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Article type : Brief Report

**Title:** Radiographic progression is less in psoriatic arthritis achieving a good response to treatment: data using newer composite indices of disease activity

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**Abstract**

**Objectives:** The purpose of this study was to compare radiographic outcomes according to the magnitude of the response utilizing three new psoriatic composite disease activity measures (the Psoriatic Arthritis Disease Activity Score (PASDAS), the GRAPPA Composite Exercise (GRACE), and the Disease Activity in PsA (DAPSA). The data were taken from the GO-REVEAL dataset, a large randomised, double-blind, study which evaluated the safety and efficacy of 2 doses of the TNF inhibitor golimumab in subjects with active PsA.

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**Methods:** Response criteria at 24 weeks were applied across the whole dataset, irrespective of treatment group. Radiographic scores at baseline and 24 weeks were assessed using the Sharp van der Heijde method, modified for PsA.

**Results:** Overall, for each measure, radiographic progression was significantly greater in subjects with a moderate or poor outcome, and absent in those with a good outcome. The proportion of subjects without radiographic progression in the good outcome group was: PASDAS, 83% ,  $\chi^2 = 7.9$ ,  $p = 0.02$  ; GRACE, 80%,  $\chi^2 = 5.8$ ,  $p = 0.05$  ; DAPSA, 76%  $\chi^2 = 3.4$ ,  $p = 0.19$ .

**Conclusions:** Response criteria for disease specific composite measures enable separation between groups in terms of radiographic progression and may therefore be used as suitable targets for interventional studies, as well as in the clinic.

**Key words:** psoriasis, psoriatic arthritis, outcome measures, TNF inhibitors, golimumab, radiographic scoring

Significance and innovation

- Some new composite disease activity measures for psoriatic arthritis measure across the disease spectrum, others are mainly articular based.
- Irrespective of the spectrum of disease manifestations assessed, each of the measures were able to distinguish between a good, moderate and poor outcome, based on radiographic progression.
- New composite disease activity measures, and their response criteria, are suitable targets for interventional studies, and in the clinic.

## Introduction

PsA is a heterogeneous disease, characterized by involvement of skin and nails, peripheral joints, entheses, and axial joints. To comprehensively assess disease activity in heterogeneous conditions, such as PsA, and also to assess changes in disease activity with time, composite measures should assess all relevant clinical outcomes. Composite measures may incorporate several dimensions of disease status by combining different domains into a single score. Composite measures can potentially provide a summary outcome for different groups of signs and symptoms at a specific time point.

In rheumatoid arthritis controlling disease activity inhibits the progression of peripheral joint damage as assessed radiographically; a similar paradigm appears to occur in PsA (1). The GO-REVEAL trial demonstrated improvement across clinical domains as well as inhibition of radiographic progression with the use of a highly efficacious medication, the TNF inhibitor

golimumab (2), Data from the study offered the opportunity to examine radiographic progression according to clinical outcomes based on newly developed, PsA specific, composite measures.

## Methods

These analyses used data from the GO-REVEAL study (2). Briefly, the GO-REVEAL study was a randomised placebo controlled trial of golimumab in 405 patients with active, predominantly polyarticular, PsA. The definition of active psoriatic arthritis included the presence of at least 3 swollen and 3 tender joints and the presence of plaque psoriasis with a qualifying lesion at least 2 cm in diameter. Patients were required to have active disease despite treatment with disease modifying drugs but prior treatment with biologic drugs was prohibited. Patients were randomized to receive treatment with placebo, or with golimumab at doses of 50mg or 100 mg subcutaneously every 4 weeks. Patients not achieving a 10% reduction in swollen and tender joint count at week 16 (n = 87) were re-randomised (placebo to golimumab 50mg, golimumab 50mg to golimumab 100mg and golimumab 100mg remained on the same treatment) until the end of the placebo controlled phase at week 24. Data from a random sample of all GO-REVEAL patients (n=312) at baseline and 24 weeks were available for this analysis, but analysis was confined to those patients at week 24 who were in their original allocated treatment group giving a final sample size of 222. Individual patient data were analysed. Only available data were used; there were no imputations for random missing data in this analysis.

