# Patient-acceptable Symptom State as an Outcome Measure in the Daily Care of Patients with Ankylosing Spondylitis 

CARLOS RODRÍGUEZ-LOZANO, MARÍA-ÁNGELES GANTES, BEATRIZ GONZÁLEZ, JOSÉ A. HERNÁNDEZ-BERIAIN, ANTONIO NARANJO, VANESA HERNÁNDEZ, JUAN C. QUEVEDO-ABELEDO, M. JOSÉ FALCÓN, SERGIO MACHÍN, and MIGUEL A. DESCALZO


#### Abstract

Objective. We assessed the prevalence of patients with ankylosing spondylitis (AS), rating their state as acceptable (patient-acceptable symptom state; PASS), among 190 patients with AS seen in daily practice. Factors associated with PASS status and PASS thresholds for outcome measures were also analyzed. Methods. The characteristics of patients with affirmative and negative assignment to PASS were compared. Associated factors were estimated by logistic regression models and PASS thresholds by the 75th percentile and receiver-operating characteristic curve methods. Results. A total of $77 \%$ of patients rated their state as acceptable ( $95 \%$ CI 62-91). These patients were taking fewer nonsteroidal antiinflammatory drugs and corticosteroids, practiced more exercise, had less anxiety and depression, and had lower values of all patient-reported outcome measures, physicians' assessment, AS Disease Activity Score (ASDAS) and C-reactive protein. Lower values of Bath AS Disease Activity Index and physician's global assessment were independent factors associated with acceptable symptom state. High rates of anxiety and depression were found in patients not in PASS. The thresholds with the 75 th percentile approach were 4.55 for the BASDAI and 2.84 for the ASDAS. Fifty-three percent of patients in PASS had a high or very high disease activity state according to ASDAS cutoff values. Conclusion. A high percentage of patients with AS in daily practice declared that their symptom state was acceptable. PASS status correlated with physician global assessment and BASDAI. PASS thresholds for common recommended outcome measures were relatively high and many patients in PASS had unacceptably high disease activity states according to ASDAS. Other factors such as psychological problems may influence a negative PASS state. (First Release June 1 2012; J Rheumatol 2012;39:1424-32; doi:10.3899/jrheum.111481)


Key Indexing Terms:
ANKYLOSING SPONDYLITIS CROSS-SECTIONAL STUDIES

ASSESSMENTS PATIENT SATISFACTION

## PATIENT OUTCOMES QUALITY OF LIFE

Inflammatory rheumatic diseases are generally multifaceted disorders and therefore measurement of multiple outcomes is relevant to most of these diseases. For daily clinical practice, outcome measures should reflect the patients' state and be easily derivable. Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease with significant effects on patient function and quality of life ${ }^{1,2}$. The core set of
domains of the ASessment in Ankylosing Spondylitis (ASAS) Working Group ${ }^{3,4,5}$ include outcome measures such as patient self-reported outcomes (PRO), the Bath AS Disease Activity Index (BASDAI), the Bath AS Functional Index (BASFI), physician-based assessments, and AS quality of life (ASQOL). Recently, the composite AS Disease Activity Score (ASDAS) ${ }^{6,7,8}$ has been established as a key

[^0][^1]element in evaluation of the patient's condition and response to antirheumatic therapies.

Other useful measures are the minimal clinically important difference (MCII) and the patient-acceptable symptom state (PASS) ${ }^{9,10,11,12}$. MCII is defined as the smallest change in measurement that signifies an important improvement according to the patient's perception, even in the case that the patient has not reached an acceptable state. The PASS has been defined as the highest level of symptoms beyond which patients consider themselves well. Measurement of patient well-being also enables evaluation of how soon and for how long a patient feels good. The PASS requires only that the clinician ask the patient a question requiring a yes or no answer: "Considering all the different ways your disease is affecting you, if you would stay in this state for the next months, do you consider that your current state is satisfactory?" Achievement of PASS indicates that a patient feels well, and therefore the PASS question could be a simple measure to include in the assessment of patients in routine clinical practice.

A few studies have assessed PASS in patients with AS. In a cross-sectional postal survey of patients with AS in Canada, $58.1 \%$ answered affirmatively to the PASS question ${ }^{13}$. In addition, PASS thresholds for ASAS core outcome measures, BASDAI, ASQOL, and fatigue were reported. In the context of a randomized, double-blind, placebo-controlled study of adalimumab in AS, PASS showed high reliability, excellent discriminant capacity, and external validity ${ }^{14}$. Using data from a multicenter, randomized controlled trial designed to assess the symptomatic effects of 2 doses of celecoxib versus diclofenac in patients with AS, the PASS estimates were stable over time ${ }^{15}$. However, recent data from another randomized, placebo-controlled study of adalimumab showed that PASS thresholds for PRO changed over time, and that these thresholds as well as attainment of the PASS were affected by covariates unrelated to treatment ${ }^{16}$, raising doubts about the usefulness of the PASS to assess absolute health status in clinical research.

To provide further data on the value of PASS in daily rheumatology practice, we conducted a cross-sectional study with the following 3 aims: (1) to assess the prevalence of patients with AS rating their state as acceptable (PASS); (2) to investigate factors associated with attaining PASS; and (3) to identify PASS thresholds for common outcome measures.

