

# Performance of patient-reported outcomes in the assessment of rheumatoid arthritis disease activity: the experience of the ESPOIR cohort

H. Che<sup>1</sup>, B. Combe<sup>1</sup>, J. Morel<sup>1</sup>, A. Cantagrel<sup>2</sup>, L. Gossec<sup>3</sup>, C. Lukas<sup>1</sup>

<sup>1</sup>Rhumatologie, Hôpital Lapeyronie, Montpellier University, France;

<sup>2</sup>Rhumatologie, Hôpital Pierre-Paul Riquet, Toulouse University, France;

<sup>3</sup>Rhumatologie, Hôpital Pitié Salpêtrière, UPMC Paris 6 University, France.

---

## Abstract

### Objective

Rheumatoid arthritis (RA) activity can be assessed by several outcome measures. The importance of patient-reported outcomes (PROs) has recently been advocated. Our objective was to determine whether patient self-assessment can reflect RA disease activity.

---

### Methods

Data from patients included in the early arthritis ESPOIR cohort and fulfilling 2010 ACR/EULAR criteria for RA at month 12 were used. Data for several PROs (visual analogue scale for fatigue, pain, patient assessment of disease activity; Health Assessment Questionnaire [HAQ]; Medical Outcomes Study Short Form 36 [SF36]; Echelle de Mesure de l'Impact de la polyarthrite Rhumatoïde-court [EMIR-court] and Routine Assessment of Patient Index Data 3 [RAPID3]) were collected and their association with disease activity measured by Disease Activity Score in 28 joints-3 variables (DAS28-3v) was assessed. The association of PROs and disease activity was assessed by explained variance, Pearson correlation and performance of each PRO in differentiating low versus high disease activity states.

---

### Results

We evaluated data for 677 patients. Whatever the disease activity, less impaired PROs was associated with the lowest disease activity. All PROs were moderately correlated with RA disease activity. The RAPID3 had the best association with DAS28-3v in determining RA disease activity state ( $r=0.45-0.55$ , explained variance 30–45%, sensitivity 69–100% and specificity 55–78%). Global PROs (RAPID3, EMIR-court) had the highest association with disease activity, followed by PROs assessing physical function.

---

### Conclusion

The association of PROs and RA disease activity (DAS28-3v) remains moderate. RAPID3, a global PRO, had the best association with disease activity as compared with other analysed PROs.

---

### Key words

patient-reported outcomes, rheumatoid arthritis, disease activity, ESPOIR cohort

Helene Che, MD  
 Bernard Combe, MD, PhD  
 Jacques Morel, MD, PhD  
 Alain Cantagrel, MD, PhD  
 Laure Gossec, MD, PhD  
 Cedric Lukas, MD, PhD

Please address correspondence to:  
 Dr Helene Che,  
 Département de Rhumatologie,  
 Hôpital Lapeyronie,  
 371 Avenue du Doyen Gaston Giraud,  
 34295 Montpellier Cedex 5, France.  
 E-mail: che.helene@yahoo.fr

Received on June 28, 2015; accepted in  
 revised form on January 19, 2016.

© Copyright CLINICAL AND  
 EXPERIMENTAL RHEUMATOLOGY 2016.

## Introduction

Rheumatoid arthritis (RA) is the most frequent chronic inflammatory arthritis, affecting 0.3% to 0.8% of the general population. It may be associated with the development of osteoarticular lesions causing irreversible functional disability as well as increased cardiovascular morbidity and mortality. These consequences are mainly driven by the level of disease activity over time; therefore, most recent efforts have involved “treat-to-target” therapy (*i.e.* by disease activity state). The level of disease activity can be assessed by several validated tools, with Disease Activity Score (DAS) and its versions (DAS44, DAS28, DAS28-C-reactive protein level), Simple Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI), the most frequently used, both in clinical trials and for routine care of patients (1). Indeed, treating according to a predefined goal based on these indexes improves long-term functional and global prognosis (2).

All these instruments represent a combination of assessments of different aspects of disease activity summarised into a single value that represents a global measurement of inflammatory activity in a single patient. They usually combine clinical assessments (number of tender or swollen joints), results of biological tests and patient-reported outcomes (PROs). Besides these instruments, with patient opinion only part of the final measurement, other PROs have been developed to evaluate outcomes that cannot be measured objectively by clinicians and appear to be important parameters in patient healthcare (3-5). PROs are questionnaires used in clinical trials and daily care, with answers directly collected from patients. They allow the evaluation of domains that are often neglected (fatigue, quality of life, subjective disease activity, sleep disorders, etc.) (6-8). Indeed, self-management programmes that directly involve patients, are increasingly offered to RA patients because they are considered a key element of quality care and show health criteria improvement and pain reduction (9).

Different kinds of PROs are available, either unidimensional or multidimen-

sional and specific or general, according to the number of domains they reflect (4). PROs are used as multifunctional criteria and therefore can be used as prognostic (10, 11), therapeutic-evaluation (12, 13) or therapeutic-decision (14, 15) outcomes.

Many studies have compared patient self-assessment and evaluation of disease activity by an experienced clinician to determine whether substituting patient assessment of disease activity is possible (16, 17). Patient self-assessment appears to be as reproducible as formal joint count by an experienced clinician (18). Likewise, physical function assessed by a self-administered questionnaire, such as occupational disability, mortality, socio-economic cost, or the need for prosthetic surgery, is as informative as laboratory tests in determining the prognosis of RA (2, 19).

We aimed to compare the performance of different PROs in assessing RA disease activity using one specific disease activity index: DAS28-3 variables (DAS28-3v) and then determine which PRO is most associated with and representative of disease activity.

## Material and methods

We conducted an observational study of data from the French cohort ESPOIR (Etude et Suivi des Polyarthrites Indifférenciées Récentes) to evaluate the performance of PROs in assessing disease activity in RA.

