Clinical and Experimental Rheumatology 2010; 28: 748-751.

Persistence on therapy is a major determinant of patient-, physician- and laboratory-reported outcomes in recent-onset rheumatoid arthritis patients

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Received on March 3, 2010; accepted in revised form on May 18, 2010.

Key words: Persistence on therapy, disease outcomes

Competing interests: none declared.

ABSTRACT

Objectives. *To evaluate impact of persistence on therapy on sustained major patient-, physician- and laboratory-reported outcomes (PROs, PHYROs and LAROs, respectively) in 112 recent-onset rheumatoid arthritis (RA) patients.*

Methods. *At each visit a rheumatologist interviewed patients regarding therapy, morning stiffness and fatigue, scored the 28-joint disease activity score and a visual analogue scale (VAS) and determined acute-phase-reactants. The patients completed the Hispanic version of the Rheumatoid Arthritis Disease Activity Index, the Medical Outcome Short Form 36 (SF-36), the Health Assessment Questionnaire (HAQ), a pain-VAS and an overall-disease activity-VAS. Persistence was defined by self-report through directed interview. Sustained major PROs, PHYROs and LAROs were defined according to cut-offs, when maintained for ≥6 months and until last follow-up. Descriptive statistics, Kaplan-Meier curves and Cox models were used.*

Results. *Total person-time of receiving therapy was of 375.5 patient-years. From February 2004 to June 2009, 36 (32.1%) patients were persistent. Baseline PROs/PHYROs/LAROs showed active disease and poor health status in both groups, but persistent patients (PP) had significantly lower HAQ (p=0.03) and overall-disease activity-VAS (p=0.01). More PP reached a sustained major SF-36-physical function-score (p=0.02). Persistence was the greatest independent risk factor for sustained major PROs (but absence of fatigue) and PHYROs, (p≤0.04). Time from baseline to major and sustained PROs (excluded absence of fatigue), PHYROs and C-reactive protein were shorter in PP (p≤0.04).*

Conclusion. *Persistence was a strong predictor for major and sustained outcomes in early RA. Favourable outcomes appear earlier in persistent than in non-persistent patients.*

Introduction

Rheumatoid arthritis (RA) is a chronic disabling disease which primary objectives of treatment are to improve and maintain physical and social functioning (1). Current management guidelines recommend incorporating patient-reported measures of functioning and quality of life (PROs) into clinical trials (2, 3) as they are as effective as the traditional physician- or laboratory- reported outcomes (PHYROs and LAROs, respectively) in reflecting long-term morbidity and mortality (4), easier to administer and less expensive than physician-observed health status measures.

RA outcomes are influenced by medication adherence (*how well* patients take their medications) and medication persistence (*how long*) (5). Both are two different constructs frequently monitored in the clinical setting through patient self-reports (6).

We recently showed that non-persistence on DMARDs from patients with recent-onset active RA had a negative impact on disease activity and on disability (7). There are no longitudinal data as to whether DMARDs-P affects long-term PROs which include the advantage of measuring outcomes using the values of patients. The present study evaluates the effect of DMARDs-P on sustained major PROs in a cohort of early RA patients prospectively followed from February 2004 to June 2009. We expanded the data to identify potential differences within persistence-impact and patient-, physician-, and laboratory reported outcomes.

Methods

Setting and study population

One hundred and twelve consecutive patients with early RA, at least six months of follow-up and DMARD indication were included in the study. Medical evaluations were performed every 2, 4 or 6 months and included the 28 joints-disease activity score (DAS28) (8), a physician-filled visual analogue scale (VAS) for overall disease activity (Phy-VAS), erythrocyte sedimentation rate (ESR) determination by Westergren, C-reactive Protein (CRP) determination by nephelometry, comorbidity established by record review, DMARD persistence defined though patients self-report after a structured interview (6), and PROs which included Hispanic versions of the Rheumatoid Disease Activity Index (RADAI) (9), the Medi-

cal Outcomes Study Short Form 36 (SF-36, mental and physical subscores) (10), the Health Assessment Questionnaire (HAQ) (11), a pain- and overall disease activity-VAS (pain-VAS and O-VAS, respectively) and presence/absence of morning stiffness and of substantial fatigue.

