The dynamics of response as measured by multiple composite outcome tools in the TIght COntrol of inflammation in early Psoriatic Arthritis (TICOPA) trial.

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Abstract

Background

We aimed to evaluate the dynamics of treatment response with different composite measures in the Tight Control of Inflammation in early Psoriatic Arthritis (TICOPA) trial.

Methods

Participants with early, DMARD naïve psoriatic arthritis (PsA) were randomised 1:1 to either tight control (TC, 4 weekly review with therapy escalation if criteria not met) or standard care (SC, 12 weekly review). We calculated the Psoriatic ArthritiS Disease Activity Score (PASDAS), GRAPPA Composite scorE (GRACE) and Composite Psoriatic Disease Activity Index (CPDAI) at baseline and every 12 weeks to 48 weeks by blinded assessor. For missing data we used the last observation carried forward. Comparison between groups was made by analysis of covariance and comparison of area under the curve (AUC).

Results

206 people were randomised to TC (n=101) or SC (n=105). Significant differences between treatment groups were seen ($p < 0.0001$ for all composite measures). AUC analysis demonstrated a significant difference between groups for the PASDAS but not GRACE and CPDAI. For participants with oligoarthritis a significant difference between groups was seen for each measure, although the significance levels were greatly diminished (PASDAS, $p = 0.04$; GRACE $p = 0.01$; CPDAI $p = 0.04$). For oligoarthritis using AUC analysis, none of the measures could distinguish between groups.

Conclusions

Composite measures of disease activity were able to distinguish between TICOPA treatment arms , although all measures showed diminished ability to distinguish treatment effects for those with oligoarthritis. Further data are needed to inform the preferred composite measure for use as the primary outcome in PsA trials.

Key words: psoriatic arthritis, treatment, composite measures, disease activity, outcome assessment

Introduction

Psoriatic arthritis (PsA) is a heterogeneous disease which can manifest in several ways including arthritis, enthesitis, dactylitis, axial disease and skin/nail involvement. The lack of a specific validated target for PsA means that the primary outcome measure used in recent interventional studies has been the American College of Rheumatology 20% improvement (ACR20) criteria, a measure originally developed for rheumatoid arthritis focusing on peripheral joint activity (1). However, new composite targets encompassing the complex manifestations of PsA have been developed. These include the Psoriatic Arthritis Disease Activity Score (PASDAS) and the GRAPPA CompositE Index (GRACE) (2), and, in addition, the Composite Psoriatic Disease Activity Index (CPDAI) (3). In addition to measuring disease activity at any point in time, these indices can also serve as responder indices and cut-offs for response have been developed (4).

The TIght COntrol in Psoriatic arthritis (TICOPA) study was the first study to demonstrate that tight control of disease utilising pre-defined activity levels to guide therapeutic changes resulted in significantly better clinical outcomes compared to standard care (5). In the TICOPA study the odds of achieving an ACR20 response at 48 weeks was twofold higher in the treat to target arm. However, the outcomes at intervening time points for each arm of the study were not described, nor were validated composite disease activity measures for PsA reported. In this study we evaluated treatment responses in the TICOPA study using the PASDAS, GRACE and CPDAI indices and compared their performance.

Methods

The primary results of the TICOPA study have already been published (5). In brief this randomised, controlled, parallel group, open label, multi-centre clinical trial recruited people with early (less than 2 years), treatment naive PsA. The full trial protocol is also available (6).The primary objective of the trial was to compare tight control (TC) with standard care (SC), using minimal disease activity (MDA(7)) as the treatment target. Participants received either TC or SC for a period of 48 weeks. Participants randomised to TC were seen every 4 weeks by the study physician and treated according to a predefined treatment protocol. Participants randomised to the SC arm were treated in a general rheumatology outpatient clinic supervised by a consultant rheumatologist. These patients were generally reviewed every 12 weeks but were seen more often if clinically indicated, with no formal measures of disease activity used in clinical decision making. A blinded assessor collected clinical assessments and patient

reported outcomes every 12 weeks, and the composite disease activity measures were derived from these.

Composite measures:

Derived Psoriatic Arthritis Disease Activity Score (PASDAS)

The PASDAS is a weighted index comprising assessments of joints, function, acute phase response and quality of life and patient and physician visual analogue scores (VAS). It is given by the formula:

PASDAS = (((0.18 x √Physician global VAS) + (0.159 x √Patient global VAS) - (0.253 x √SF36 - PCS) + (0.101 x LN (Swollen joint count + 1)) + (0.048 x LN (Tender joint count + 1)) + (0.23 x LN (Leeds Enthesitis Count + 1)) + (0.377 LN (Dactylitis count + 1)) + (0.102 x LN (CRP + 1)) +2)*1.5.