## MATERIALS AND METHODS

Patients. Our cross-sectional study was conducted between November 2008 and November 2009. The PASSEA study (Identification of Ankylosing Spondylitis Patients' Acceptable Symptom State in routine clinical practice) was designed with the main objective of assessing the percentage of patients with AS seen in daily practice who answered that their state was acceptable (PASS). Secondary objectives included identification of factors affecting PASS status and determination of PASS thresholds for common PRO and health-related measurements. The study enrolled consecutive
patients aged $\geq 18$ years with a diagnosis of AS based on the modified New York criteria ${ }^{17}$ who attended outpatient clinics of 4 hospitals in the Canary Islands, Spain. The visit was scheduled as part of systematic followup. These hospitals serve the entire population from 2 islands (Gran Canaria and Tenerife) because there are no community-based hospitals with rheumatology services. Patients were excluded if they had other spondyloarthropathies, a legal dispute related to occupation, or were participating in a randomized clinical trial. All patients signed a consent form and the study received ethical approval from the Ethics Committee of Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria. All the participating rheumatologists belonged to the Spondyloarthropathy Study Group from de Canarian Society of Rheumatology.
Data collection. At scheduled visits and before clinical consultation, the following PRO were assessed: global pain, nocturnal pain, fatigue, and global assessment of disease activity measured by a 100 mm visual analog scale (VAS), duration of morning stiffness (min), BASDAI (100 mm VAS), BASFI (100 mm VAS), the ASQOL ( $0-18$ scale, higher values indicate worse QOL) ${ }^{18}$, and the Hospital Anxiety and Depression Scale (HADS; total score $0-21$, where $\leq 7=$ normal; $8-10=$ borderline; $\geq 11=$ presence of anxiety, depression, or both $)^{19,20}$. Only ASQOL was included as a specific questionnaire for health-related QOL because the Spanish version of ASQOL has been validated and cross-culturally adapted, and it has shown highly significant correlation with Medical Outcomes Study Short Form-36 questionnaire scores ${ }^{21}$. Finally, patients' opinions of their symptom state were recorded as a "yes" or "no" answer to the anchoring question, "Considering all the different ways your disease is affecting you, if you would stay in this state for the next months, do you consider that your current state is satisfactory?" This question was chosen as the PASS case definition for calculating the prevalence and establishing cutoff points because it was used in recent studies of PASS in patients with $\mathrm{AS}^{13,14}$. Other studies have also used the following question: "Is your current condition satisfactory, when you take your general functioning and your current pain into consideration? ${ }^{15}$. At the time of the protocol design, we were not aware of any standardization in the wording of the PASS questions ${ }^{22}$.

The following data were collected: patient demographics; education level (no studies, primary education, secondary education or higher); work activity (no activity, sedentary/minor effort, moderate/high effort); employment status (active, currently employed; active, currently in transient work incapacity; active, currently unemployed; inactive in permanent work incapacity; inactive: retired; and others); duration of illness; predominant clinical type (axial, peripheral, mixed, enthesitis); HLA-B27 status; and presence of uveitis or other comorbidities. Radiographic structural damage was assessed by sacroiliitis grade ( 2 to 4) and the modified Stoke Ankylosing Spondylitis Spine Score method (mSASSS; range 0-72) from radiographs of the pelvis and lumbar and cervical spine performed in the previous year or during the 6 months following the study visit. Current and past pharmacologic and nonpharmacologic treatment as well as degree of compliance were recorded. Regular physiotherapy was defined as performing exercises at least 1 hour a week. Physicians examined axial mobility and peripheral disease was recorded with the number of tender and swollen joints (range 0-44). Enthesitis was evaluated with the Maastricht Ankylosing Spondylitis Enthesitis Score index (range 0-13) ${ }^{23}$.

The evaluating physician, who was unaware of the results of PRO and other scales, assessed the disease activity using a 100 mm VAS (where $0=$ none, $100=$ highest disease activity) and made decisions regarding treatment, including when to begin, increase the dose, switch or combine dis-ease-modifying antirheumatic drugs (DMARD), start biologic therapy, or increase the dose of infliximab. ASDAS composite indexes were calculated according to the corresponding formulas using the patient's responses to the BASDAI questionnaire, patient global assessment ( 100 mm VAS), and results for erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) ${ }^{4}$. ASDAS-CRP was chosen as the reference index and ASDAS-ESR is presented as an alternative version.

Statistical analysis. To assess the prevalence of patients rating their state as
acceptable (PASS) and based on previous findings of our group, for a result of $60 \%$ of patients being in PASS, with an alpha error of 0.05 , and precision of $\pm 7 \%$ in a 2 -sided test, the minimum number of patients to be recruited was 182 . The clinical characteristics of patients with affirmative and those with negative answers to PASS were compared by Student $t$ test for continuous variables or for the nonparametric version for non-Gaussian variables, Mann-Whitney U test. For categorical variables, chi-square test or Fisher's exact test was used. Kruskal-Wallis test and ANOVA were used to compare measures for more than 2 groups. The relationship between PRO measures and HADS scores was assessed with Spearman's rank-order correlation coefficient. Concordance between PASS status and relevant change in treatment was analyzed. PASS thresholds for BASDAI, BASFI, VAS pain, and other PRO were calculated by 3 methods: (1) as the 75th percentile of the cumulative distribution for each outcome for patients who rated their condition as PASS-positive; (2) by plotting receiver-operating characteristics (ROC) curves and identifying cutoffs that yielded $80 \%$ specificity; and (3) by plotting ROC curves and identifying cutoffs that yielded the smallest number of false-positives and false-negatives ${ }^{12,13}$. Associated factors for being in PASS were estimated by logistic regression models. Bivariate and multivariate analyses were done using backward stepwise selection of all variables with $\mathrm{p}<0.2$ in the bivariate analysis. Models were adjusted by age, sex, and hospital center. Nested models were compared with the likelihood ratio test and non-nested models with the Bayesian information criterion. Results are expressed as OR (95\% CI). All analyses were performed with Stata release 10.1 (Stata Corp., College Station, TX, USA).

## RESULTS

PASS status. A total of 190 patients with AS were recruited: 143 men and 47 women, with a mean age of 48.4 (SD 11.7) years and disease duration of 20.2 (SD 11.0) years. In total 128 patients had pure axial clinical involvement, 56 had mixed forms, 5 had predominantly peripheral forms, and none had enthesitic forms. In 1 patient, the clinical presentation type was not available.

The PASS question was answered by $100 \%$ of patients, and $146(76.8 \%$; $95 \%$ CI $62.3 \%-91.4 \%)$ rated their state as acceptable. There were no significant differences in the percentage of PASS-affirmative answers among the 4 participating hospitals.
Factors associated with PASS. As shown in Table 1, patients with affirmative answers to the PASS question showed statistically significant differences in current pharmacological treatment including lower use of nonsteroidal antiinflammatory drugs ( $28.8 \%$ vs $56.8 \% ; \mathrm{p}=0.001$ ) and corticosteroids ( $0.7 \%$ vs $11.4 \% ; \mathrm{p}=0.003$ ) and higher practice of regular physical exercise ( $70.6 \%$ vs $52.3 \%$; p $=0.025$ ). HLA-B27 was less frequent ( $86.2 \%$ vs $97.5 \%$; $\mathrm{p}=0.046$ ) and there were some differences in the sacroiliitis grade ( $p=0.005$ ). Differences were not observed in demographic data, duration of disease, education level, work activity, employment status, history of uveitis, comorbidity, mSASSS, and attendance at a rehabilitation service.