At study entry complete medical history and demographic data were recorded, rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides determined by nephelometry and second generation ELISA, respectively.

Definitions

Non-persistence was defined when DMARDs were discontinued for ≥7 consecutive days.

Sustained major PROs (RADAI, SF-36, HAQ, patient's VAS, morning stiffness and fatigue), PHYROs (DAS 28, physician VAS) and LAROs (ESR and CRP) were defined when the following outcomes were maintained for at least 6 months and until last follow-up: RADAI ≤1, SF-36 global, mental and physical scores ≥80, HAQ ≤0.20, VAS ≤10, absence of morning stiffness and of substantial fatigue, DAS28 <2.4, ESR<30mm/h or <20 mm/h for a female or male, respectively, and CRP ≤1.57mg/dL (Beckman Coulter, Inc).

Ethics

The study was approved by IRB and written informed consent was obtained.

Table I. Baseline characteristics in the study population and in persistent *vs*. non-persistent patients.

Variables	Population n=112*	Persistent patients, n=36*	Non-persistent patients, n=76*	*p*-value
Socio-demographic				
Females, n. (%)	97 (86.6)	30 (83.3)	67 (88.2)	0.56
Age at baseline, years	38.2 (27.1-46.1)	33.8 (25.8–44.9)	39.4 (28.5–47.9)	0.14
Years of education	11 (5–6)	12 (9–16)	11 (9–12)	0.09
Disease characteristics				
Number of ACR criteria	5 (5–6)	5 (5–6)	5 (5–6)	0.62
Time since 1st symptom, months	4.9 (3–6.8)	4.7 (3.2–6.7)	5 (3–7)	0.74
n. (%) patients with RF	85 (75.9)	27 (75)	58 (76.3)	1
n. (%) patients with a-CCP	82 (73.9)**	26 (72.2)**	56 (74.7)	0.82
Patient-reported outcomes				
RADAI (0-10)	5.3 (3.7–6.9)***	5 (3.6–6)	5.7 (3.8–7.2)	0.12
SF-36, physical score (0-100)	29.8 (21.5–43.7)	32.7 (25.6–44)	27.8 (19.9–42.7)	0.08
SF-36, mental score (0-100)	38.9 (28.5–55.3)	41.1 (32.8–71.3)	37.3 (27.2-52.1)	0.13
HAQ (0-3)	1.5 (0.9–2.1)	1.3 (0.8–1.6)	1.6 (1–2.4)	**0.03**
Pain-VAS (0-100)	62 (40.8–78.4)	55.5 (40.8–67.8)	67 (39.3–80.8)	0.09
Overall-disease-VAS (0-100)	67.5 (37.4–82)	53.8 (29.8–72.5)	73 (44.5–86.8)	**0.01**
Morning stiffness, n. (%)	108 (96.4)	34 (94.4)	74 (97.4)	0.59
Duration of MS, min	70 (40–300)	120 (40–300)	65 (40–242.5)	0.52
Substantial fatigue, n. (%)	57 (50.9)	16 (44.4)	41 (53.9)	0.42
Physician-reported outcomes				
DAS28 (0-10)	6.1 (5.2–7.1)	5.9 (4.8–6.6)	6.3 (5.4–7.3)	0.06
Physician-VAS (0-100)	43 (30–56.8)	39 (30–50)	45 (31.3–58)	0.33
Laboratory-reported outcomes				
ESR, mm/H	23.5 (17.3–44)	23.5 (18.3–43.5)	24 (17–39)	0.77
CRP, mg/dL	2 (1.3–2)	1.3 (0.2–3.6)	0.96 (0.3–3.3)	0.90
n. (%) patients with comorbidity	56 (50)	22 (61)	34 (44.7)	0.16
Baseline treatment				
Corticosteroids, n. (%)	37 (33)	12 (33)	25 (32.9)	1
n. DMARDs/patient	2 (1.3–2)	2 (2–2)	2 (1–3)	0.45
n. Drugs for comorbidity/patient	1 (1–2)	1 (1–2)	1 (1–2)	0.96