Where LN = natural logarithm, PCS = physical component summary scale of SF36, CRP = C reactive protein in mg/L. All VAS scores are 0 – 100 mm. Swollen joint count is 66 joints, and tender joint count 68. In this study the SF36 was not completed so an estimate of this outcome was calculated using the following formula:

sf36pcs = 51.615 - (6.52 * HAQ) - (1.529 * BASDAI) - (0.429 * PsAQoL)
where: sf36pcs is the estimated physical component score of the SF36, HAQ is the Heath Assessment Score (range 0 – 3)(8), BASDAI is the Bath Ankylosing spondylitis Disease Activity Index (range 0 – 10) (9), and PsAQoL is the psoriatic arthritis quality of life measure (10). This formula was obtained by regression analysis using the GRACE data set (2) and explained 71% of the variance in sf36pcs scores (R^2adj = 0.71).
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The score range of the PASDAS is 0 – 10, with worse disease activity represented by higher scores.

Modified GRACE index

The GRACE is a composite score comprising assessments of joints, skin, pain, function and health related quality of life. Each domain is transformed into a ‘desirability’ scale and the items then combined arithmetically (4). The variables transformed are:

- 68 tender joint count
- 66 swollen joint count
- Health assessment questionnaire (HAQ)
- Patient global assessment of disease activity by VAS

- Patient VAS for skin
- Patient VAS for joints
- Psoriasis area and severity index (PASI)
- Psoriatic arthritis quality of life index (PsAQoL)

In the TICOPA study a VAS for skin was not collected and this item was thus omitted from the scale. Omitting the VAS for skin does not affect the score range as the score reflects the arithmetic mean of the individual components.

The GRACE index has a score range of 0 – 10 with worse disease activity represented by higher scores.

Modified Composite psoriatic arthritis disease activity index (CPDAI).

This index measures disease activity in 5 domains: peripheral joints, skin, enthesitis, dactylitis, and spine (3). Within each domain severity was graded as 0 (none), 1 (mild), 2 (moderate) and 3 (severe), according to pre-defined cut-offs (indicated in online supplementary table S1).

In the TICOPA study the Ankylosing spondylitis Quality of Life index was not obtained so this was substituted by the PsAQoL, scaled to a 0 – 22 range. In addition the DLQI was estimated using the following equation:

DLQI =0.533 + (1.98 * HAQ) + (0.165 * PSAQOL) + (0.405 * PASI).

This formula was obtained by regression analysis using the GRACE data set (2) and explained 35% of the variance in DLQI scores (R^2adj = 0.35).

Statistical Analysis

All statistical analyses were carried out in SPSS version 21. Where necessary, missing component data were replaced by carrying forward the last available observation. Comparison between groups at 48 weeks was made using an analysis of covariance with baseline values as the covariate. In addition, treatment groups were compared by calculating the area under the curve and comparing the area with independent t tests. We performed these analyses for all participants and, in addition, for those with oligoarthritis. Using previously defined cut-offs we examined the proportion of people in each arm of the trial achieving good, moderate or poor outcome for each composite measure at 48 weeks (4), comparing these proportions with the chi squared test.

Results

The study population consisted of 206 patients randomly assigned to either the TC (n=101, 49·0%) or SC (n=105, 51·0%). The baseline demographics of participants was, for TC and SC respectively, age 46y and 45y, males 53% and 52%, and duration of disease 0.9 months and 0.7 months. In TC, 89·1% (n=90) of patients completed treatment and follow-up to week 48 with a similar proportion in SC (n=92, 87·6%).

Baseline composite scores differed, with the tight control having higher baseline scores. Mean scores for each measure at each major timepoint are given, along with the statistical analysis, in Table 1. The baseline individual domain scores for each of the composite measures for the entire population are given in the online supplementary table S2. Analysis of covariance, adjusting for baseline data, for all available data demonstrated a highly significant difference for each of the composite measures. AUC analysis also showed significant differences between groups for PASDAS but not GRACE and CPDAI. The dynamics of change for each composite measure are illustrated in the Figure. For all measures there was separation between the groups at the first 'blinded' assessment point, with further divergence at subsequent time points.

The data for patients with oligoarthritis at study entry are given in Table 2. The basekube individual domain scores for the group with oligoarthritis are given in the online supplementary table S3. Although comparison of groups by analysis of covariance achieved significance, the statistics were smaller than those found for the entire cohort, and the mean values for each measure were reduced. Further, AUC analysis failed to show a difference between treatment arms for all of the measures tested but the number of participants for the analysis was small. Of note, the mean figures for each composite measure did not diverge until 24 weeks for this PsA subgroup.