The group of patients with PASS-affirmative answers showed significantly lower scores for the results of PRO and other scales, including physician's assessment of disease activity, ASDAS components, ASQOL, and HADS for anxiety and depression. Serum CRP, but not sedimentation rate,
was also significantly lower in this group of patients (Table 2). ASDAS-CRP was available for 163 patients and distribution according to recent disease activity states was as follows: inactive disease (ASDAS < 1.3), 19\%; moderate disease activity (ASDAS 1.3-2.1), 19\%; high disease activity (ASDAS 2.1-3.5), 46\%; and very high disease activity (ASDAS > 3.5), $16 \%$. Sixty-seven patients ( $53 \%$ ) who were in PASS had a high or very high disease activity state according to the ASDAS cutoff values. Mean ASDAS-CRP value was 2.1 (SD 1.1) in the patients with an acceptable symptom state as compared with 3.5 (SD 1.0) in PASS-negative patients ( $\mathrm{p}<0.001$ ). The percentages of patients with anxiety ( $21 \%$ ) and depression (6\%) were significantly lower in patients in PASS than in those not in PASS ( $48 \%$ and $25 \%$, respectively). HADS scores for anxiety and depression correlated significantly with all disease activity measures (data not shown).

In the logistic regression model (Table 3), lower BASDAI (OR 0.61, 95\% CI 0.47-0.80) and lower physician global assessment (OR 0.97, 95\% CI 0.95-0.99) were independent variables associated with being in PASS. Area under the ROC curve (AUC) of the model was 0.87 (95\% CI $0.82-0.93$ ).

The physicians, without knowledge of PASS status, considered it necessary to prescribe a relevant change in treatment in 48 patients ( $25.3 \%$ ), mainly starting or modifying DMARD or anti-tumor necrosis factor (TNF) drugs. Twenty-one of these 48 patients ( $44 \%$ ) considered themselves as being in PASS (Table 4). The concordance between PASS status and relevant change in treatment was 0.46 ( $95 \%$ CI $0.30-0.59$ ). The group of 21 patients who disagreed with the physician's opinion had a mean ASDAS-PCR value of 3.1 (SD 0.8) compared to 3.8 (SD 0.9 ) in the group of 27 patients in agreement with the physician's opinion about change in treatment. A BASDAI > 4 was found in 14 (67\%) and 26 ( $96 \%$ ) patients, respectively A progressive gradient was observed in almost all PRO scores, ASDAS, and CRP: the lowest values were found in patients in whom a change of treatment was not indicated and who had a concordant affirmative answer to PASS. By contrast, the highest values were found in patients with negative answers to the PASS question and a change in treatment indicated by their physicians. In the middle, there were patients with very close values in almost all measures, with the exception of higher scores for anxiety and depression in those patients with negative answers to the PASS question and a change of treatment not indicated by their physicians (Table 4).
Thresholds of PRO for being in PASS. Table 5 shows the values of different cutoffs for PRO and other variables analyzed by 3 methods. Sensitivity, specificity, and the AUC are also shown. The threshold for BASDAI using the 75th percentile was 4.55 and using the ROC curve approach was 4.20. Thresholds for ASDAS-CRP using the 75th percentile

Table 1. Demographic and clinical data of patients with ankylosing spondylitis (AS) according to patient-acceptable symptom state (PASS) status.

| Characteristic | All Patients, $\mathrm{n}=190$ | PASS Affirmative <br> Answer, $\mathrm{n}=146$ | PASS Negative <br> Answer, $\mathrm{n}=44$ | p |
| :---: | :---: | :---: | :---: | :---: |
| Male sex, n (\%) | 143 (75) | 108 (74) | 35 (80) | 0.453 |
| Age, mean $\pm$ SD yrs | $48.4 \pm 11.7$ | $49.2 \pm 11.7$ | $45.7 \pm 11.5$ | 0.080 |
| Disease duration, mean $\pm$ SD yrs | $20.2 \pm 11$ | $20.4 \pm 10.7$ | $19.4 \pm 12.0$ | 0.304 |
| Education level, n (\%) |  |  |  | 0.296 |
| No studies/primary education | 57 (30) | 42 (28.8) | 15 (34.1) |  |
| Secondary education or higher | 133 (69.9) | 104 (71.2) | 29 (65.9) |  |
| Work activity, n (\%) |  |  |  | 0.175 |
| No activity | 64 (33.7) | 46 (31.5) | 18 (40.9) |  |
| Sedentary/minor effort | 70 (36.8) | 59 (40.4) | 11 (25.0) |  |
| Moderate/high effort | 56 (29.5) | 41 (28.1) | 15 (34.1) |  |
| Employment status, n (\%) |  |  |  | 0.999 |
| Unemployment/transient work incapacity/ employed | 128 (67.4) | 98 (67.1) | 30 (68.2) |  |
| Permanent work incapacity/retired | 55 (28.9) | 42 (28.8) | 13 (29.6) |  |
| Other | 7 (3.7) | 6 (4.1) | 1 (2.2) |  |
| Clinical type of disease, n (\%) |  |  |  | 0.126 |
| Axial disease | 128 (67.7) | 103 (70.6) | 25 (58.1) |  |
| Mixed + peripheral | 61 (32.3) | 43 (29.4) | 18 (41.9) |  |
| HLA-B27-positive | 151 (88.8) | 112 (86.2) | 39 (97.5) | 0.046 |
| History of uveitis | 51 (26.8) | 40 (27.4) | 11 (25.0) | 0.753 |
| Comorbidity | 121 (64.4) | 90 (62.5) | 31 (70.5) | 0.335 |
| Sacroiliitis, grade |  |  |  | 0.005 |
| 2 | 33 (18.9) | 30 (22.6) | 3 (7.2) |  |
| 3 | 69 (39.4) | 44 (33.1) | 25 (59.5) |  |
| 4 | 73 (41.7) | 59 (44.3) | 14 (33.3) |  |
| Modified SASSS, median (IQR) | 14 (5-31) | 14 (5-32) | 10 (6-26) | 0.504 |
| Current pharmacologic treatment, n (\%) |  |  |  |  |
| None | 16 (8.4) | 16 (11.0) | 0 (0) | 0.012 |
| Analgesics | 25 (13.2) | 18 (12.3) | 7 (15.9) | 0.538 |
| NSAID daily | 67 (35.3) | 42 (28.8) | 25 (56.8) | 0.001 |
| Corticosteroids | 6 (3.2) | 1 (0.7) | 5 (11.4) | 0.003 |
| Disease-modifying antirheumatic drugs | 44 (23.2) | 34 (23.3) | 10 (22.7) | 0.938 |
| Biologic agents | 64 (33.7) | 51 (34.9) | 13 (29.6) | 0.508 |
| Regular physical exercise, n (\%) | 126 (66.3) | 103 (70.6) | 23 (52.3) | 0.025 |
| Duration of weekly physical exercise, hours, median (IQR) | 4 (2-7) | 4 (2-7) | 3 (2-5) | 0.264 |
| Attendance at rehabilitation service, n (\%) | 13 (6.9) | 9 (6.3) | 4 (9.1) | 0.524 |