*Data presented as median (25th percentile–75th percentile)) unless otherwise indicated. **1 baseline missing data. ***4 missing values, 2 from each group.

n.: Number of patients; ACR: American College of Rheumatology; RF: Rheumatoid factor; a-CCP: Antibodies to cyclic citrullinated peptides; RADAI: Rheumatoid Arthritis Disease Activity Index; SF-36: Medical Outcomes Study Short Form 36; HAQ: Health assessment questionnaire; VAS: Visual analogue scale; MS: Morning stiffness; DAS28: Disease activity score, 28 joints evaluated; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; DMARDs: Disease modifying anti-rheumatic drugs.

Statistics

Student's *t*-test, χ^2 test and Mann-Whitney U-test were used. Serial treatment for each patient was summarised by mean of drugs [DMARD(s) and drug(s) for comorbid conditions].

The unadjusted association between DMARDs-P and sustained major outcomes was assessed using the Kaplan-Meier curves and compared using the log rank test. Multivariate Cox proportional hazard models were constructed. The dependent variable was each major and sustained outcome. In the adjusted models, correction for potential confounders and for those variables with $p \leq 0.10$ in the univariate analysis was done. Correlations between selected variables were examined. All statistical tests were 2-sided and evaluated at the 0.05 significance level. Statistical analyses were performed using the SPSS/PC program (v.12.0; Chicago IL).

Results

The total person-time of receiving DMARDs was of 375.5 patient-years with (mean±SD) follow-up of 40.2±15.2 months. At cut-off, 36 patients were persistent, 76 non-persistent and their (mean±SD) days of DMARDs discontinuation was of 50±43.3. Percentage of time with DMARDs discontinuation ranged from 0.5% to 14.4%.

Table I shows baseline variables. Most of them were similar across subpopulations but PP showed significant lower [median, (25^{th}-75^{th} percentiles)] HAQ [1.3 (0.8–1.6)] and patient overall-disease VAS [53.8 (29.8–72.5)] than non-PP [*vs*.1.6 (1–2.4), p=0.03 and *vs*. 73 (44.5–86.8), p=0.01, respectively].

During follow-up, mean DMARD treatment and drugs for comorbid conditions (per patient) were similar between persistent and non-persistent patients: 2.3±0.7 *vs*. 2.4±0.7, p=0.5 and of 1.8±0.9 *vs*. 1.8±0.9, p=0.9, respectively, as was percentage of patients receiving corticosteroids: 38.9% *vs*. 50%, p=0.3.

Relationship between persistence on medication and sustained major PROs, PHYROs and LAROs

A higher proportion of PP reached sustained major PROs, PHYROs and

LAROs when compared to non-PP. Differences were statistically significant for major and sustained SF-36 physical function: 26 (69.6%) patients *vs*. 34 (44.7%) patients, p=0.02.

Cox regression analysis included confounders variables (age at baseline, gender, RF and a-CCP status, the baseline value of the corresponding outcome and serial DMARD/s treatment) and variables with $p \leq 0.10$ in the univariate analysis (years of education, baseline HAQ, SF-36 physical score, both patient-overall disease and pain VAS, DAS28 and follow-up). As shown in Table II, persistence on DMARDs was the strongest predictor for sustained PROs (but absence of substantial fatigue) and for PHYROS after controlling for the variables above described. Persistence did not impact LAROs.