### ESPOIR cohort

From December 2002 to March 2005, 813 French patients with early arthritis were included in the ESPOIR cohort (20, 21). In the ESPOIR cohort, patients with inflammatory arthritis (with at least 2 swollen joints and symptom onset between 6 months and 6 weeks) were systematically included if the local investigator considered the patient had RA or undifferentiated arthritis prone to become RA, after exclusion of differential diagnoses. Patients were followed at 1 of 14 hospital centres every 6 months for 2 years and every year thereafter. At each visit after baseline, sociodemographics, disease severity and RA management data were collected. At every visit, patients complet-

Competing interests: none declared.

ed PROs (visual analogue scale [VAS] for fatigue, pain, and patient activity; Health Assessment Questionnaire [HAQ], Medical Outcomes Study Short Form 36 [SF36], Echelle de Mesure de l'Impact de la polyarthrite Rhumatoïde-court [EMIR-court], Routine Assessment of Patient Index Data 3 [RAPID3]). The ethics committee of Lapeyronie Hospital, Montpellier University, approved the ESPOIR research protocol in July 2002. All patients signed an informed consent form before inclusion.

#### *Population included in our study*

For the current study, we selected, among the ESPOIR cohort, only the patients fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA at the 12-month visit.

#### *PROs analysed*

The VAS for fatigue, pain and global disease activity involved self-assessment on a uni-dimensional scale from 0 (minimum) to 100 (maximum).

#### • HAQ

The HAQ concerns functional disability and pain in inflammatory rheumatic diseases (22). Physical function is assessed with 20 questions about daily activities grouped in 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach and grip. The final score, ranging from 0 (no difficulty in performing the task) to 3 (failure to achieve the task), corresponds to the mean of the sum of these 8 category scores (each category score obtained by using the highest sub-category score) and takes into account the use of aids or devices.

#### • EMIR-court

The EMIR-court is the French version of the Arthritis Impact Measurement Scale 2, considered valid, reliable and sensitive (23, 24). This questionnaire contains 5 components with a total of 26 questions on physical activity, pain, depression and anxiety, social activities, and work. Each component is measured on a 5-point Likert scale

and the final score is the mean score for these 5 components, which is then normalised from 0 (good health status) to 10 (poor health status).

#### • SF36

The SF36 is a generic questionnaire of quality of life with 36 questions divided into 8 domains, scored from 0 (worst quality of life) to 10 (best quality of life): physical function (PF), bodily pain (BP), vitality (VT), social function (SF), mental health (MH), general health (GH), role physical (RP), role emotional (RE) (25). The SF36 can be presented as the physical component score (PCS) and mental component score (MCS).

#### • RAPID3

RAPID3 is a health assessment questionnaire assessing 3 domains: physical function, pain and disease activity (19, 26). Each domain is scored from 0 to 10 and the final score is the sum of the 3 domains. High scores represent the most altered health state.

#### *RA disease activity assessed by DAS28-3v*

DAS28-3v was calculated as follows:  $[0.56 \cdot \sqrt{\text{TJC}} + 0.28 \cdot \sqrt{\text{SJC}}] + 0.70 \cdot \ln(\text{ESR}) \cdot 1.08 + 0.16$ , where TJC represents tender joint count; SJC, swollen joint count; and ESR, erythrocyte sedimentation rate. The DAS28-3v was preferred to the DAS28-4 variables (DAS28-4v) to limit the subjectivity of the patient in assessing disease activity (27). According to the DAS28-3v, remission was considered  $<2.6$ , low disease activity 2.6 to 3.2, moderate disease activity 3.2 to 5.1 and high disease activity  $>5.1$ . ACR/EULAR2010 remission was defined by a swollen joint count  $\leq 1$ , a tender joint count  $\leq 1$ , a patient global assessment  $\leq 1/10$  and a C-reactive protein  $\leq 1\text{mg/L}$ .

#### *Statistical analysis*

Demographic, clinical and biological characteristics of included patients and PRO values collected during follow-up are described with number (%) or mean (SD): age, sex, presence of an anxiety-depressive disorder (defined by anxiety, depression or intake of anxiolytics or

antidepressants), active smoking, current alcohol consumption, characteristics at baseline (disease duration, presence of nocturnal awakening, presence of morning stiffness longer than 30 minutes, serologic status, radiographically eroded joints  $\geq 3$ ), joint counts, biological inflammation (erythrocyte sedimentation rate, C-reactive protein), disease activity and PROs.

We dichotomised the characteristics of population on the observed median value, then compared mean values of each PRO across the defined subcategories of characteristics, by Student *t*-tests. Only variables that potentially affected PRO values (*i.e.* with a  $p < 0.10$  in univariate analysis) were used for adjustment on multivariate analysis. We analysed the association of PROs and RA disease activity by comparing mean values of the analysed PROs by disease activity status (remission, or low or high disease activity based on the DAS28-3v).

We evaluated the correlation between PROs and disease activity by the DAS28-3v by Pearson correlation analysis.

Then, the association of PROs and DAS28-3v was assessed by ANOVA, adjusting for potentially influencing variables as determined above. We evaluated the proportion of variance in RA activity that could be explained by each analysed PRO using the variance estimates generated by each respective ANOVA model.

We used receiver operating characteristic (ROC) curve and discriminant analyses to assess the performance of PROs in determining several predefined disease activity states such as ACR/EULAR remission, DAS28-3v remission and low and high disease activity to evaluate which PRO had the best discriminatory ability. Sensitivity (Se), specificity (Sp), positive predictive value and negative predictive value of each PRO and for every disease activity state were determined. After determining the most discriminating value of each PRO in differentiating low versus high disease activity (based on the areas under the ROC curve [AUC]), we determined sensitivity and specificity for each PRO to deter-