IQR: interquartile range (25th-75th percentile); SASSS: Stoke Ankylosing Spondylitis Spine Score; NSAID: nonsteroidal antiinflammatory drugs.
and the ROC curve approach were 2.84 and 2.54 , respectively, with an AUC of 0.8369 . According to the recently defined ASDAS cutoff values for disease activity states, both values corresponded to high disease activity state ${ }^{8}$. All cutoff points observed by the $80 \%$ specificity method were higher than those found with the other methods (Table 5).

## DISCUSSION

Our study showed that a high proportion $(77 \%)$ of patients with AS seen in routine followup rheumatology care have an acceptable symptom state. We believe that our cohort is representative of routine nonselected clinical practice because the 4 rheumatology services cover the entire population from the 2 islands where the study was carried out. Moreover, the clinical characteristics of our patients are
quite similar to those described in the REGISPONSER, the Spondyloarthropathy Register in Spain, where the patients were also recruited consecutively in 12 hospital rheumatology clinics ${ }^{24}$. This percentage is higher than $58.1 \%$ reported in a cross-sectional cohort of patients with AS in Canada, conducted by postal survey in $2003^{13}$. The clinical characteristics of the Canadian patients were similar to our cohort, but their therapies, including anti-TNF drugs, were not documented. Perhaps the relatively high use of biologic therapies among our patients ( $34 \%$ ) explains some of the differences in PASS status between these 2 cohorts. In the Norwegian DMARD register (NOR-DMARD), the percentage of patients with AS reporting they were in PASS increased from $29 \%$ at baseline to $62 \%$ after 3 months' treatment with DMARD ${ }^{25}$. In 2 prospective, randomized, place-

Table 2. Patients' reported outcomes, physicians' assessment, and laboratory values according to PASS status. Values are median (interquartile range, 25th -75 th percentile) unless otherwise indicated.

| Characteristic | All Patients, $\mathrm{n}=190$ | PASS Affirmative <br> Answer, $\mathrm{n}=146$ | PASS Negative <br> Answer, $\mathrm{n}=44$ | p |
| :---: | :---: | :---: | :---: | :---: |
| Patients' global assessment ( $100-\mathrm{mm}$ VAS) | 40 (20-60) | 30 (10-50) | 60 (50-80) | < 0.001 |
| Total pain (100-mm VAS) | 40 (15-65) | 30 (10-60) | 60 (44-70) | <0.001 |
| Nocturnal pain (100-mm VAS) | 30 (10-60) | 20 (5-50) | 55 (40-80) | < 0.001 |
| Fatigue (100-mm VAS) | 30 (10-50) | 30 (10-50) | 50 (30-70) | <0.001 |
| Morning stiffness, min | 20 (10-60) | 20 (10-45) | 60 (30-90) | < 0.001 |
| Physicians' global assessment ( $100-\mathrm{mm}$ VAS) | 25 (10-40) | 20 (10-30) | 50 (30-70) | < 0.001 |
| BASDAI (0-10 scale) | 3.5 (1.8-5.4) | 2.8 (1.3-4.6) | 5.4 (4.6-6.8) | < 0.001 |
| BASFI (0-10 csale) | 3.7 (1.5-5.4) | 2.6 (1-5.2) | 5.1 (3.1-7.5) | 0.001 |
| ASQOL (0-18 scale) | 6 (2-11) | 4.6 (1-8.2) | 11 (6-13) | <0.001 |
| ASDAS-CRP, mean $\pm$ SD | $2.5 \pm 1.2$ | $2.1 \pm 1.0$ | $3.5 \pm 1.0$ | < 0.001 |
| ASDAS-ESR, mean $\pm$ SD | $2.4 \pm 1.1$ | $2.2 \pm 1.1$ | $3.2 \pm 0.8$ | <0.001 |
| HADS, anxiety (0-21 scale) | 7 (5-11) | 7 (4-9) | 10 (7-14.5) | 0.003 |
| HADS, anxiety ( $\geq 11$ ), n (\%) | 51 (27.6) | 30 (21.3) | 21 (47.7) | 0.001 |
| HADS, depression (0-21 scale) | 4 (1-7) | 3 (1-6) | 8 (4.5-11) | < 0.001 |
| HADS, depression ( $\geq 11$ ), n (\%) | 20 (11) | 9 (6) | 11 (25) | < 0.001 |
| ESR, first hour, mm | 14 (6-24) | 13 (6-22) | 17 (8-31) | 0.222 |
| Serum C-reactive protein, mg/dl | 0.5 (0.2-1.2) | 0.4 (0.2-0.9) | 0.8 (0.4-2.3) | 0.011 |

PASS: patient-acceptable symptom state; VAS: visual analog scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQOL: Ankylosing Spondylitis Quality of Life questionnaire; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score, based on C-reactive protein; ASDAS-ESR: Ankylosing Spondylitis Disease Activity Score, based on erythrocyte sedimentation rate; HADS: Hospital Anxiety Depression Scale.

