Patient self-report outcomes to guide a treat-to-target strategy in clinical trials and usual clinical care of rheumatoid arthritis

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Received and accepted on September 25, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 73): S50-S55.

Key words: rheumatoid arthritis, patient-reported outcomes, questionnaires, treat-to-target

Competing interests: T. Pincus has consulted for and received honoraria from Baxter, Janssen Pharmaceuticals and Medac, and receives support for an educational programme from Abbott, Amgen and UCB;
I. Castrejón has declared no competing interests.

ABSTRACT

Patient self-report questionnaires provide an easily-implemented approach for quantitative assessment of patients with rheumatoid arthritis (RA) in usual care settings. Patient reported outcomes (PROs) on these questionnaires and an index including only patient self-report measures, RAPID3 (Routine Assessment of Patient Index Data), distinguish active from control treatments as effectively as other measures in clinical trials of methotrexate, leflunomide, adalimumab, abatacept, and certolizumab. RAPID3 is correlated significantly with indices that include formal joint counts and laboratory tests, such as disease activity score 28 (DAS28) and clinical disease activity index (CDAI), in clinical trials and clinical care, including categories for high, moderate, low severity, and remission. Patient self-report questionnaires present additional advantages that the same observer (the patient) completes quantitative scores at each encounter regardless of the setting and the patient does most of the work to provide an index. Completion of a questionnaire helps the patient prepare for the visit, and improves doctor-patient communication. This article summarises evidence concerning PROs in clinical trials and clinical care in documenting low disease activity and remission, including a meta-analysis of studies that document the value of using PROs to implement "treat-to-target." Patient self-report questionnaires must be complemented by a careful joint examination, and do not prevent performance of a formal joint count or any other measure by a treating physician. Patient self-report questionnaires may provide a useful, cost-effective method to implement treat-to-target in patients with RA as well as other rheumatic diseases.

Introduction

Patient-reported outcomes (PROs) on self-report questionnaires are well-established to monitor status of patients with rheumatoid arthritis (RA) in both clinical trials and usual clinical care (1), recognised by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) 6 conference (2). Although PROs are regarded by many physicians as "subjective" and less valid than "objective" joint counts and laboratory tests, interpretation of these measures was more consistent for patient global assessment than for physician global assessment or joint counts (3). In general, physicians tolerated higher values on the patient global scale than on the physician global scale suggesting that physicians tend to assume that patients rate their disease activity as more severe than their physicians, in agreement with observed results in various studies (4-6). Since no absolute "gold standard" to estimate global disease activity exists, a "true" global activity estimate is not possible.

There are several advantages in using the most common reported PROs in trials in routine care, particularly if a questionnaire is distributed to each patient at each visit in the infrastructure usual care (7). The patient does most of the work, and is the most knowledgeable person concerning pain and global estimate (8). Completion of a questionnaire helps the patient prepare for the visit and improves doctor-patient communication. A self-report questionnaire does not replace a joint count, but is complementary to a careful joint examination including a formal joint count (1).

A systematic literature review identified 63 tools or measures of PROs in 109 articles (9); the most frequent domain reported was functional assessment, primarily using a Health Assessment Questionnaire (HAQ) (83.4%), followed by patient global assessment (PATGL) (63.3%), primarily using a VAS (visual analogue scale), followed by pain, also using a VAS (55.9%) (9).

Table I. Measures included in indices to assess patients with rheumatoid arthritis (RA).