Hazard function curves (Fig. 1) showed that [median of months, 95% confidence interval (C.I.)] time from study entry to sustained major outcome achievement (besides sustained absence of fatigue and sustained low ESR) was significantly shorter in PP than in non-PP: RADAI, 7.5 (4.2–10.7) *vs*. 17.6 (13.3–21.8), $p \leq 0.001$; SF-36, 16.9 (2.8–31.1) *vs*. 42.2 (24.6–59.7), p=0.002; HAQ, 4.4 (3.6–11.6) *vs*. 16 (7.7–24.3), p=0.007; pain-VAS, 8.3 (5.8–10.7) *vs*. 10.4 (4.8–16), p=0.02; patient-overall-disease-VAS, 4.4 (2.4–6.4) *vs*. 12.6 (8.6–16.5), $p \leq 0.001$; absence of morning stiffness, 4.1 (2.3–5.8) *vs*. 10.4 (6.2–14.6), $p \leq 0.001$; DAS28 remission, 8.3 (0–16.6) *vs*. 47.9 (33.2–62.7), $p \leq 0.001$; physician-overall-disease-VAS, 6.2 (4.5–7.9) *vs*. 21 (12.8–29.2), $p \leq 0.001$ and sustained low CRP, 2 (1.9–2.2) *vs*. 9.9 (2.6–24.7), p=0.002.

Table II. Impact of persistence on DMARDs on sustained major patient-, physician- and laboratory-reported outcomes.

	OR	95%CI	*p*-value	Other significant predictors
Sustained major PROs				
RADAI ≤1	2.8	1.7–4.7	**≤0.001**	Follow-up, SF-36 mental score
SF-36 ≥80	1.8	1.1–3	**0.03**	Age, SF-36 physical score, years of education
HAQ ≤0.20	1.7	1.1–2.7	**0.04**	Follow-up
Pain-VAS ≤10	1.7	1.1–2.7	**0.02**	Age
Overall-disease-VAS ≤10	2.3	1.5–3.6	**≤0.001**	Age, SF-36 mental score
Absence of morning stiffness	2.1	1.3–3.4	**0.002**	HAQ, pain-VAS
Absence of substantial fatigue	1.2	0.8–1.9	0.4	No predictor was found
Sustained major PHYROs				
DAS28 <2.4	1.9	1.1–3.5	**0.03**	Baseline DAS28
Overall disease-VAS ≤10	2.3	1.3–3.9	**0.002**	Male gender, patient-overall-disease-VAS
Sustained major LAROs				
ESR <20 (M) and <30mm/H (F)	1.4	0.9–2.4	0.1	Follow-up, SF-36 physical score
CRP ≤1.57 mg/dL	1.7	0.9–2.8	0.06	a-CCP, follow-up, baseline DAS28

OR: Odds ratio; CI: Confidence interval; PROs: Patient-reported outcomes; RADAI: Rheumatoid arthritis disease activity index; SF-36: Medical Outcomes Study Short Form 36; HAQ: Health assessment questionnaire; VAS: Visual analogue scale; PHYROs: Physician-reported outcomes; DAS28: Disease activity score, 28 joints evaluated; LAROs: Laboratory-reported outcomes; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