Radiographic data were read blind to treatment group using the modified Sharp/van der Heijde method (3). Essentially this method scores individual joints in the hands and feet, assessing joint space narrowing and erosions. The modification is the inclusion of the distal inter-phalangeal joints. The scores for joint space narrowing and erosions are recorded separately, and then added to produce a total score (range 0 – 528).

The following data were used to calculate the composite measures:

### PASDAS

The PASDAS (Psoriatic Arthritis Disease Activity Score) was calculated as previously described (4). The following variables were used: patient global VAS (rescaled from 0 – 10 to 0 – 100), physician global VAS (rescaled from 0 – 10 to 0 – 100), swollen joint count (0-66), tender joint count (0-68), C reactive protein (rescaled from mg/dL to mg/L), enthesitis (measured in GO-REVEAL as modified MASES and re-scaled to a 0 – 6 range, by multiplying by a factor of 6/15, for this analysis), tender dactylitis count (the GO-REVEAL study scored each digit from 0 – 3 and these were re-coded to 0 – 1, where

any score greater than zero equalled 1) and, finally, the physical component summary scale of the SF36 (PCS). The PASDAS is then given by the formula:

$$\text{PASDAS} = (((0.18 \times \sqrt{\text{Physician global VAS}}) + (0.159 \times \sqrt{\text{Patient global VAS}}) - (0.253 \times \sqrt{\text{SF36 - PCS}}) + (0.101 \times \text{LN}(\text{Swollen joint count} + 1)) + (0.048 \times \text{LN}(\text{Tender joint count} + 1)) + (0.23 \times \text{LN}(\text{Leeds Enthesitis Count} + 1)) + (0.377 \times \text{LN}(\text{Dactylitis count} + 1)) + (0.102 \times \text{LN}(\text{CRP} + 1)) + 2) \times 1.5.$$

The GRAPPA Composite Exercise outcome measure (GRACE)

The GRACE was calculated by transforming the following variables, using pre-defined algorithms, and expressing the total score as a mean, with a score range of 0 -1, where 1 indicates a better state than 0 (4): swollen joint count (0-66), tender joint count (0-68), patient joints VAS (using data for patient pain VAS and rescaled from 0 – 10 to 0 – 100), patient global VAS (rescaled from 0 – 10 to 0 – 100), psoriasis area and severity instrument (PASI, 0 – 72), and health assessment questionnaire (HAQ, 0 – 3). Because the VAS for skin was not collected in GO-REVEAL, this component of the AMDF was omitted (as the index is an arithmetic mean this omission does not affect the score range of 0 – 1). Because the PsAQoL was not specifically collected, values for it were derived from a transformation algorithm:

$$\text{PsAQoL} = 25.355 + 2.367 \times \text{HAQ} - 0.234 \times \text{PCS} - 0.244 \times \text{MCS}$$

where HAQ is the Health Assessment Questionnaire, PCS is the physical component summary scale of SF36, and MCS is the mental component summary scale of SF36.

This equation was derived from the GRACE dataset(4) using linear regression in which the  $R^2$  value was 0.804 and the Pearson's correlation between actual and predicted PsAQoL was 0.89.

Disease activity in Psoriatic Arthritis (DAPSA)

DAPSA was calculated as the sum of the following components: Tender joint count (0 – 68). Swollen joint count (0 – 66), CRP (mg/dL), patient VAS for pain (0 – 10) and patient VAS for global disease activity (0 – 10) (5).

## Statistics

Patients were analysed independent of allocated treatment group. All patients were categorised by responder status according to previously defined cut offs for response for each of the composite measures: response categories were 'poor', 'moderate', and 'good' (6). Statistical comparisons across outcome categories for each composite measure were made using analysis of variance. The proportion of people without radiographic progression was compared across the outcome groups for each composite measure and these data were compared using chi-squared statistics.