ACR Core Data Set	DAS28	CDAI	RAPID3
Physician/assessor measures			
n. tender joints	0.28 × sq rt (TJC28)	0–28	--
n. swollen joints	0.28 × sq rt (SJC28)	0–28	--
Physician/assessor global estimate	--	0–10	--
Laboratory measures			
ESR or CRP	0.70 × ln (ESR)	--	--
Patient-reported measures			
Patient function	--	--	0–10
Patient pain	--	--	0–10
Patient global estimate	0.014 × PTGL	0–10	0–10
TOTAL	0 – 10	0–76	0–30

These are the three patient-reported measures included in the RA Core Data Set: physical function, pain and patient global estimate (10). An index which includes only these 3 PROs, RAPID3 (Routine Assessment of Patient Index Data), is as efficient as DAS28 (disease activity score with 28 joint count) (11) and CDAI (clinical disease activity index) (12) to distinguish active from control treatments in clinical trials involving methotrexate (13), leflunomide (13), anakinra (14), adalimumab (15), abatacept (16), and certolizumab (17). RAPID3 scores are correlated significantly with DAS28 and CDAI scores in clinical trials (15, 17-19) and usual clinical care (20, 21), including categories for high, moderate, low severity and remission (Table I). Physical function scores on MDHAQ and other questionnaires are far more significant than radiographs or laboratory tests in the prognosis of severe outcomes in RA, including functional status (22, 23), work disability (24-26), costs (27), joint replacement surgery (28) and premature death (22, 29-35) – all except radiographs (1).

These observations suggest that PROs and RAPID3 may be of potential value to implement a treat-to-target (36), tight control strategy in routine care of patients with RA, as summarised in this article.

Patient-reported outcome measures document advantages of treat-to-target in clinical trials and formal research studies similarly to DAS28

All clinical trials involving a treat-to-target strategy have documented better clinical outcomes of a targeted approach compared with a routine approach in patients with RA (37-44). The primary outcome in most of these trials was DAS or DAS28. Reports of certain trials also included data for individual PROs, including physical function, pain and patient global estimate of status on the health assessment questionnaire (HAQ). It should be noted that a patient global estimate is included in all widely-used indices of RA disease activity, including DAS, DAS28, and CDAI. Therefore, at least one PRO is measured in all RA clinical research, although not always reported as an individual measure.

In the TICORA (Tight Control for Rheumatoid Arthritis) trial in Scotland (see also article by Porter in this Supplement), patients were randomly allocated to either intensive management or routine care (37). Patients assigned to the intensive group were seen every month by the same rheumatologist, and treatment was adjusted depending on the DAS score. The strategy of intensive management led to significantly greater improvement in disease activity, radiographic progression, quality of life and scores for physical function, pain and patient global estimate of status on the HAQ compared to routine care (37) (Table II).

The CAMERA (Computer-Assisted Management in Early Rheumatoid Arthritis) study in the Netherlands (see

Table II. Change from baseline for patient-reported outcomes in treat-to-target *versus* routine care groups in five studies.

Study	Target	Follow-up	Routine Care				Treat-to-target			
			n	HAQ Physical function (0–3)	Pain (VAS 0–100)	PATGL (VAS 0–100)	n	HAQ Physical function (0–3)	Pain (VAS 0–100)	PATGL (VAS 0–100)
Grigor 2004 (37) TICORA (37)	DAS≤2.4	18 m	50	-0.47 (0.9)	-20 (31)	-21 (34)	53	-0.97 (0.8)	-45 (24)	-51 (30)
Verstappen 2007 CAMERA (38)	ACR remission	2 year	148	-0.42 (0.76)	-26 (31)	-22 (28)	151	-0.41 (0.64)	-34 (31)	-30 (31)
Goekoop-Ruiterman 2009 (46) BeST (46)	DAS≤2.4	1 year	201	-0.55 (-0.7)	NR	NR	234	-0.70 (-0.7)	NR	NR
Soubrier 2011 ESPOIR-GUEPARD (39)	DAS28 (ESR)≤3.2	12 m	130	-0.65 (0.74)	-24.1 (26.3)	-30.5 (30.9)	65	-0.97 (0.61)	-44.9 (25.2)	-50.2 (25.3)
Schipper 2012 (47) Inception cohorts (47)	Remission DAS28 ≤2.6	1 year	126	-0.3 (-0.8, 0)*	-16 (28)	-16 (27)	126	-0.5 (-1, -0.2)*	-30 (27)	-32 (28)

