitivity and specificity were 1.00 and 0.82, respectively. The decision was to go with the rounded mean, and a patient was classified as in MDA when they met 5 of 7 of the following MDA 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; and tender entheseal points ≤ 1.

These MDA criteria were then tested in the University of Toronto PsA database[18]. Between 2003 and 2007, all the above criteria were reported for 344 patients. Of these, 59% were male, the mean age was 43 years, and the mean age of onset of PsA was 36 years. Patients had a mixture of oligo- and polyarticular disease. Over the study period, 61% of the patients achieved MDA at some time, while 34% achieved MDA for over 12 months. The median duration of MDA was 28 months (range 12 to 48). Of the patients who achieved MDA, 10% experienced a flare and stopped meeting MDA criteria, whereas the remaining 90% were still in MDA at latest followup. About one-third of patients achieved 5 criteria, one-third achieved 6 criteria, and one-third achieved 7 criteria. The most common high domain was skin (PASI), and the next most common high domain was patient global VAS. Swollen joint count was always ≤ 1. Predictors for achieving MDA were earlier age at onset and use of biologic therapy. Preliminary analysis revealed that there was less progression of joint damage in those achieving MDA for at least 12 months than those not achieving MDA.

**Composite Measures Breakout Groups. Discussion Group Leaders: Oliver FitzGerald, Dafna Gladman, Philip Mease, Abrar Qureshi, Jerry Krueger, Chris Ritchlin, Arthur Kavanaugh**

Following the above presentations the audience was divided into 7 groups. Each group was asked to address the following questions:

1. Are we happy with the response criteria in RA to be used for PsA?
2. Should we include dactylitis, enthesitis, and skin assessment as part of the response index?
3. Is the proposed PsAJAI index enough or do we develop a new responder index?
4. Is the proposed composite psoriatic disease activity index enough or do we develop a new responder index?
5. What are the key properties to be included in a psoriatic disease activity measure?
6. Should the MDA be used in clinical trials and longitudinal observational studies?

**Are response criteria for RA adequate for use in PsA? What are considerations for the development of a composite index in PsA, and what should be its key components?**

The consensus among breakout groups was that response criteria currently used for RA are not adequate for PsA. A composite index for PsA should also account for components that encompass the spectrum of psoriatic disease, including sacroiliitis, spondylitis, enthesitis, and dactylitis, as well as skin and nails. Additional components that were considered included patient-reported outcomes as well as related comorbidities such as ocular, bowel, and cardiovascular diseases.

It was acknowledged further that disease activity or response to treatment in one domain (i.e., skin or nails) may not correlate with another (i.e., joints). Although the composite measure is one tool, it should permit separate analysis of domains, each of which alone may drive treatment. Also through such a composite measure, achieving the primary endpoint through treatment in one or more domains, but not the complete index, may be considered treatment success. A specific consideration felt to be important in developing response criteria for PsA was to discern disease activity from function and damage, which should not be included in any strict definition of activity. It was also felt that patient-reported outcomes needed to be included as part of the index, in congruence with an increasing effort at the US Food and Drug Administration to include disease-customized patient-reported outcomes [i.e., the Patient-Reported Outcomes Measurement Information System (PROMIS)] when assessing efficacy of drugs in trials.

Once developed, the composite measure would need to be validated in cohorts, perhaps in the setting of a clinical trial. Further, if the measure were to be used in clinical practice, it needed validation among individuals, rather than just in cohorts through trials.

**Should dactylitis, enthesitis, and skin assessments be included as part of a PsA response index?**

While it was acknowledged that the PASI score had several limitations, it was felt to be the best available assessment tool for evaluating the skin as part of the composite. The body surface area as well as the patient PASI score were given further consideration. Quality of life measures for skin disease were felt to be important; however, it was thought that the Dermatology Life Quality Index (DLQI) may not be specific enough to psoriasis for inclusion. The modified Nail Psoriasis Severity Index (mNAPSI) was felt to be the appropriate measure for the assessment of nail disease, and the VAS for nails was also given consideration. Dactylitis was felt to be important to include, especially given its relative specificity for disease. Distinction between activity and damage in dactylitis was necessary. In evaluating enthesitis, the tool would need to grade activity as well as discriminate from fibromyalgia.

**Are the proposed PsAJAI and Composite Psoriatic DAI indices adequate, or does the need exist for a new responder index?**

There was appreciation of the quality of the methodology that went into the development of the PsAJAI. In general, the group felt that we needed to learn more about the index through validation in cohorts, perhaps in clinical trials and through comparison with existing measures. The

CPDAI index was well received, and the group thought it needed some further thought prior to validation. The tool was felt to be patient-centered and practical in the clinic setting.

**Should MDA be used in clinical trials and longitudinal observational studies?**

There was appreciation for the concept of MDA, and that it should be developed and measured alongside the composite measures. The group felt it was important to determine a representative definition for MDA, as well as how MDA compares with remission, and whether MDA also minimizes progression of damage and prevents cardiovascular morbidity. The MDA should have as a component a subjective measure as assessed by the patient. The concept of MDA should involve the patient to best determine final endpoints and, accordingly, the aggressiveness of therapy. It was acknowledged that application of MDA in the clinic setting might also restrict types and durations of therapies by third-party payers. Ultimately, the MDA tool should be validated in other groups, perhaps initially in clinical trials data, and against independent outcomes.

**Additional comments arising out of breakout discussions**

*Activity versus damage*. The composite measure should discern among activity, damage, and function. It was felt that function need not be included in any strict disease activity measure, since it would be influenced by damage, particularly in later disease.

**Independent analysis of components within the composite index**

It was acknowledged that there is no clear correlation with respect to activity or response to treatment among skin and nail disease, peripheral joint disease, spinal disease, and enthesitis. The developed composite index should account for this lack of correlation in the context of a varied spectrum of disease among the many different components. For example, severe disease in one component should still suggest severe disease even if all other components were only mildly active or inactive. Similarly, if the primary treatment endpoint was not achieved for one component but was achieved among other endpoints, treatment may still be considered effective.

**Composite measure for clinical trials and/or for the clinic setting**

The group felt it would be important to determine whether the developed index would be most useful in the setting of clinical trials, in the setting of the clinic (for determination of practical treatment decisions), or both.

In the clinic, patients are followed over the course of their disease with durations beyond the relatively brief windows observed in clinical trials. Further, the composite measure would need to account for reference shifts that occur with time and with treatment.

**Patient-reported outcomes**

Patient-reported outcomes were felt to be important to a composite measure index. Others felt that patient-reported outcomes, such as SF-36 and HAQ, may not correlate well with disease activity or even the underlying disease process. These measures may be better placed as part of a responder index that is inclusive of disease activity, patient-reported outcomes, and damage.

**Inclusion of comorbidity in a composite index**

There was considerable discussion whether comorbidities, such as cardiovascular disease, should be included as part of a composite measure in PsA. One argument is that cardiovascular disease is very much a part of disease activity, in which ongoing inflammation contributes to atherogenesis. On the other hand, cardiovascular disease may be considered an outcome, rather than a disease activity measure, and as such should be included as part of a damage index along with ocular disease and radiographic progression, for example. In general, it was felt that inclusion of cardiovascular disease in any measurement of disease activity at this point is premature since the complex association with cardiovascular disease is still being defined.

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