## Results

201 subjects had complete data that allowed calculation of all 3 composite measures. Radiographic progression was greater in subjects with a poor outcome, and not seen in those with a good outcome. Radiographic change scores were intermediate for those with a moderate outcome (Table 1). Analysis of variance statistics were significant for all three measures, although the 'F' statistics vary (for PASDAS, GRACE and DAPSA, the magnitude of F was 6.11, 7.61, and 5.07 respectively).

The proportion of subjects in whom no radiographic progression was seen (defined as change in vdH score of  $\leq 0$ ) are given in Table 2. The table indicates that the better the outcome, the greater the proportion of patients without radiographic progression, for each of the measures tested.

## Discussion

Psoriatic arthritis is a complex condition affecting both articular and non-articular structures. Ideally, outcome measures used for assessing PsA in both clinical trials, as well as in the clinic, should capture disease involvement and activity across all domains (7). As part of the process of validation of composite disease activity measures external validity is a necessary property. In addition, it is appropriate to assess the extent to which composite measures are able to predict the consequences of disease activity, such as structural damage. In this study all three of the composite measures assessed, including those which measure across the disease spectrum, were able to differentiate the progression of structural damage of peripheral joints in relation to disease outcome.

All three of the composite measures examined include a tender and swollen joint count so it is not surprising that radiographic progression was reflected by clinical outcome according to these measures, as previously noted (8). What is perhaps surprising is the inability of the DAPSA to distinguish those in whom no radiographic progression occurred. This is likely a function of the cut-offs used with this measure in this analysis. The cut-offs used herein were

derived from a combination of observed data (the GRACE study) and patient and physician opinion. They were derived in a manner similar to those for the DAS28 except that more weight was put on the patient opinion of response. Alternative cut-offs for the DAPSA have been proposed and it is likely that use of these would have produced different results (9).

This study has several potential limitations. Only a proportion of the total study population could be used for these analyses. Also, as with all such studies, the use of the modified Sharp/van der Heijde method to assess structural damage in PsA is open to question.

Psoriatic arthritis is a disease that affects small joints of the hands and feet differently to RA, the disease in which the original SVDH method was developed (10). It could also be argued that the time frame for the development of structural damage in the GO-REVEAL was too short. The relatively large percentage of patients who did not experience any radiographic progression, and the relatively small mean scores for changes in radiographic scores would support this assertion. Nevertheless, significant differences in structural damage were demonstrated according to outcome status and this may reflect the fact that enrolment of patients into this clinical trial was predicated upon active peripheral arthritis.

In summary, all composite measures tested in this analysis demonstrated a relationship between radiographic progression and clinical outcome, further vindicating their validity in this condition.

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Table 1. Total radiographic change score for each response category for each outcome measure. Figures are mean (standard error of mean). F = statistic from analysis of variance.

	Good response	Moderate response	Poor response	F	p
PASDAS	- 0.27 ± 0.15 N = 86	+ 0.18 ± 0.10 N = 76	+ 0.49 ± 0.19 N = 39	6.11	0.003
GRACE	- 0.33 ± 0.17 N = 72	+ 0.05 ± 0.10 N = 75	+ 0.51 ± 0.16 N = 54	7.61	0.001
DAPSA	- 0.22 ± 0.23 N=46	- 0.06 ± 0.10 N=104	+ 0.50 ± 0.16 N=51	5.07	0.007

Table 2. Number (percentage within category) of people with no radiographic progression by response category for each composite measure. The chi-squared statistic is derived from the 3x2 table generated for each outcome measure.

	Good response	Moderate response	Poor response	$\chi^2$	p
PASDAS	71 (83)	51 (67)	24 (62)	7.9	0.02
GRACE	56 (80)	55 (75)	33 (61)	5.8	0.05
DAPSA	35 (76)	79 (76)	32 (63)	3.4	0.19