Table 3. Results of multivariate analyses. Factors associated with pa-tient-acceptable symptom state.

| Multivariate Model | OR (95\% CI) | p |
| :--- | :---: | :---: |
| Physicians' global assessment |  |  |
| $\quad(100-\mathrm{mm}$ VAS $)$ | $0.97(0.95$ to 0.99$)$ | 0.002 |
| BASDAI (0-10 scale) | $0.61(0.47$ to 0.80$)$ | 0.000 |
| Age, yrs | $1.04(0.99$ to 1.08$)$ | 0.084 |
| Female sex | $1.40(0.52$ to 3.82$)$ | 0.507 |

VAS: visual analog scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.
bo-controlled trials of adalimumab ${ }^{14}$ and etanercept ${ }^{26}$, the percentage of patients in PASS after treatment was even lower, $42 \%$ and $50 \%$, respectively. Easy accessibility to the Spanish Health Service, which is free and universal, the relatively high use of biological therapies, or certain adaptations to disease symptoms in our patients with AS could explain the differences in prevalence of PASS with other studies.

The independent factors associated with being in an acceptable symptom state in our study were to have low scores in the BASDAI index and in the physician global assessment scale. In the Canadian cross-sectional study ${ }^{13}$, being in PASS was independently associated with increasing age, lower patient assessment of global disease activity, and better functional status (BASFI). In contrast, in the place-bo-controlled clinical trial of adalimumab ${ }^{16}$, age $<40$ years was independently associated with attainment of the PASS (OR $1.85, \mathrm{p}=0.02$ ). In our study, clinical or demographic
variables such as age, sex, disease duration, occupation, or education level were not associated with PASS status, a result similar to that in a study of PASS in hip and knee osteoarthritis ${ }^{11}$. As might be expected, values reflecting lower disease activity (BASDAI), better function (BASFI), and higher quality of life (ASQOL) were found in patients with PASS-affirmative responses, consistent with previous studies ${ }^{13}$. A low score in physician global assessment was an independent factor associated with PASS status, an important fact, as physicians rated their patients without knowledge of the PRO scores. Acute-phase reactants, especially CRP, are considered important variables to monitor disease activity. Higher CRP values were associated with not being in PASS, and this is relevant because laboratory measurements are objective and are not influenced by patient's opinion. It is well known that the presence of peripheral arthritis, particularly hip arthritis, is a marker of poor disease outcome ${ }^{27,28,29}$. A mixed type of disease was present in $32 \%$, and many of these patients had been treated with DMARD and anti-TNF drugs compared with patients with the axial type of disease. In agreement with this, among the patients who rated their state as not acceptable, there was a higher proportion with the mixed clinical type of disease (42\%) compared with $29 \%$ in those patients in PASS, but the differences were nonsignificant.

A novel aspect of our study is the assessment of PASS according to the presence of psychological factors. In the general population, the prevalence of anxiety and depression using the HADS instrument is $7 \%$ and $5 \%$, respectively, and this may increase to $36 \%$ and $29 \%$ in patients with

Table 4. PASS according to change in treatment indicated by physician. Values are median (interquartile range, 25 th -75 th percentile) unless otherwise indicated.

| Variable | No Change in Treatment Indicated by Physician,$\mathrm{n}=142$ |  | Change in Treatment Indicated by Physician,$\mathrm{n}=48$ |  | p |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | PASS <br> Affirmative | PASS <br> Negative | PASS <br> Affirmative | PASS Negative |  |
| Number (\%) | 125 (88) | 17 (12) | 21 (44) | 27 (56) |  |
| Physician global assessment ( $100-\mathrm{mm}$ VAS) | 20 (10-30) | 30 (10-40) | 50 (40-70) | 60 (50-80) | < 0.001 |
| Patients' global assessment ( $100-\mathrm{mm}$ VAS) | 30 (10-50) | 50 (40-60) | 50 (40-70) | 70 (60-80) | <0.001 |
| Total pain ( $100-\mathrm{mm}$ VAS) | 30 (10-50) | 50 (30-60) | 60 (40-90) | 70 (60-80) | < 0.001 |
| Fatigue ( $100-\mathrm{mm}$ VAS) | 25 (10-40) | 50 (35-70) | 60 (40-80) | 50 (30-70) | <0.001 |
| BASDAI (0-10 scale) | 2.4 (1.1-3.9) | 4.9 (4.3-5.4) | 5 (3.9-6.2) | 6 (4.9-7) | <0.001 |
| BASDAI > 4; n (\%) | 29 (24) | 13 (81) | 14 (67) | 26 (96) | <0.001 |
| BASFI (0-10 scale) | 2.4 (0.9-4.8) | 4.2 (3.8-6.7) | 5.6 (2.2-7.4) | 5.5 (2.9-7.5) | < 0.001 |
| ASQOL (0-18 scale) | 4 (1-8) | 11 (4-14) | 10 (6-12) | 10 (8-13) | <0.001 |
| HADS anxiety (0-21) | 6 (4-9) | 10 (6-14) | 8 (7-12) | 10 (7-15) | <0.001 |
| HADS depression (0-21) | 3 (1-6) | 8 (6-13) | 5 (2-7) | 8 (4-9) | <0.001 |
| Serum C-reactive protein, mg/dl | 0.3 (0.2-0.8) | 0.6 (0.3-1.4) | 0.7 (0.4-1.5) | 1.3 (0.4-3.1) | <0.001 |
| ASDAS-CRP, mean $\pm$ SD | $2.0 \pm 0.9$ | $2.9 \pm 0.7$ | $3.1 \pm 0.8$ | $3.8 \pm 0.9$ | <0.001 |

PASS: patient-acceptable symptom state; VAS: visual analog scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQOL: Ankylosing Spondylitis Quality of Life questionnaire; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score, based on C-reactive protein; HADS: Hospital Anxiety Depression Scale.