**Table I.** Characteristics of 677 patients with rheumatoid arthritis (RA) from the ESPOIR cohort.

DEMOGRAPHIC CHARACTERISTICS						
Patients, n	677					
Mean age, mean (SD)	48.6 (12.3)					
Female gender, n(%)	524 (77.4%)					
Anxiodepressive disorder	111 (16.4%)					
Active smoking	146 (21.6%)					
Active alcohol consumption	107 (15.8%)					
CLINICAL AND PARACLINICAL CHARACTERISTICS						
Disease duration at baseline, months, mean (SD)	3.41 (1.74)					
Nocturnal awakening at baseline	455 (67.2%)					
Morning stiffness > 30 min, at baseline	507 (74.9%)					
Serologic status, at baseline	RF+ or ACPA+	405 (60.5%)				
	RF+	368 (54.4%)				
	ACPA+	292 (43.1%)				
Radiographic erosions ≥3, at baseline	102 (15.1%)					
	M0		M12		M60	
TJC, mean (SD)	9.5 (7.1)		4.0 (6.0)		3.0 (5.2)	
SJC, mean (SD)	8.0 (5.4)		2.3 (3.3)		1.3 (2.7)	
ESR, mean (SD)	30.2 (24.8)		15.6 (14.4)		14.8 (13.4)	
CRP, (mg/L), mean (SD)	21.0 (33.4)		7.2 (11.6)		7.1 (12.3)	
DAS28-3v, mean (SD)	5.0 (1.2)		3.2 (1.3)		2.8 (1.2)	
DAS28-4v, mean (SD)	5.3 (1.2)		3.3 (1.4)		2.8 (1.4)	
2010 ACR/EULAR remission	0 (0%)		99 (16.3%)		132 (27.5%)	
DAS28-4v remission	8 (1.2%)		220 (36.4%)		241 (51.2%)	
DAS28-4v ≤ 3.2	19 (2.8%)		97 (16.0%)		69 (14.6%)	
DAS28-4v 3.2–5.1	270 (40.7%)		221 (36.5%)		128 (27.2%)	
DAS28-4v > 5.1	367 (55.3%)		67 (11.1%)		33 (7.0%)	
PROs						
	M0		M12		M60	
VAS fatigue (/100), mean (SD)	48.9 (27.4)	n= 664 (98.0%)	38.6 (29.0)	n= 605 (89.4%)	33.5 (27.7)	n= 469 (69.3%)
VAS pain (/100), mean (SD)	39.6 (27.8)	n= 664 (98.0%)	23.7 (25.2)	n= 605 (89.4%)	17.9 (22.5)	n= 469 (69.3%)
VAS patient activity (/100), mean (SD)	61.9 (24.3)	n= 664 (98.0%)	32.8 (26.6)	n= 605 (89.4%)	26.8 (25.5)	n= 471 (69.6%)
HAQ (/3), mean (SD)	1.03 (0.685)	n= 666 (98.4%)	0.54 (0.59)	n= 605 (89.4%)	0.52 (0.60)	n= 469 (69.3%)
SF36 PCS (/100), mean (SD)	37.9 (8.4)	n= 660 (97.5%)	44.2 (8.9)	n= 604 (89.2%)	44.8 (9.4)	n= 484 (71.5%)
SF36 MCS (/100), mean (SD)	39.3 (10.8)	n= 660 (97.5%)	43.9 (11.7)	n= 604 (89.2%)	45.7 (11.2)	n= 484 (71.5%)
EMIR-court (/10), mean (SD)	4.4 (1.5)	n= 571 (84.4%)	3.1 (1.6)	n= 541 (79.9%)	2.8 (1.5)	n= 396 (58.5%)
RAPID3 (/30), mean (SD)	12.2 (5.4)	n= 662 (91.9%)	6.5 (5.6)	n= 60 (89.2%)	5.3 (5.3)	n= 468 (69.1%)
Data are no. (%) unless indicated. n: number of available data; SD: standard deviation; TJC: tender joint count; SJC: swollen joint count; ESR: erythrocyt sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; DAS28-3v: Disease Activity Score in 2 joints-3 variables; DAS28-4v: DAS28-4 variables; PROs: patient-reported outcomes; M0: Month 0; M12: Month 12; M60: Month 60; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; SF36: Medical Outcomes Study Short Form 36; PCS: physical component score; MCS: mental componen score; EMIR-court: Echelle de Mesure de l’Impact de la polyarthrite Rhumatoïde-court; RAPID3: Routine Assessment of Patient Index Data 3.						

mine a given status of disease activity. Statistical analyses were repeated with data collected at months 0, 12 and 60, to assess performance in patients with substantial disease activity (at inclusion) and in patients with usually more limited disease activity (patients with active treatment after inclusion). This process served as a sensitivity analysis, especially comparing data at months 12 and 60, to test the robustness of our results. The statistical analyses were performed, using the software SPSS (v. 15).  $p < 0.05$  was considered statistically significant.

## Results

### Characteristics of population and disease (Table I)

Among the 813 patients of the ESPOIR cohort, 677 (83.2%), fulfilling the 2010 ACR/EULAR criteria for RA at month 12, were included in our study. The characteristics of patients and their rheumatologic disease are in Table I. Patients had high disease activity at inclusion, with, consequently, impaired functional status and high negative impact on all domains assessed by the PROs evaluated. Because of the active therapeutic approach initiated after baseline visit,

most patients had reduced disease activity at 12 and 60 months, and the self-assessments showed an improvement at these visits when compared to baseline (Table I).

### Association of PROs and characteristics of patients and disease

At every evaluation time (month 0 [M0], M12 and M60), all analysed PRO values were significantly associated with disease activity assessed by the DAS28-3v ( $p < 0.001$ ), with better self-assessed values for patients with low disease activity or in remission. Sex,

serologic status and structural damage were not associated with DAS28-3v, and were therefore not used as adjustment variables. However, age greater than the median (50.5 years old) was significantly associated with poor outcomes, in particular with high HAQ score ( $p < 0.05$ ), altered SF36 physical score ( $p < 0.05$  at M12 and M60) and impaired EMIR-court score ( $p < 0.05$  at M12 and M60). Anxiodepressive disorders were also significantly associated with altered PRO values ( $p < 0.05$ ). At all 3 evaluation times (M0, M12 and M60), active alcohol consumption was associated but not always significantly with increased HAQ score ( $p = 0.038$ – $0.085$ ), whereas active tobacco consumption was associated with altered VAS fatigue and patient activity scores ( $p = 0.001$ – $0.120$  and  $0.025$ – $0.230$ , respectively).