The proportion of people achieving 'good', 'moderate' and 'poor' response at 48 weeks, for each measure, is given in Table 3. For the PASDAS 64.5% of people who achieved a 'good' response were in the TC arm, and 68.9% of those who achieved a 'poor' response were in the SC arm. The figures for the GRACE index were 63.6% and 66.3% respectively, and for the CPDAI 66.7% and 63.7%. For each measure the difference in proportions was highly significant.

Discussion

The TICOPA study was the first to show that a treat to target approach improved clinical outcomes for patients with early PsA. The primary outcome was the composite measure developed for RA clinical trials, the ACR20. However, secondary outcomes demonstrated benefits across both articular and skin domains, although not for dactylitis and enthesitis. The current study describes the treatment response in terms of disease activity using three validated composite disease activity measures, all of which assess disease activity across several domains. Early separation was seen between the treatment groups with significant differences at 48 weeks and significantly more patients in the TC arm achieving a good clinical outcome. However, it must be acknowledged that these three composite measures were not assessed in their entirety in the TICOPA study, and that adaptations had to be made for the scores to be obtained. If the required data had been available it is possible that the measures would have behaved differently.

The early separation between treatment groups at 12 weeks was probably due to the more aggressive use of methotrexate. As reported in the original paper, subjects in the TC arm had rapid escalation of oral methotrexate to 25mg weekly and this was reflected in the numbers achieving that dose at 3 months (TC 82.2%; SC 7.6%). If the minimal disease activity target had not been reached at 12 weeks sulfasalazine was added to methotrexate so that the continued and more pronounced separation of treatment groups between 12 and 24 weeks was partly attributable to this combination therapy. This is important as it would be advantageous to be able to predict who would respond to either methotrexate alone or combination conventional disease modifying therapy. Beyond 24 weeks TC patients who continued to have active disease were eligible for biologic therapy with TNF blockers and the further relative improvement seen in the TC arm beyond 24 months probably reflects this.

In the subgroup of people with oligoarthritis contrasting results were obtained. The composite scores were lower at baseline, as would be expected, but the early difference seen for the entire cohort was not seen for the oligoarthritis sub-group alone. This result may reflect the possibility that none of the composite measures is appropriate for assessing disease activity where joint counts are low. An alternative explanation is that there is a a lack of effect of methotrexate in patients with oligoarthritis. In this respect it is worth noting that in the landmark methotrexate in psoriatic arthritis (MIPA) trial better results were seen in the polyarticular subset of the disease (11). More data is needed on the appropriate treatment strategy for this common subgroup of PsA.

At the time the TICOPA study was commenced validated composite measures for psoriatic arthritis were unavailable so that not all appropriate outcomes were measured to allow calculation of the PASDAS, CPDAI and GRACE. However, we were able to make an

allowance for the missing measures, either by estimating, using available measures or, in the case of the GRACE instrument, a modular measure, to omit the outcome (a skin VAS score). The effect of these modifications on the performance of the measures is difficult to assess: an independent data set in which all these variables are collected would inform this question. The new composite measures assess disease activity in domains other than the joints, and offer more responsiveness, together with larger effect sizes, in clinical trials (12). In future it would be appropriate to use such measures as the primary outcome in clinical trials as it is likely that fewer patients will be needed to show a difference in treatment arms. The PASDAS is currently being used in this way (13).

Which of the composite measures performs best in this study? In the overall patient population there is probably little to choose between them, although the statistics for the PASDAS exceed those for the GRACE and CPDAI. Similarly, the PASDAS outperforms the GRACE and CPDAI using area under the curve analysis. Similar contrasts are evident in the analysis of the oligoarthritis patients. Each of the measures differs in construction: the PASDAS uses a weighted formula, the GRACE a modular scheme with each domain using a 'desirability' scale, and the CPDAI also using a modular scheme in which patients are categorised within domain (2). Each of the measures covers a similar range of domains but the CPDAI is the only measure addressing the five major domains of joints, skin, enthesitis, dactylitis and spine. The relative performance of the measures may have been a function of the patients enrolled in the study - spinal involvement was not prominent, nor was the skin component – and the measures may perform relatively differently in alternative patient populations. In terms of outcome all three measures gave a similar result (Table 3) but it is worth noting that the cut-offs for outcome are still preliminary, although they have demonstrated good ability to distinguish radiographic progression in an alternative data set (14).