Values are expressed as mean (SD) difference from baseline, except *expressed as median interquartile range (IQR).
NR: not reported; PATGL: patient global estimate of status; VAS visual analogue scale.

also article by Jacobs in this Supplement) compared intensive treatment with methotrexate according to a protocol with predefined improvement criteria versus conventional treatment (38). Improvement was adjusted according to a computer program. The primary outcome for this study was the number of patients in DAS remission for at least three months. Scores for physical function were improved similarly from baseline to 2 years follow-up in both groups, but scores for pain and patient global estimate were improved at significantly higher levels in the intensive group (38) (Table II).

In the BeSt (Behandel Strategien or "treatment strategies") trial in the Netherlands (45, 46), four strategies were compared. Patients in a treat-to-target group had better clinical outcomes after 1 year of follow-up compared to patients treated with routine care. Mean improvement in physical function – the only PRO reported in this study – was 0.70 in the treat-to-target group compared to 0.55 in the routine care group (p=0.029) (Table II).

The GUEPARD (Guérir la PolyArthrite Rhumatoide Débutante) trial of tight control in France was compared with routine care in patients from the ESPOIR (Etude et Suivi des Polyarthrites Indifférenciées Récentes) cohort (39). All variables showed greater improvement in the treat-to-target group, including all three RA Core Data Set PRO variables for physical function, pain and patient global estimate (Table II).

A study of two early arthritis inception cohorts in The Netherlands (47) compared a protocol-driven treatment adjustment strategy with a usual care cohort. The tight-control group had greater improvement in physical function, pain and patient global estimate (Table II).

A meta-analysis was performed of combined results according to PROs in these five studies (Fig. 1A-C). All measures in individual studies indicated better outcomes in the treat-to-target versus control groups. The overall weighted mean difference for physical function (0–3 scale) was 0.16 in favour of the treat-to-target strategy (range across all studies: 0.07–0.25; p=0.01 *vs*. usual care); 15.34 (0–100 scale) for pain (range 11.50–19.18; p=0.02); and 15.52 (0–100 scale) for patient global estimate (range: 11.61–19.42; p=0.01). Therefore, PROs documented significantly better clinical outcomes with treat-to-target strategies.