#### Correlation between PROs and disease activity (Table II)

Correlations were moderate ( $r$  between 0.4 and 0.6) between PROs and DAS28-3v, in decreasing order, HAQ ( $r$  between 0.45 and 0.53), RAPID3 ( $r$  between 0.45 and 0.50), SF36-PCS ( $r$  between -0.44 and -0.47), EMIR-court ( $r$  between 0.43 and 0.46) (Table II). When correlating PROs with each other, RAPID3 was most consistently correlated with the remaining indexes.

#### Variance of disease activity explained by PROs

The PROs best associated with DAS28-3v were the RAPID3, then EMIR-court. In particular, RAPID3 explained up to 30% to 43% of the variance of the DAS28-3v and thus could be considered a fairly good marker of disease activity, whereas VAS pain and fatigue had the lowest association with DAS28-3v (Fig. 1). Sensitivity analyses sometimes showed considerable fluctuation in variance of DAS28-3v explained by PROs across the different evaluation times, especially for the SF36. The variance in DAS28-3v was explained by tender joint count (TJC) up to 62% to 72% and swollen joint count (SJC) up to 40% to 45%, 2 intrinsic components of DAS28-3v. The values obtained for TJC and SJC

**Table II.** Pearson correlation analysis of age and patient-reported outcomes (PROs) with DAS28-3 variables (DAS28-3v).

Variables	DAS28-3v		
	Month 0 $r$	Month 12 $r$	Month 60 $r$
Age	0.13	0.15	0.12
VAS fatigue	0.20	0.30	0.34
VAS pain	0.24	0.46	0.40
VAS patient activity	0.34	0.51	0.50
HAQ	0.53	0.50	0.45
SF36-PCS	-0.44	-0.47	-0.45
SF36-MCS	-0.20	-0.25	-0.30
EMIR-court	0.46	0.46	0.43
RAPID3	0.45	0.46	0.50
DAS28-4v	0.97	0.97	0.97

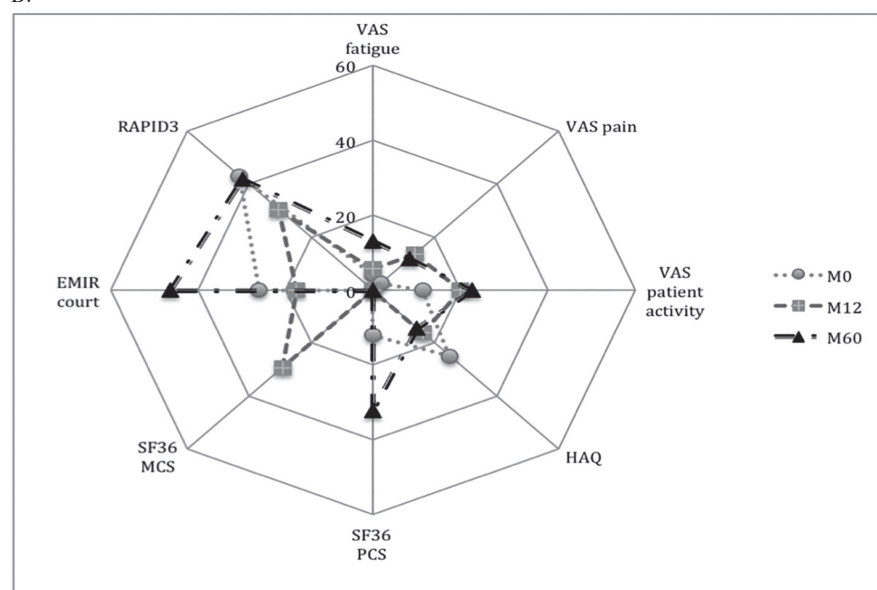
DAS28-3v: Disease Activity Score in 28 joints-3 variables; DAS28-4v: DAS28-4 variables; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; SF36: Medical Outcomes Study Short Form 36; PCS: physical component score; MCS: mental component score; EMIR-court: Echelle de Mesure de l'Impact de la polyarthrite Rhumatoïde-court; RAPID3: Routine Assessment of Patient Index Data 3; TJC: tender joint count; SJC: swollen joint count;  $r$ : Pearson correlation coefficient.

$p$ -value  $< 0.01$  for all data.

A.

	Month 0	Month 12	Month 60
VAS fatigue	4.25	5.8	13.2
VAS pain	2.8	13.7	12.0
VAS patient activity	11.5	20.1	22.8
HAQ	24.8	16.1	14.4
SF36-PCS	12.0	0.0	32.1
SF36-MCS	0.0	3.5	0.0
EMIR-court	26.0	17.4	46.3
RAPID3	43.2	30.5	42.0