In conclusion, the performance of several novel composite disease activity measures have been examined using data from the TICOPA trial. Each measure was able to distinguish between treatment arms, although all three showed diminished ability to distinguish treatment effect for patients with oligoarthritis. Further data are needed to guide the decision on selecting a preferred composite measure for use as the primary outcome in PsA clinical trials.

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Figure legend. Change in scores for each composite measure in each treatment arm in the TICOPA study.

Table 1. Comparison of composite measures with analysis of covariance and area under of curve for all patients.

'F' and 't' are test statistics.

		n	Tight control N = 101	n	Standard Care N = 105	Analysis of covariance F	p	N	Area under curve t	p
PASDAS	Baseline	88	5,36 ± 1.42	85	5.09 ± 1.33					
	12 weeks	87	4.08 ± 1.37	85	4.44 ± 1.64					
	24 weeks	88	3.60 ± 1.58	85	4.25 ± 1.88					
	36 weeks	88	3.34 ± 1.74	85	4.21 ± 1.73					
	48 weeks	88	3.17 ± 1.64	85	4.02 ± 1.80	18.0	< 0.0001	173	2.57	0.01
GRACE	Baseline	97	4.37 ± 1.68	96	4.06 ± 1.64					
	12 weeks	96	3.27 ± 1.70	96	3.44 ± 1.78					
	24 weeks	97	2.76 ± 1.77	96	3.21 ± 1.98					

	36 weeks	97	2.55 ± 1.97	96	3.21 ± 2.03					
	48 weeks	96	2.32 ± 1.96	96	2.98 ± 2.00	14.5	< 0.0001	192	1.44	0.15
CPDAI	Baseline	89	7.83 ± 2.74	89	7.26 ± 2.62					
	12 weeks	89	5.88 ± 2.80	89	6.06 ± 2.81					
	24 weeks	88	5.21 ± 2.70	89	5.91 ± 3.13					
	36 weeks	89	4.79 ± 2.82	89	5.56 ± 3.02					
	48 weeks	88	4.46 ± 2.63	89	5.60 ± 3.10	15.9	< 0.0001	177	1.22	0.23

Table 2 Comparison of composite measures with analysis of covariance and area under of curve for patients with oligoarthritis at study entry.

'F' and 't' are test statistics.

		n	Tight control N = 27	n	Standard Care N = 30	Analysis of covariance F N p			Area under curve t p	
PASDAS	Baseline	21	4.14 ± 1.10	23	4.15 ± 0.80					
	12 weeks	20	3.30 ± 1.33	23	3.24 ± 1.04					
	24 weeks	21	2.82 ± 1.35	23	3.49 ± 1.65					
	36 weeks	21	2.97 ± 1.87	23	3.45 ± 1.49					
	48 weeks	21	2.61 ± 1.50	23	3.48 ± 1.53	4.7	0.04	44	0.94	0.35
GRACE	Baseline	26	2.77 ± 1.06	28	2.74 ± 1.09					
	12 weeks	25	2.23 ± 1.41	28	2.21 ± 1.10					
	24 weeks	26	1.80 ± 1.42	28	2.24 ± 1.51					
	36 weeks	26	1.76 ± 1.86	28	2.40 ± 1.75					
	48 weeks	26	1.39 ± 1.49	28	2.29 ± 1.61	6.6	0.01	54	0.97	0.34
CPDAI	Baseline	22	5.86 ± 2.12	24	5.38 ± 2.22					

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	12 weeks	22	4.64 ± 2.11	24	4.58 ± 2.17					
	24 weeks	21	4.00 ± 1.76	24	4.54 ± 2.64					
	36 weeks	22	4.00 ± 2.76	24	4.46 ± 2.57					
	48 weeks	22	3.59 ± 2.24	24	4.46 ± 2.45	4.5	0.04	46	0.37	0.72

Table 3. Numbers achieving 'good', 'moderate' and 'poor' response according to each measure

	Tight control			Standard care			X^2	p
	'Good' response	'Moderate' response	'Poor' response	'Good' response	'Moderate' response	'Poor' response		
PASDAS N (%)	40 (64.5)	29 (58.0)	19 (31.1)	22 (35.5)	21 (42.0)	42 (68.9)	15.1	0.001
GRACE N (%)	35 (63.6)	32 (62.7)	29 (33.7)	20 (36.4)	19 (37.3)	57 (66.3)	16.5	0.000
CPDAI N (%)	34 (66.7)	15 (62.3)	33 (36.3)	17 (33.3)	9 (37.5)	58 (63.7)	14.0	0.001

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