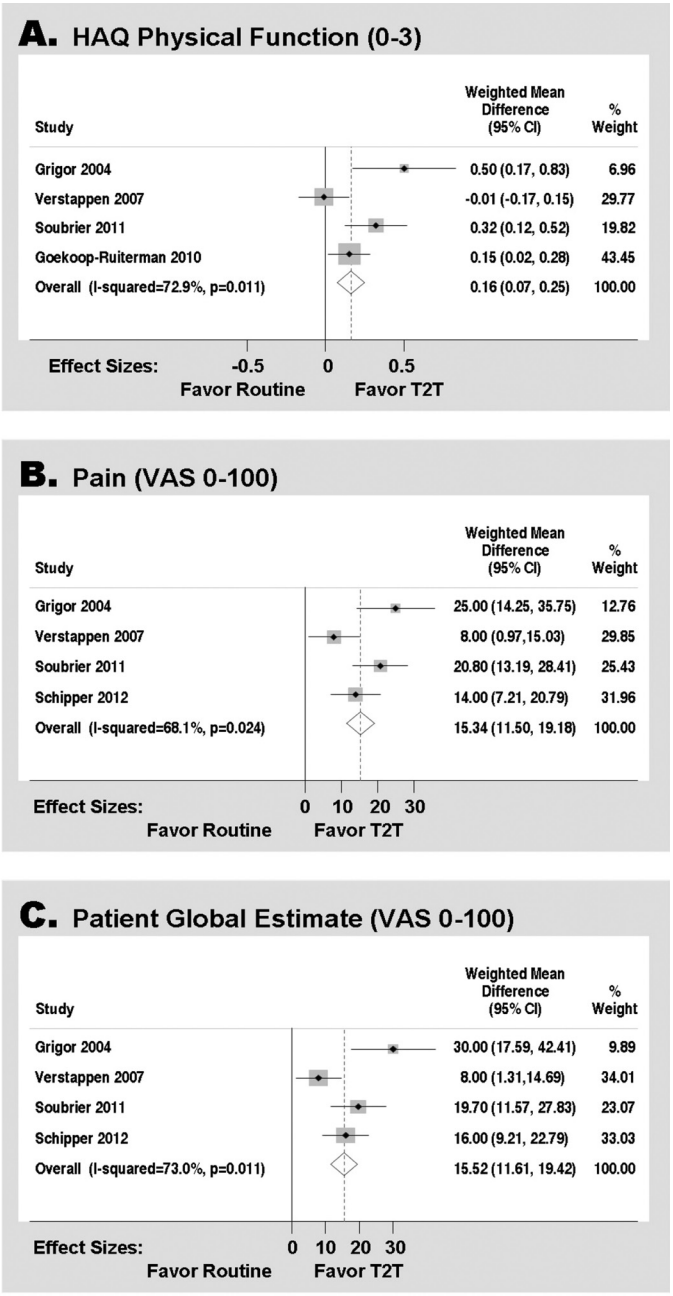

Fig. 1. Meta-analysis of combined results of 5 treat-to-target studies [Grigor 2004 (37), Verstappen 2007 (38), Soubrier 2011 (39), Goekoop-Ruiterman 2010 (46), Schipper 2012 (47)], according to patient-reported outcome measures (PROs): **A:** physical function from a health assessment questionnaire (HAQ) (0–3 scale); **B:** pain from a visual analogue scale (VAS) (0–100 scale); and **C:** patient global estimate of status from a VAS (0-100 scale). Effect sizes less than zero favour routine care; effect sizes greater than zero favour treatment according to a treat-to-target (T2T) strategy.

Quantitative scores for low activity/remission according to RAPID3 compared to DAS28 and CDAI in 3 clinical trials and 2 studies from usual clinical care

RAPID3 is a composite index calculated from the 3 RA Core Data Set measures for physical function, pain and patient global estimate, each scored 0–10 for a total score range of 0–30 (48) (Table I). RAPID3 severity categories, designed in comparison with DAS28 (49), are ≤3 for remission, 3.1-6.0 for low activity, 6.1-12.0 for moderate activity, and >12 for high activity (20). RAPID3 scores are correlated significantly with DAS28 and CDAI (17, 21) (Fig. 2). RAPID3 distinguishes active from control treatment as efficiently as DAS28 and CDAI in clinical trials (17, 18, 49, 50), reflecting that PROs have relative efficiencies similar to or greater