Table 5. PASS thresholds for patient-reported outcomes and other measures in PASS-positive patients ( $\mathrm{n}=149$ ).

| Variable | 75 th Percentile | Sensitivity/ <br> Specificity | $80 \%$ Specificity <br> Cutoff | Sensitivity/ <br> Specificity | ROC Cutoff | Sensitivity/ <br> Specificity | AUC |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Patients' global assessment | 50 | $80 / 64$ | 60 | $61 / 81$ | 40 | $93 / 53$ | 0.7945 |
| (100-mm VAS) |  |  |  |  |  |  |  |
| Total pain (100-mm VAS) | 60 | $61 / 74$ | 70 | $45 / 81$ | 50 | $75 / 66$ | 0.7554 |
| Nocturnal pain (100-mm VAS) | 50 | $66 / 72$ | 70 | $41 / 83$ | 40 | $82 / 66$ | 0.7777 |
| Fatigue (100-mm VAS) | 50 | $67 / 71$ | 70 | $33 / 87$ | 50 | $67 / 71$ | 0.6943 |
| BASDAI (0-10 scale) | 4.55 | $77 / 75$ | 5.30 | $58 / 81$ | 4.20 | $91 / 73$ | 0.8262 |
| BASFI (0-10 scale) | 5.20 | $49 / 75$ | 5.60 | $47 / 82$ | 2.70 | $81 / 52$ | 0.7037 |
| ASQOL (0-18 scale) | 8.23 | $66 / 75$ | 11 | $52 / 83$ | 8.00 | $73 / 71$ | 0.7673 |
| ASDAS-CEP | 2.84 | $76 / 75$ | 2.96 | $70 / 80$ | 2.54 | $86 / 63$ | 0.8369 |
| ASDAS-ESR | 3.45 | $68 / 75$ | 3.57 | $65 / 80$ | 2.79 | $95 / 53$ | 0.8016 |
| HADS anxiety | 9 | $57 / 67$ | 12 | $36 / 83$ | 8 | $70 / 60$ | 0.6966 |
| HADS depression | 6 | $70 / 69$ | 8 | $52 / 86$ | 4 | $86 / 54$ | 0.7528 |

ROC: receiver-operating characteristics curve; AUC: area under the curve; PASS: patient-acceptable symptom state; VAS: visual analog scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQOL: Ankylosing Spondylitis Quality of Life questionnaire; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score, based on C-reactive protein; ASDAS-ESR: Ankylosing Spondylitis Disease Activity Score, based on erythrocyte sedimentation rate; HADS: Hospital Anxiety Depression Scale.
chronic low back pain ${ }^{30}$. In a study of psychological status in patients with AS, a prevalence of $25 \%$ for anxiety and $15 \%$ for depression was found ${ }^{31}$; the authors suggested that patients' subjective responses to questionnaires were influenced by many factors, including the psychological aspects. These data were quite similar in our study, with presence of anxiety in $28 \%$ and depression in $11 \%$ of patients. We found higher anxiety and depression rates in patients with PASS-negative answers. In addition, both anxiety and depression correlated significantly with physicians' global assessment, PRO, and ASDAS. Another study also found
that psychological variables contributed significantly to the variance in BASDAI scores, specifically arthritis helplessness and depression ${ }^{32}$. We recommend that psychological status should be taken into account in assessment of disease activity in patients with AS, and its influence in patient-subjective reported outcomes should be considered.

Current pharmacological and nonpharmacological treatment was evaluated. Our patients with an acceptable symptom state were taking fewer NSAID and corticosteroids, which is interpreted as need for less symptomatic treatment in patients with a better clinical condition. Use of NSAID is
effective to reduce pain and stiffness ${ }^{33}$ and it has been shown that a strategy of continuous use of NSAID reduces radiographic progression in symptomatic patients with $\mathrm{AS}^{34}$. Nevertheless, only $35 \%$ of our patients had daily intake of NSAID, and even 19 out of 44 patients (43\%) not in an acceptable symptom state did not use NSAID daily. The reasons for this were not recorded, but the figures are similar to those reported in the GESPIC cohort (Germany), where $43 \%$ of patients did not use NSAID daily, despite having active disease (BASDAI $>4$ ), mainly for fear of side effects ${ }^{35}$. The number of patients receiving corticosteroids was too small to draw any conclusion. Most of the patients who were receiving biological therapies rated their state as acceptable and even those patients who were receiving anti-TNF drugs and had a negative answer to the PASS question had relatively low ASDAS values. The results suggest that factors other than disease activity, such as psychological aspects or comorbidity, might influence PASS status. Exercise was practiced by more patients in an acceptable symptom state, a situation that may reflect the well-known benefits of physical therapy for patients with $\mathrm{AS}^{36}$, or just that patients in a better symptom state are those able to undertake more exercise.

The ASDAS values found in our study and their relation with other outcomes are difficult to interpret. Sixty-two percent of the patients and $53 \%$ of those in PASS had a high or very high disease activity state according to the proposed ASDAS cutoff values for disease activity states ${ }^{8}$. This percentage contrasts with the high prevalence of PASS state ( $77 \%$ ) in the global population and with the median score for physician global assessment, which was 25 (interquartile range 10 to 40 ). In the same direction, $46 \%$ of the patients with high or very high ASDAS disease activity states had scores $<40 \mathrm{~mm}$ in the VAS for physician global assessment of activity, meaning that they were considered not very active by their physicians. Moreover, a relevant change in treatment was indicated in only a quarter of patients, a situation that is difficult to understand if nearly two-thirds of our patients were in a high or very high ASDAS disease activity state. All these findings reflect the complexity of measuring disease activity in AS, as assessments are mostly based on subjective scales. Do the ASDAS cutoff points for disease activity reflect the real state in patients with AS in routine clinical practice? Does the high proportion of PASS-affirmative answers reflect an excess of adaptation or resignation with the symptoms? More studies are needed in other daily practice populations to answer these questions. We consider that a relevant change in treatment (i.e., DMARD or biological therapy) is an objective measure reflecting the physician's real assessment of patients with AS in daily care. The mean ASDAS for patients with no indication of a treatment change was 2.1 (SD 1.0) compared with 3.5 (SD 1.0) in patients who had treatment changed. Those values coincide with cutpoints to separate moderate
to high disease activity and high to very high disease activity, respectively. Considering that at the time the study was done the ASDAS cutpoint had not been published, this reflects that in daily clinical practice, physicians offered relevant changes in treatment only to patients in the highest states of ASDAS disease activity. PASS status was compared in these patients. As noted, a gradient of scores was found for most outcome measures, and we found patients concordant for change in treatment and PASS in the extremes of the gradient and those discordant in the middle, and these patients differed mostly in psychological status. We propose that other clinical problems not directly related to AS, such as anxiety or depression, should be investigated in patients with PASS-negative responses, as PRO and ASDAS scores could be abnormally high in these patients These factors may contribute to the moderate degree of agreement observed in this and other studies between patients' and physicians' assessments ${ }^{37}$.