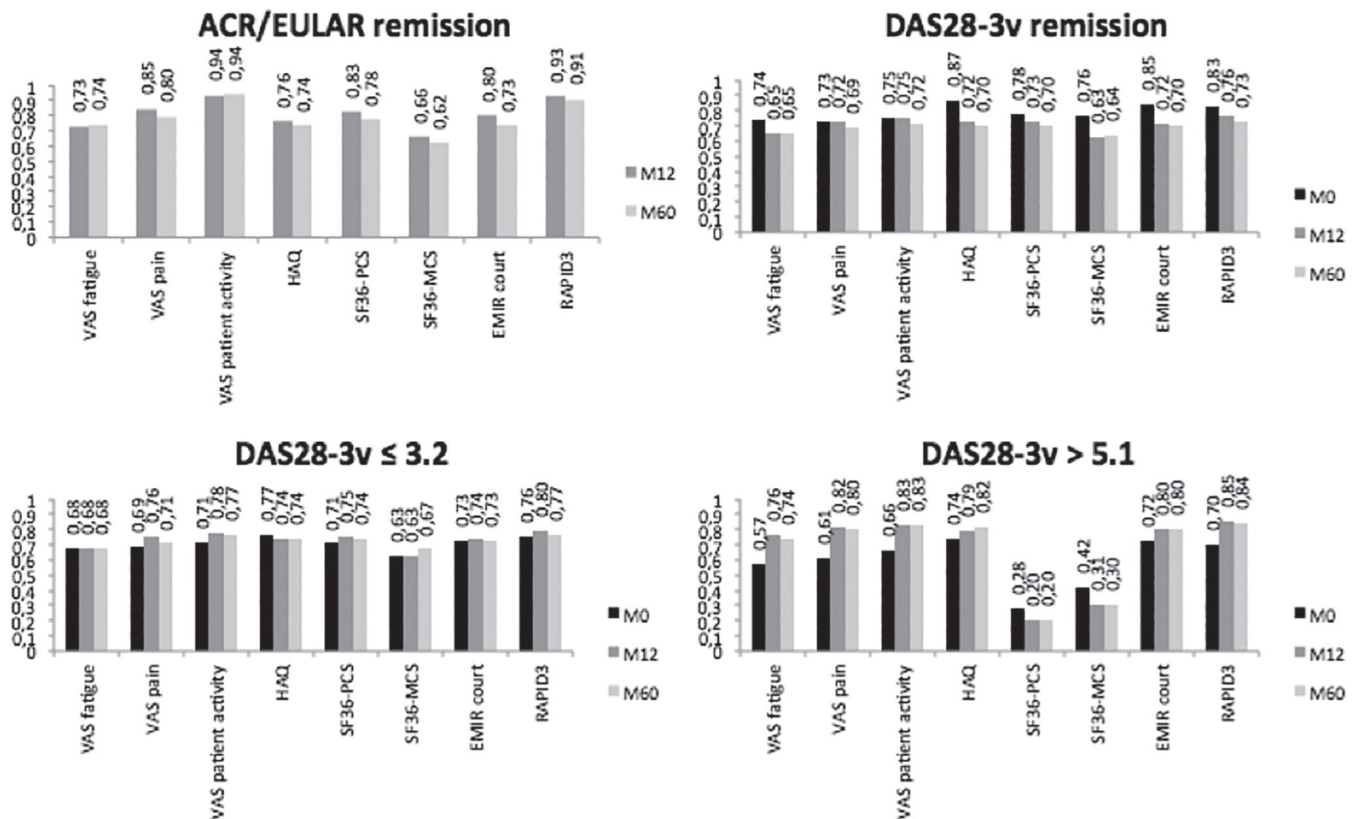
B.



**Fig. 1.** Proportion of variance (in percentage) in Disease Activity in 28 joints-3 variables (DAS28-3v) explained by patient-reported outcomes: A. Values in percentage, B. Radar chart.

DAS28-3v: Disease Activity Score in 28 joints-3 variables; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; SF36: Medical Outcomes Study Short Form 36; PCS: physical component score; MCS: mental component score; EMIR-court: Echelle de Mesure de l'Impact de la polyarthrite Rhumatoïde-court; RAPID3: Routine Assessment of Patient Index Data 3.





**Fig. 2.** Area under the receiver operating characteristic curve for PROs for discriminating between disease activity states at 3 evaluation times.

DAS28-3v: Disease Activity Score in 28 joints-3 variables; M0, M12, M60: months 0, 12, 60; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; SF36: Medial Outcomes Study Short Form 36; PCS: physical component score; MCS: mental component score; EMIR-court: Echelle de Mesure de l'Impact de la Polyarthrite Rhumatoïde-court; RAPID3: Routine Assessment of Patient Index Data 3.

can thus serve as references when appreciating the part of variance of disease activity explained by each PRO. Indeed, as these 2 items are included in DAS28-3v calculation, appreciating their respective contributions to the total value can figure out what to ideally expect. Therefore, RAPID3 explained variation of DAS28-3v almost as much as SJC though sharing no measures.

#### Performance of PROs in determining disease activity/intrinsic discrimination

The performance of the PROs in determining different disease activity states is in Table III. PROs with highest AUCs, stable at the 3 evaluation times, were mainly RAPID3 (AUC 0.702–0.930), HAQ (AUC 0.702–0.871) and EMIR-court (AUC 0.698–0.847) (Fig. 2).

##### • ACR/EULAR remission

In determining ACR/EULAR remission at M12 and M60 (no patient was in ACR/EULAR remission at M0), globally, all PROs had relatively good sen-

sitivity and specificity. PROs with the best performance were, in decreasing order, VAS patient activity, RAPID3 and SF36-PCS (Table III).

##### • DAS28-3v remission ( $DAS28-3v < 2.6$ )

For DAS28-3v remission, all PROs had a specificity close to 60%; sensitivity was variable depending on evaluation time, with better sensitivity found for the HAQ, followed by EMIR-court and SF36-PCS (Table III).

##### • DAS28-3 variables low disease activity ( $DAS28-3v \leq 3.2$ )

In determining low disease activity, the PROs with the best sensitivity and specificity, in decreasing order, were RAPID3, HAQ and EMIR-court (Table III).

##### • DAS28-3v high disease activity ( $DAS28-3v > 5.1$ )

In determining high RA disease activity, all PROs had fairly good sensitivity and specificity. The best values were

found with RAPID3, VAS patient activity, EMIR-court, SF36-PCS and HAQ (Table III).

#### Sensitivity analyses

We performed complementary analyses to evaluate the performance of the PROs in determining disease activity as assessed by indices other than the DAS28-3v, such as DAS28-4v and CDAI. The conclusions were the same as with DAS28-3v analyses: the explained variance was greater with TJC than SJC in determining disease activity state. Again, RAPID3 contributed to most of the explained variance, followed by EMIR-court. RAPID3, followed by VAS patient activity showed the best sensitivity and specificity in determining different disease activity states via the CDAI (data not shown).