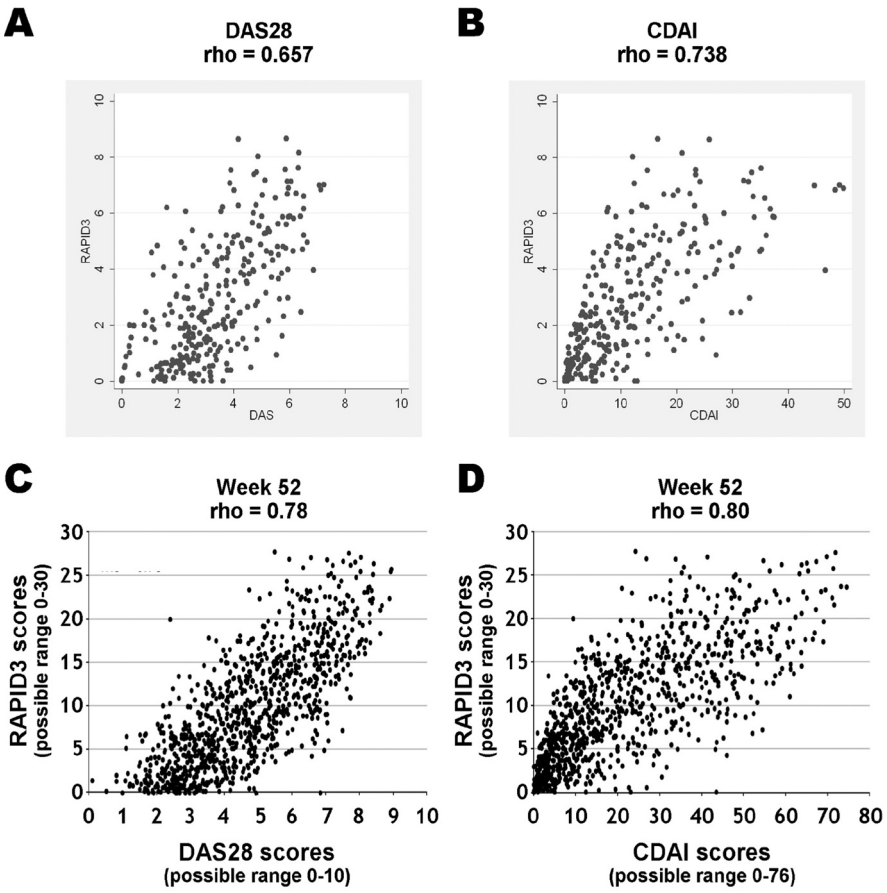

Fig. 2. RAPID3 scores are correlated significantly with DAS28 and CDAI in clinical trials and clinical care.
Panels A, B: In 285 patients with rheumatoid arthritis (RA) seen in usual clinical care (21), RAPID3 was correlated with **A:** DAS28 at rho=0.657 and with **B:** CDAI at rho=0.738.
Panels C, D: In 982 patients in the Rheumatoid Arthritis Prevention of Structural Damage (RAPID1) clinical trial of certolizumab pegol (CZP) *versus* placebo, Spearman correlations of RAPID3 with **C:** DAS28(ESR) scores and **D:** CDAI scores at 52 weeks were 0.78 and 0.80, respectively (17). Both correlations are statistically significant (p<0.001).
DAS28: disease activity score; CDAI: clinical disease activity index; RAPID3: routine assessment of patient index data; RAPID1: Rheumatoid Arthritis Prevention of Structural Damage clinical trial.

than swollen and tender joint counts or laboratory tests (15). However, RAPID3 requires 5 seconds to score, compared to almost 2 minutes for DAS28 and CDAI (21).

Comparisons of categories of high, moderate and low severity and remission have been reported according to RAPID3 compared to DAS28 in two studies from usual clinical care (20, 21) and post hoc analyses of clinical trials involving abatacept (18) and certolizumab (17) (Table III). Similar analyses comparing RAPID3 and CDAI categories have been reported for the clinical care studies (20, 21) and the RAPID1 certolizumab clinical trial (17) (Table IV).

These comparisons indicate concordance of RAPID3 with DAS28 categories of high/moderate activity and low activity/remission ranging from 69% to 83%, with discordance ranging from 17% to 31%. Kappa values ranging from 0.27 to 0.49 (Table III). Greater concordance was seen of RAPID3 with CDAI categories, ranged from 76% to 81%, with discordance of 20%–23%, and kappa values of 0.44-0.51 (Table IV).

RAPID3 may be quite useful clinically to identify low disease activity, but like DAS28 it appears insufficiently stringent to identify remission as recommended by the ACR/EULAR committee for Boolean and ≤3.3 criteria (51, 52). Preliminary analyses have suggested that two additional strategies identify patients in remission quite similarly to ACR/EULAR criteria than RAPID3 alone (Castrejón, unpublished data).

One approach involves inclusion of findings on a careful joint examination, but not a formal joint count, indicating no more than one swollen joint in addition to RAPID3 ≤3. A second approach is to include a physician global score and/or careful joint examination. Further research concerning possible use of RAPID3 to identify patients who might be in remission is ongoing.