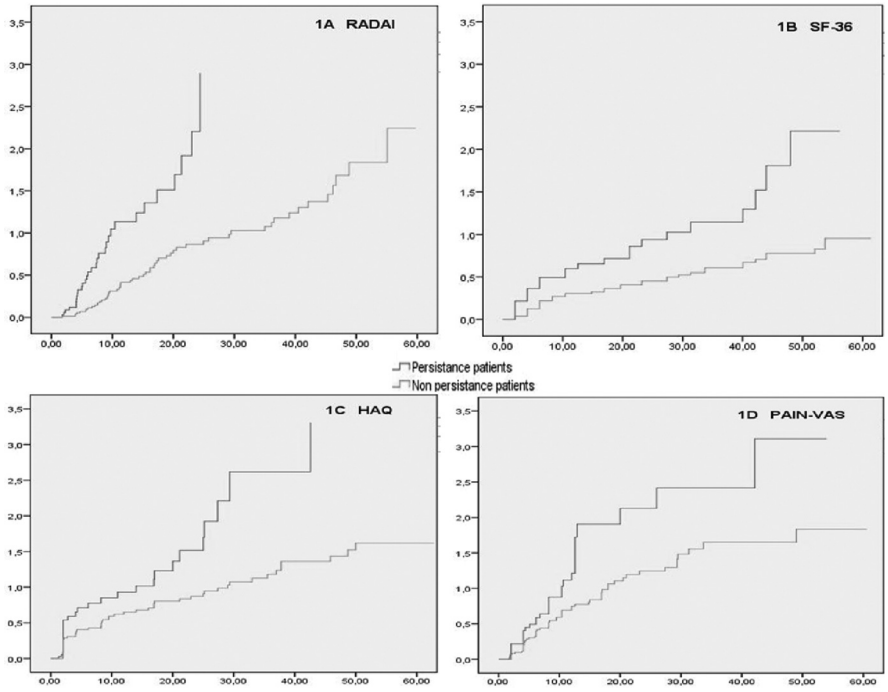

Fig. 1. Hazard function curves of sustained desirable patient-reported outcome achievement (see definition in the text) achievements which appear significantly earlier in persistent (upper line) than in non-persistent patients (lower line): **1A** for the RADAI, **1B** for SF-36, **1C** for HAQ and **1D** for pain-VAS. The x-axis represents months of follow-up and the y-axis cumulative hazard for specific sustained and major outcomes.

Discussion

In patients with clinically active early RA, persistence on DMARDs translated into longstanding major improvements which additionally appeared early on (2 to 39 months). Persistence on therapy had the greatest impact and results were confirmed in the Cox analysis after correction for confounders among which were baseline differences regarding disease activity and disability. This suggests that greater and earlier improvements in persistent patients were mostly related to persistence, although a deleterious clinical status at baseline may additionally affected patient's therapy behaviour. Patients discontinue DMARDs for a relatively short period of time although its impact on self-reported outcomes was critical. Few studies have addressed this topic and showed similar results. Viller *et al*. (12) found decreased HAQ in consistently compliant European RA patients over 3 years follow-up than in those

who changed behaviour. They included 556 patients with <5 years of disease duration and compliance with drug dosages and dosing times was assessed yearly using a questionnaire. In a previous study from the same inception cohort, with reduced number of patients and shorter follow up we reported similar data but limited to the HAQ and the DAS28 (7). Different studies have also addressed the topic of how clinical and serological statuses prior to therapeutic intervention impacted patient's therapy behaviour (13) and favour the concept that adherence/persistence and disease outcomes are certainly related, although the specific direction of this relationship is not clear.

Major and sustained laboratory-reported outcomes were minimally affected by persistence on DMARDs. Evidence already exists that patient-reported outcomes measures surpasses the acute phase reactants in sensitivity to change, discriminative power and as predictors for future disability and mortality (4). Nonetheless, normal cut-offs for ESR and for CRP were arbitrarily chosen and may not reflect their behaviour in our population. Also, cumulative days of therapy discontinuation were short and it remains to be questioned if longer period of therapy interruption do affects LAROs.

The study has several limitations. We did not use a well-validated questionnaire scale to assess persistence (14) and arbitrarily choose a lag time of one week to define therapy discontinuation. Nonetheless, our rate of self-reported nonpersistence was consistent with persistence rates using other measures in related studies (12, 14). We arbitrarily choose a 6 continuous month's lag time to meet the definition of "sustained" outcome similar to what has been proposed in the field of juvenile idiopathic arthritis. Intentional and non-intentional sources of non-persistence were not measured which difficult a comprehensive appreciation of factors influencing persistence. We realise that the DAS28 is a composite index that includes ESR and a measurement for VAS global health; accordingly it should not be characterised as a physician-reported outcome. Some of the questionnaires are known to perform well in well-educated urban populations (9) and their metrics properties should be tested before using it in dissimilar populations. Finally, this study was done in an inception cohort of recent-onset RA patients, with particular socio-demographic characteristics, ethnicity, treatment and health system and our results should not be generalised (15).

Persistence on DMARDs of patients with early and active RA positively influences disease's outcomes. Patient's perspectives revealed the true impact of the disease on patient's lives and should be included when addressing the topic of compliance.

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