#### Discussion

In this study, we have shown that the tested PROs have disparate ability for use as a surrogate for disease activity in

**Table III.** Sensitivity and specificity of PROs in determining disease activity states at 3 evaluation times.

2010 ACR/EULAR remission			
	Sensitivity (%) / Specificity (%)		
	Month 0	Month 12	Month 60
VAS fatigue	ND / ND	70.7 / 60.4	68.2 / 69.7
VAS pain	ND / ND	90.9 / 64.7	81.7 / 70.0
VAS patient activity	ND / ND	100.0 / 86.2	100.0 / 85.1
HAQ	ND / ND	84.7 / 58.0	71.0 / 66.3
SF36-PCS	ND / ND	73.2 / 70.0	70.2 / 74.8
SF36-MCS	ND / ND	66.0 / 61.0	67.2 / 52.2
EMIR-court	ND / ND	75.3 / 72.6	70.2 / 68.5
RAPID3	ND / ND	100.0 / 55.2	90.8 / 74.1
DAS28-3v remission			
	Sensitivity (%) / Specificity (%)		
	Month 0	Month 12	Month 60
VAS fatigue	69.2 / 62.5	61.1 / 59.6	62.8 / 59.1
VAS pain	84.6 / 56.7	63.9 / 66.1	69.7 / 58.9
VAS patient activity	76.9 / 51.3	70.8 / 64.8	70.3 / 66.4
HAQ	100.0 / 66.3	74.0 / 58.5	67.2 / 62.3
SF36-PCS	69.2 / 79.3	70.0 / 60.5	70.0 / 61.3
SF36-MCS	84.6 / 66.5	70.0 / 51.2	75.1 / 52.6
EMIR-court	100.0 / 63.2	69.3 / 63.3	66.3 / 65.5
RAPID3	76.9 / 66.3	71.2 / 67.9	70.9 / 63.6
DAS28-3v $\leq 3.2$			
	Sensitivity (%) / Specificity (%)		
	Month 0	Month 12	Month 60
VAS fatigue	59.5 / 63.3	59.4 / 65.3	69.1 / 59.5
VAS pain	69.0 / 57.6	76.6 / 61.8	71.0 / 59.1
VAS patient activity	76.2 / 52.6	66.9 / 73.3	67.2 / 76.9
HAQ	76.2 / 67.8	70.5 / 66.4	64.8 / 71.1
SF36-PCS	71.4 / 57.6	70.0 / 63.3	75.0 / 62.9
SF36-MCS	71.4 / 55.5	70.0 / 49.5	74.4 / 59.7
EMIR-court	68.4 / 64.2	64.0 / 69.8	63.1 / 73.7
RAPID3	169.0 / 67.7	73.0 / 70.5	73.5 / 71.1
DAS28-3v $> 5.1$			
	Sensitivity (%) / Specificity (%)		
	Month 0	Month 12	Month 60
VAS fatigue	59.1 / 54.4	70.5 / 73.3	70.8 / 65.4
VAS pain	58.7 / 58.5	79.5 / 65.6	91.7 / 58.2
VAS patient activity	63.4 / 59.6	77.3 / 74.9	87.5 / 64.9
HAQ	72.8 / 63.6	75.6 / 67.5	91.7 / 55.1
SF36-PCS	50.0 / 22.4	38.6 / 20.1	41.7 / 26.4
SF36-MCS	69.7 / 20.2	59.1 / 22.7	50.0 / 21.0
EMIR-court	67.6 / 63.0	79.5 / 72.1	71.4 / 76.5
RAPID3	69.5 / 59.6	81.8 / 78.0	70.8 / 77.5

PROs: patient-reported outcomes; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; DAS28-3v: Disease Activity Score in 28 joints-3 variables; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; SF36: Medical Outcomes Study Short Form 36; PCS: physical component score; MCS: mental component score; EMIR-court: Echelle de Mesure de l'Impact de la polyarthrite Rhumatoïde-court; RAPID3: Routine Assessment of Patient Index Data 3; ND: not determinable.

RA. Several PROs, especially RAPID3 and EMIR-court, have substantial potential in reflecting disease activity in a patient, but most remain insufficient and should be considered sources of

additional information, rather than a substitute for disease activity. For even the best-performing PRO tested, RAPID3, the depiction of disease activity remained partial, making a sub-

stitution of the usual assessment tools such as the DAS28 illusory.

PROs have been considered relevant in evaluating RA in both clinical trials and daily practice, but data are limited on their performance in assessing RA disease activity. A Dutch study (28), of 159 RA patients, evaluated the performance of the HAQ, Rheumatoid Arthritis Disease Activity Index, and VAS fatigue in reflecting DAS28 $>3.2$ . PROs were completed online and on a monthly basis. The authors concluded that predicting a certain disease activity by a single PRO remained difficult and potentially misleading. Combining the 3 PROs together led to moderate performance (Se=61%, Sp=75%) in predicting DAS28 $>3.2$ .

Gossec *et al.* showed that PROs could be as sensitive to change as objective measures of disease activity (29), but a possible limitation of PROs, as revealed by several other studies, is their potentially important fluctuation in values over time (28, 30).

As confirmed by our analyses, most PROs have low value in appreciating disease activity in a patient: in the literature, the level of fatigue has low discriminatory ability to differentiate patients in remission and those with active disease (Cohen's size effect 1.35) (31). However, RAPID3 is considered the best-performing instrument in this context. The RAPID3 score, computable in 5 seconds, is well correlated with disease activity (DAS28 and CDAI) and might be able to distinguish adequate and non-adequate response to treatment with disease-modifying anti-rheumatic drugs (32). The agreement between ACR/EULAR remission and RAPID3 remission was found to be moderate (85.8%, kappa 0.55), and was better between ACR/EULAR remission and RAPID3 remission with one SJC (92.8%, kappa 0.73) (33). RAPID3 remission has good sensitivity (92.5%) and good specificity (84.8%) in determining ACR/EULAR remission (33). RAPID3 might be a potentially relevant tool in clinical practice for easier and quicker detection of remission in RA patients (33). This result should however be considered with caution as it might be applicable only in a restricted

category of patients in remission or a near-remission state.