Conclusion

Extensive evidence indicates that the management of RA patients with a treat-to-target strategy confers better outcomes than usual care. Evidence in all reports of PROs from these clinical trials suggests that PROs and RAPID3 might be useful to define remission and to guide a treat-to-target strategy in usual clinical care. Although clinical remission should be the primary target, a level of low disease activity may be a more realistic alternative for many patients to pursue. Remission remains uncommon in patients with RA and low disease activity may also be associated with favourable outcomes.

Implementation of tight control into routine care may be facilitated by quick and simple validated tools such as RAPID3. The patient does almost all the work involved in obtaining the quantitative PROs included in RAPID3, and there is almost no additional burden to the doctor's office if patients are given a questionnaire as a component of the infrastructure of routine care. In addition, RAPID3 not only provides simplicity but also incorporates the patient perspective of disease activity allowing patients to be further involved in their care. RAPID3 scores appear adequate to identify low disease activity, although there appears a need to add a careful joint examination and/or physician global score to provide stringent criteria for remission (Castrejon, unpublished data), comparable to the Boolean and SDAI criteria of the ACR/EULAR committee (51, 52). Even these proposed additions do not require a formal joint count, which involves considerable time, and has poor measurement properties (1).

It is important to remain aware that treat-

Table III. Concordance and discordance between DAS28 and RAPID3 categories of high/moderate disease activity and low disease activity/remission in patients with rheumatoid arthritis (RA) in analyses of 5 studies.

Study (Reference)	CONCORDANT			DISCORDANT			Weighted kappa
	DAS28 High/Moderate RAPID3 High/Moderate	DAS28 Low/Remission RAPID3 Low/Remission	Total*	DAS28 High/Moderate RAPID3 Low/Remission	DAS28 Low/Remission RAPID3 High/Moderate	Total*	
Usual care 2008 (n=285) (20)	114 (40%)	98 (34%)	74%	26 (9%)	47 (17%)	26%	0.44
Usual care 2010 (n=200) (21)	97 (48%)	42 (21%)	69%	24 (12%)	37 (19%)	31%	0.27
AIM abatacept trial (n=374) (18)	211 (56%)	67 (18%)	74%	61 (16%)	35 (9%)	25%	0.42
ATTAIN abatacept trial (n=179)	(18) 127 (71%)	21 (12%)	83%	23 (13%)	8 (4%)	17%	0.40
Certolizumab trial (n=777) (17)	404 (52%)	186 (24%)	76%	139 (18%)	48 (6%)	24%	0.49

*Totals may not equal 100% due to rounding.

Table IV. Concordance and discordance between CDAI and RAPID3 categories of high/moderate disease activity and low disease activity/remission in patients with rheumatoid arthritis (RA) in analyses of 3 studies.

Study (Reference)	CONCORDANT			DISCORDANT			Weighted kappa
	CDAI High/Moderate RAPID3 High/Moderate	CDAI Low/Remission RAPID3 Low/Remission	Total*	CDAI High/Moderate RAPID3 Low/Remission	CDAI Low/Remission RAPID3 High/Moderate	Total*	
Usual care 2008 (n=285) (20)	117 (41%)	101 (35%)	76%	23 (8%)	44 (15%)	23%	0.51
Usualcare 2010 (n=200) (21)	113 (57%)	47 (24%)	81%	19 (10%)	21 (11%)	21%	0.44
Certolizumab trial (n=777) (17)	368 (47%)	254 (33%)	80%	71 (9%)	84 (11%)	20%	0.49

*Totals may not equal 100% due to rounding.

ment targets must be adapted to the individual patient as agreed upon between doctor and patient (36), given that comorbidities, drug toxicity and therapeutic options, may lead to deviation from single score numbers of disease activity recommended as treatment targets. Further studies of PROs in helping to define an optimal target for a treat-to-target strategy will help improve outcomes for patients with RA.

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