Cutoff points reflecting PASS for different health status measurements and PRO have been studied in patients with rheumatoid arthritis, psoriatic arthritis, and $\mathrm{AS}^{12,13,14,}$ 15,25,38 , although consensus on the methods that should be used for PASS calculation has not been achieved. Our proposal was to identify PASS thresholds for common outcome measures in a routine nonselected clinical practice population. We found that the 75th percentile thresholds were higher than cutoffs based on optimal values for sensitivity and specificity defined by ROC analysis. The cutoff points for PASS condition in our cohort of patients with AS seen in daily rheumatology practice were close to those found in patients with AS in Canada ${ }^{13}$, which the authors considered unexpectedly high. In accord with the previous comments about ASDAS, a value of 2.84 as the PASS threshold means that a high proportion of patients rate their symptom state as acceptable, even though they are classified as being in a high disease activity state by ASDAS.

Our study has some limitations. The cross-sectional design allowed assessment of patient's situation in only a single visit. A longitudinal design is needed to draw definitive conclusions on the value of PASS as an outcome measure. Patients were recruited from the outpatient clinics of 4 different rheumatology services in routine daily practice conditions, resulting in potential for selection bias. However, demographic and clinical features of our patients were similar to those of other cohorts. Also, physicians were explicitly advised to evaluate their patients after clinical examination, with no knowledge of the patients' answers to the PASS question, but compliance with this recommendation could not be guaranteed.

Our study of a cross-sectional cohort of Spanish patients with AS seen in daily practice has shown that as many as $77 \%$ of patients considered themselves in an acceptable symptom state. The PASS status can easily be determined by incorporating a simple question into the set of validated

PRO measures in routine clinical practice. It is a useful measure because it reflects the satisfaction of patients with their condition reasonably well and correlates with other assessment measures. Nevertheless, the PASS thresholds for common recommended outcome measures were relatively high and within the range for high disease activity by the ASDAS, which should not be acceptable for the treating physician. Concerning treatment, a physician should rely on ASDAS values, because patients in the highest disease activity states probably need further treatment to minimize radiological changes, and also on his or her own global assessment. Patient-reported outcomes, including PASS, should be considered as additional measures to facilitate the physician global assessment. If there are supporting results among these measurements, the treatment decision will be easier. In the case of discordant results, efforts should be made to find the causes and try to solve them. If a treatment is indicated for patients who consider themselves in PASS, the reasons for it should be explained clearly to enhance patient compliance. In the case of a low ASDAS disease activity state, in which a change of treatment is not considered, although the patient is not in PASS, the physician should investigate other factors not related to disease activity, such as psychological problems. Longitudinal studies in daily clinical practice are needed to confirm the usefulness of the PASS question in assessment of the patient with AS.

## ACKNOWLEDGMENT

The authors are grateful to Marta Pulido, MD, for editorial assistance and Loreto Carmona, MD, for scientific advice.

## REFERENCES

1. Dagfinrud H, Mengshoel AM, Hagen KB, Loge JH, Kvien TK. Health status of patients with ankylosing spondylitis: A comparison with the general population. Ann Rheum Dis 2004;63:1605-10.
2. Ariza-Ariza R, Hernández-Cruz B, Navarro-Sarabia F. Physical function and health-related quality of life of Spanish patients with ankylosing spondylitis. Arthritis Care Res 2003;49:483-7.
3. Van der Heijde D, Bellamy N, Calin A, Dougados M, Khan MA, van der Linden S, and the Assessments in Ankylosing Spondylitis Working Group. Preliminary core sets for endpoints in ankylosing spondylitis. J Rheumatol 1997;24:2225-9.
4. Van der Heijde D, Dougados M, Davis J, Weisman MH, Maksymowych W, Braun J, et al. ASsessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. Arthritis Rheum 2005;52:386-94.
5. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: A guide to assess spondyloarthritis. Ann Rheum Dis 2009;68 Suppl:ii1-ii44.
6. Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18-24.
7. Van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, et al. The ASDAS is a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811-8.
8. Machado P, Landewé R, Lie E, Kvien T, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): Defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis 2011;70:47-53.
9. Tubach F, Wells GA, Ravaud P, Dougados M. Minimal clinically important difference, low disease activity state and patient acceptable symptom state: Methodological issues. J Rheumatol 2005;32:2025-9.
10. Tubach F, Dougados M, Falissard B, Baron G, Logeart I, Ravaud P. Feeling good rather than feeling better matters more to patients. Arthritis Rheum 2006;55:526-30.
11. Tubach F, Ravaud P, Baron G, Falissard B, Logeart N, Bellamy N, et al. Evaluation of clinically relevant states in patient-reported outcomes in knee and hip osteoarthritis: The patient acceptable symptom state. Ann Rheum Dis 2005;64:34-7.
12. Kvien TK, Heiberg T, Hagen KB. Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): What do these concepts mean? Ann Rheum Dis 2007;66:40-1.
13. Maksymowych W, Richardson R, Mallon C, van der Heijde D, Boonen A. Evaluation and validation of the patient acceptable symptom state (PASS) in patients with ankylosing spondylitis. Arthritis Rheum 2007;57:133-9.
14. Dougados M, Luo MP, Maksymowych WP, Chmiel JJ, Chen N, Wong RL, et al. Evaluation of the patient acceptable symptom state as an outcome measure in patients with ankylosing spondylitis: Data from a randomized controlled trial. Arthritis Rheum 2008;59:553-60.
15. Tubach F, Pham T, Skomsvoll JF, Mikkelsen K, Bjorneboe O, Ravaud P, et al. Stability of the patient acceptable symptomatic state over time in outcome criteria in ankylosing spondylitis. Arthritis Rheum 2006;55:960-3.
16. Maksymowych W, Gooch K, Dougados M, Wong RL, Chen N, Kupper H, et al. Thresholds of patient-reported outcomes that define the patient acceptable symptom state in ankylosing spondylitis vary over time and by treatment and patient characteristics. Arthritis Care Res 2010;62:826-34.
17. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
18. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: A quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20-6.
19. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67:361-70.
20. Crawford JR, Henry JD, Crombie C, Taylor EP. Normative data for the HADS from a large non-clinical sample. Br J Clin Psychol 2001;40:429-34.
21. Ariza-Ariza R, Hernández-Cruz B, López-Antequera G, Toyos FJ, Navarro-Sarabia F. Cross-cultural adaptation and validation of a Spanish version of a specific instrument to measure health-related quality of life in patients with ankylosing spondylitis. Reumatol Clin 2006;2:64-9.
22. Tubach F, Ravaud P, Beaton D, Boers M, Bombardier C, Felson DT, et al. Minimal clinically important improvement and patient acceptable symptom state for subjective outcome measures in rheumatic disorders. J Rheumatol 2007;34:1188-93.
23. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewe R, van der Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis 2003;62:127-32.
24. Collantes E, Zarco P, Muñoz E, Juanola X, Mulero J, Fernández-Sueiro JL, et al. Disease pattern of spondyloarthropathies in Spain: Description of the first national registry (REGISPONSER) - extended report. Rheumatology