The strengths of our study are the large collection of data in a cohort of patients with early arthritis representative of the general population, which allows for a reliable description and analysis of disease activity states and their consequences as assessed by the available PROs. Moreover, the analyses were conducted and compared in distinct situations: in patients with active disease at the diagnostic phase, when no specific treatment had been started, and also at 2 different follow-up visits, with patients showing a large spectrum of disease states as observed in clinical practice. As well, PRO information had been simultaneously collected in these patients, which allowed for comparing their respective performance in evaluating disease activity. We also focused on an outcome for disease activity, namely the DAS28-3v, to limit the input of subjective and patient-derived appreciation when defining the level of disease activity. Indeed, the use of the classical DAS28 or other indices such as the CDAI or SDAI would have resulted in a partially "self-predictive" analysis because patient VAS for disease activity is included in these tools.

Our study has some limitations. First, determining RA disease activity by a patient-derived questionnaire is inherently difficult because it will inevitably be affected by other aspects of the disease and by external factors (disability due to sequelae or comorbidities, psychological impact of a chronic disease, comorbidities, educational level, etc.). Consequently, a reported health status can be impaired even when disease is not currently active because disentangling the impact of these influencing elements is probably artificial. As our study was initially designed to obtain general information about the association of PROs and objective measures of disease activity, whatever the treatment or context of the patient, we did not adjust for improved PRO values or disease activity by confounding factors. This might be a limitation in the potential situation of a treatment having an additional (negative or positive) effect on an independent factor, which

would itself play a role on the patient's appreciation of disease status. Also, according to the dimension of the PROs (specific or general, unidimensional or multidimensional), PROs measured different concepts and domains that could predominantly reflect disability secondary to cumulative joint damages rather than disease activity.

Moreover, assessing disease activity only by DAS28-3v could remain insufficient because DAS28-3v also has some limitations, such as taking into account swollen joints in case of persistence of chronic inactive swollen joints in patients in remission or low disease activity, and also the poor significance of DAS28 in the prognosis and identification of work disability, costs and mortality.

Second, our study has missing data. Indeed, for every patient, we had a variable number of missing values for the PRO analysed, and the missing data were not restricted to one particular PRO. These missing data can be explained by the fact that ESPOIR is a cohort, with follow-up visits every 6 months for 2 years and then every year, with a long and sometimes difficult completion time for the patient. Of note, missing data were more frequent at month 60 than at months 0 or 12, probably because of the saturation of several patients in the requested tasks. Whether this situation might have led to a bias in the interpretation of results remains uncertain, but a differential impact on completion rates by disease activity state (*i.e.* patients with high/low activity being systematically more or less prone to complete the questionnaires) seems unlikely.

Also, no outcome alone (whether only from patient-derived data or also including physician-derived or laboratory data such as DAS28, could be "sufficient" for a clinical decision.

Any clinical decision should be based on information on disease activity, but also organic damages, psychological distress, patient attitudes to therapy, in a shared decision between patient and doctor.

In summary, this study reveals a moderate correlation between PROs and RA disease activity as assessed by DAS28-

3v, among the 8 PROs studied. RAPID3 remained the PRO best reflecting RA disease activity, in terms of correlation, explained variance and intrinsic validity. Moreover, RAPID3 had the advantages of being feasible in routine care. However, these results of association, correlation, variance and performance of PROs in assessing RA disease activity remained modest. Therefore, assessment of RA disease activity, by self-questionnaire only, remains insufficient for routine application in clinical practice. A potential and exceptional implementation of these results might be a remote evaluation of disease states in patients with longstanding and stable disease, when a traditional rheumatologist visit is difficult to achieve for logistic reasons (geographic locations, long delay to available appointments...).

### Acknowledgments

We wish to thank the patients who participated in the study and the ESPOIR cohort.

### References

- GAUJOUX-VIALA C, MOUTERDE G, BAILLET A *et al.*: Evaluating disease activity in rheumatoid arthritis: which composite index is best? A systematic literature analysis of studies comparing the psychometric properties of the DAS, DAS28, SDAI and CDAI. *Joint Bone Spine* 2012; 79: 149-55.
- PINCUS T: Are patient questionnaire scores as "scientific" as laboratory tests for rheumatology clinical care? *Bull NYU Hosp Jt Dis* 2010; 68: 130-9.
- KIRWAN JR, BARTLETT SJ, BEATON DE *et al.*: Updating the OMERACT filter: implications for patient-reported outcomes. *J Rheumatol* 2014; 41: 1011-5.
- KALYONCU U, DOUGADOS M, DAURÈS J-P, GOSSEC L: Reporting of patient-reported outcomes in recent trials in rheumatoid arthritis: a systematic literature review. *Ann Rheum Dis* 2009; 68: 183-90.
- PINCUS T, SWEARINGEN CJ, BERGMAN M, YAZICI Y: RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories. *J Rheumatol* 2008; 35: 2136-47.
- KIRWAN JR, HEWLETT SE, HEIBERG T *et al.*: Incorporating the patient perspective into outcome assessment in rheumatoid arthritis—progress at OMERACT 7. *J Rheumatol* 2005; 32: 2250-6.
- TUBACH F, RAVAUD P, BEATON D *et al.*: Minimal clinically important improvement and patient acceptable symptom state for subjective outcome measures in rheumatic



- disorders. *J Rheumatol* 2007; 34: 1188-93.
8. PINCUS T, BROOKS RH, CALLAHAN LF: Prediction of long-term mortality in patients with rheumatoid arthritis according to simple questionnaire and joint count measures. *Ann Intern Med* 1994; 120: 26-34.
  9. IVERSEN MD, HAMMOND A, BETTERIDGE N: Self-management of rheumatic diseases: state of the art and future perspectives. *Ann Rheum Dis* 2010; 69: 955-63.
  10. GAUJOUX-VIALA C, GOSSEC L, DOUGADOS M, GUILLEMIN F, FAUTREL B: Favorable outcome, a new concept for the evaluation of health status in rheumatoid arthritis (RA) not so easy to achieve: Results from the ESPOIR cohort. *Ann Rheum Dis* 2013; 72 (Suppl. 3): 208;
  11. GAUJOUX-VIALA C, GOSSEC L, DOUGADOS M, FAUTREL B: Favorable outcome, a new concept for the evaluation of health state in rheumatoid arthritis (RA): Results from the French ESPOIR cohort. *Ann Rheum Dis* 2012; 71 (Suppl. 3): 653;
  12. MAINI RN, BREEDVELD FC, KALDEN JR *et al.*: Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum.* 2004; 50: 1051-65.
  13. PINCUS T, CHUNG C, SEGURADO OG, AMARA I, KOCH GG: An index of patient reported outcomes (PRO-Index) discriminates effectively between active and control treatment in 4 clinical trials of adalimumab in rheumatoid arthritis. *J Rheumatol* 2006; 33: 2146-52.
  14. DOUGADOS M, NATAF H, STEINBERG G, ROUANET S, FALISSARD B: Relative importance of doctor-reported outcomes vs patient-reported outcomes in DMARD intensification for rheumatoid arthritis: the DUO study. *Rheumatol* 2013; 52: 391-9.
  15. DOUGADOS M, SOUBRIER M, PERRODEAU E *et al.*: Impact of a nurse-led programme on comorbidity management and impact of a patient self-assessment of disease activity on the management of rheumatoid arthritis: results of a prospective, multicentre, randomised, controlled trial (COMEDRA). *Ann Rheum Dis* 2015; 74: 1725-33.
  16. BARTON JL, CRISWELL LA, KAISER R, CHEN Y-H, SCHILLINGER D: Systematic review and metaanalysis of patient self-report versus trained assessor joint counts in rheumatoid arthritis. *J Rheumatol* 2009; 36: 2635-41.
  17. JANTA I, NAREDO E, MARTÍNEZ-ESTUPIÑÁN L *et al.*: Patient self-assessment and physician's assessment of rheumatoid arthritis activity: which is more realistic in remission status? A comparison with ultrasonography. *Rheumatology* (Oxford) 2013; 52: 2243-50.
  18. UHLIG T, KVIEN TK, PINCUS T: Test-retest reliability of disease activity core set measures and indices in rheumatoid arthritis. *Ann Rheum Dis* 2009; 68: 972-5.
  19. PINCUS T, YAZICI Y, BERGMAN MJ: RAPID3, an index to assess and monitor patients with rheumatoid arthritis, without formal joint counts: similar results to DAS28 and CDAI in clinical trials and clinical care. *Rheum Dis Clin North Am* 2009; 35: 773-8, viii.
  20. COMBE B: The French early arthritis registry. *Clin Exp Rheumatol* 2003; 21 (Suppl. 31): S123-8.
  21. COMBE B, BENESSIANO J, BERENBAUM F *et al.*: The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. *Joint Bone Spine* 2007; 74: 440-5.
  22. FRIES JF, SPITZ PW, YOUNG DY: The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol* 1982; 9: 789-93.
  23. POUCHOT J, GUILLEMIN F, COSTE J, BRÉGEON C, SANY J: Validation of the French version of the arthritis impact measurement scales 2 and comparison with the French version of the Nottingham Health Profile. "Quality of Life in Rheumatology" Task Force. *Rev Rhum Engl Ed* 1996; 63: 389-404.
  24. POUCHOT J, GUILLEMIN F, COSTE J, BRÉGEON C, SANY J: Validity, reliability, and sensitivity to change of a French version of the arthritis impact measurement scales 2 (AIMS2) in patients with rheumatoid arthritis treated with methotrexate. *J Rheumatol* 1996; 23: 52-60.
  25. WARE JE, SHERBOURNE CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473-83.
  26. PINCUS T, SWEARINGEN CJ, BERGMAN MJ *et al.*: RAPID3 (Routine Assessment of Patient Index Data) on an MDHAQ (Multidimensional Health Assessment Questionnaire): agreement with DAS28 (Disease Activity Score) and CDAI (Clinical Disease Activity Index) activity categories, scored in five versus more than ninety seconds. *Arthritis Care Res* 2010; 62: 181-9.
  27. MADSEN OR: Agreement between the DAS28-CRP assessed with 3 and 4 variables in patients with rheumatoid arthritis treated with biological agents in the daily clinic. *J Rheumatol* 2013; 40: 379-85.
  28. WALTER MJ, MOHD DIN SH, HAZES JM, LESAFFRE E, BARENDREGT PJ, LUIJME JJ: Is tightly controlled disease activity possible with online patient-reported outcomes? *J Rheumatol* 2014; 41: 640-7.
  29. GOSSEC L, DOUGADOS M, AANERUD GJ *et al.*: Patient-reported outcomes (PROs) appear as sensitive to change as physician-reported outcomes- Data from the Rheumatoid Arthritis Impact of Disease (RAID) EULAR initiative. *Ann Rheum Dis* 2010; 69 (Suppl. 3): 355.
  30. BLANCHAIS A, BERTHELOT J-M, FONTENOY A-M, LE GOFF B, MAUGARS Y: Weekly home self-assessment of RAPID-4/3 scores in rheumatoid arthritis: a 6-month study in 26 patients. *Joint Bone Spine* 2010; 77: 582-7.
  31. GOSSEC L, FAUTREL B, KIRWAN J *et al.*: Doctor, will my fatigue be better if I'm in remission? An exploratory analysis of 1284 rheumatoid arthritis (RA) patients indicates fatigue is the only aspect of patient-perceived impact to remain significant in ACR/EULAR Boolean remission. *Ann Rheum Dis* 2014; 73 (Suppl. 2);
  32. PINCUS T: RAPID3, an index of only 3 patient self-report core data set measures, but not ESR, recognizes incomplete responses to methotrexate in usual care of patients with rheumatoid arthritis. *Bull Hosp Jt Dis* 2013; 71: 117-20.
  33. CASTREJÓN I, DOUGADOS M, COMBE B, GUILLEMIN F, FAUTREL B, PINCUS T: Can remission in rheumatoid arthritis be assessed without laboratory tests or a formal joint count? possible remission criteria based on a self-report RAPID3 score and careful joint examination in the ESPOIR cohort. *J Rheumatol* 2013; 40: 386-93.