2007;46:1309-15.
25. Kvamme MK, Kristiansen IS, Lie E, Kvien TK. Identification of cutpoints for acceptable health status and important improvement in patient-reported outcomes, in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol 2010;37:26-31.
26. Dougados M, Combe B, Braun J, Landewe R, Sibilia R, Cantagrel J, et al. Achievement of a patient acceptable symptom state (PASS) and of a minimum clinically important improvement (MCII) with etanercept in refractory heel enthesitis related to spondyloarthritis: Results of a double blind placebo controlled study (HEEL) [abstract]. Arthritis Rheum 2009;60 Suppl:1786.
27. Amor B, Santos R, Nahal R, Listrat V, Dougados M. Predictive factors for the long-term outcome of spondyloarthropathies. J Rheumatol 1994;21:1883-7.
28. Gran JT, Skomsvoll JF. The outcome of ankylosing spondylitis: A study of 100 patients. Br J Rheumatol 1997;36:766-71.
29. Vander Cruyssen B, Muñoz-Gomáriz E, Font P, Mulero J, de Vlam K, Boonen A, et al. Hip involvement in ankylosing spondylitis: Epidemiology and risk factors associated with hip replacement surgery. Rheumatology 2010;49:73-81.
30. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. J Psychosom Res 2002;52:69-77.
31. Martindale J, Smith J, Sutton CJ, Grennan D, Goodacre L, Goodacre JA. Disease and psychological status in ankylosing spondylitis. Rheumatology 2006;45:1288-93.
32. Brionez TF, Assassi S, Reveille JD, Green C, Learch T, Dieckman L, et al. Psychological correlates of self-reported disease activity in different perspectives. Rheumatology 2005;44:789-95.
33. Heiberg T, Kvien TK, Mowinckel P, Aletaha D, Smolen JS, Hagen KB. Identification of disease activity and health status cut-off points for the symptom state acceptable to patients with rheumatoid arthritis. Ann Rheum Dis 2008;67:967-71.
34. Song IH, Poddubnyy DA, Rudwaleit M, Sieper J. Benefits and risks of ankylosing spondylitis treatment with nonsteroidal antiinflammatory drugs. Arthritis Rheum 2008;58:929-38.
35. Wanders A, Heijde D, Landewé R, Béhier JM, Calin A, Olivieri I, et al. Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: A randomized clinical trial. Arthritis Rheum 2005;52:1756-65.
36. Rudwaleit M, Niewerth M, Listing J, Marker-Hermann E, Zeidler H, Zink A, et al. Disease activity over one year in early ankylosing spondylitis in a prospective observational cohort (GESPIC) [abstract]. Ann Rheum Dis 2005;64 Suppl:65.
37. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. Cochrane Database Syst Rev 2008;1:CD002822.
38. Spoorenberg A, van Tubergen A, Landewé R, Dougados M, van der Linden S, Mielants H, et al. Measuring disease activity in ankylosing spondylitis: Patient and physician have different perspectives. Rheumatology 2005;44:789-95.


[^0]:    From the Service of Rheumatology, Hospital Universitario de Gran
    Canaria Dr. Negrín, Las Palmas de Gran Canaria, Las Palmas; Service of Rheumatology, Hospital Universitario de Canarias, La Laguna, Tenerife; Service of Rheumatology, Hospital Universitario Ntra. Sra. de la Candelaria, Santa Cruz de Tenerife, Tenerife; Service of Rheumatology, Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria, Las Palmas; and the Research Unit of the Spanish Society of Rheumatology, Madrid, Spain.
    C. Rodríguez-Lozano, MD, Service of Rheumatology, Hospital Universitario de Gran Canaria Dr. Negrín; M-Á. Gantes, PhD, Service of Rheumatology, Hospital Universitario de Canarias; B. González, MD, Service of Rheumatology, Hospital Universitario Ntra. Sra. de la Candelaria; J.A. Hernández-Beriain, MD, Service of Rheumatology, Hospital Universitario Insular de Gran Canaria; A. Naranjo, PhD,

[^1]:    Service of Rheumatology, Hospital Universitario de Gran Canaria Dr. Negrín; V. Hernández, MD, Service of Rheumatology, Hospital Universitario de Canarias; J.C. Quevedo-Abeledo, MD, Service of Rheumatology, Hospital Universitario de Gran Canaria Dr. Negrín; M.J. Falcón, MD, Service of Rheumatology, Hospital Universitario Ntra. Sra. de la Candelaria; S. Machín, MD, Service of Rheumatology, Hospital Universitario Insular de Gran Canaria; M.A. Descalzo, PhD, Research Unit of the Spanish Society of Rheumatology.
    Address correspondence to Dr. C. Rodríguez-Lozano, Servicio de Reumatología, Hospital Universitario de Gran Canaria Dr. Negrín, C/ Barranco de la Ballena s/n, E-35011 Las Palmas de Gran Canaria, Las Palmas, Spain. E-mail: crodloz@gobiernodecanarias.org
    Accepted for publication March 15, 2012.

