

## Rate and Predisposing Factors for Sacroiliac Joint Radiographic Progression After a Two-Year Follow-up Period in Recent-Onset Spondyloarthritis

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**Objective.** To evaluate the rate of radiographic structural progression in the sacroiliac (SI) joints in patients with radiographic or nonradiographic axial spondyloarthritis (SpA), and to determine factors predisposing to such progression, over 2 years.

**Methods.** Patients with recent-onset axial SpA (from the Devenir des Spondyloarthropathies Indifférenciées Récentes cohort) were assigned a radio-

graphic SI joint score according to the modified New York criteria. Demographic characteristics, smoking status, HLA-B27 positivity, inflammation on magnetic resonance imaging (MRI) of the SI joints, disease activity, and treatment were investigated as potential predisposing factors. The main analysis consisted of the evaluation of the switch from nonradiographic to radiographic axial SpA, but other definitions of radiographic progression were also evaluated.

**Results.** Of the 708 patients enrolled, 449 had baseline and 2-year pelvic radiographs. Of these patients, 47% were men. Their mean  $\pm$  SD age was  $34 \pm 9$  years, 61% were B27 positive, and 37% had inflammation of the SI joints on MRI. The percentages of patients who switched from nonradiographic to radiographic axial SpA (4.9% [16 of 326]) and from radiographic to nonradiographic axial SpA (5.7% [7 of 123]) were low. The mean  $\pm$  SD change in the total SI joint score (range 0–8) was small ( $0.1 \pm 0.8$ ) but highly significant ( $P < 0.001$ ). The potential baseline predisposing factors for meeting the modified New York criteria in the multivariate analysis were current smoking, HLA-B27 positivity, and inflammation of the SI joints on MRI, with odds ratios of 3.3 (95% confidence interval [95% CI] 1.0–11.5), 12.6 (95% CI 2.3–274), and 48.8 (95% CI 9.3–904), respectively.

**Conclusion.** Our findings suggest that structural progression does exist in early SpA, but it is quite small and observed in a small number of patients, and that environmental (smoking status), genetic (HLA-B27 positivity), and inflammation (inflammation of the SI joints on MRI) markers might be independent predisposing factors for progression.

This study was conducted under the umbrella of the French Society of Rheumatology and INSERM. The Devenir des Spondyloarthropathies Indifférenciées Récentes (DESIR) cohort was sponsored by the Département de la Recherche Clinique et du Développement de l'Assistance Publique-Hôpitaux de Paris (AP-HP). An unrestricted grant from Pfizer was allocated for the 10-year follow-up of the recruited patients. Database management of the DESIR cohort is performed within the Department of Epidemiology and Biostatistics, Centre Hospitalier Universitaire de Nîmes, Nîmes, France (Professor Paul Landais, DIM).

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The recommended imaging investigations for patients with chronic inflammatory back pain (present for  $\geq 3$  months) occurring before the age of 45 years include both plain radiographs of the pelvis and (in the case of normal findings on radiography) magnetic resonance imaging (MRI) of the pelvis, since the suspected diagnosis in this case is axial spondyloarthritis (SpA) and the involvement of the sacroiliac (SI) joints seems to be a cornerstone of the disease (1). For epidemiologic studies and/or clinical trials, patients are enrolled according to existing classification criteria. The presence of structural damage of the SI joints observed on plain radiographs of the pelvis is mandatory in the first set of classification criteria (the New York criteria and the modified New York criteria) (2). These abnormalities on radiographs are wrongly called "sacroiliitis," since "-itis" means an inflammatory process in medicine and plain radiography cannot detect inflammation but only chronic change and structural damage, such as subchondral bone sclerosis and joint irregularities.

Axial SpA with radiographic damage is called either ankylosing spondylitis (AS) or radiographic axial SpA (3). Because the time lag between disease onset in terms of symptoms and the occurrence of structural damage may be quite long (estimated between 5 and 7 years) (4) and because some patients with SpA will never develop structural damage, other sets of criteria have been developed during the last 3 decades (e.g., the Amor criteria [5] and the European Spondylarthropathy Study Group [ESSG] criteria [6]). The Assessment of Spondyloarthritis international Society (ASAS) developed classification criteria that include patients with nonradiographic axial SpA in addition to radiographic axial SpA and integrate MRI findings (7).

The distinction between radiographic and nonradiographic axial SpA based on the presence or absence of radiographic sacroiliitis is highlighted by the fact that pharmaceutical companies have developed their compounds, in particular tumor necrosis factor (TNF) inhibitors, with reference to the modified New York criteria (8–11) and that these compounds have been approved only for patients with SI joint structural damage. Because of this restriction in the use of these compounds, pharmaceutical companies have more recently conducted specific studies in patients with nonradiographic axial SpA (i.e., excluding patients with structural damage) (12–14). The European Medicines Agency has approved TNF inhibitors for patients with nonradiographic axial SpA only if objective signs of inflammation, such as the presence of relevant SI subchondral bone marrow edema on MRI and/or an elevated C-reactive protein (CRP) level, are present. Post hoc ana-

lyses of the trials performed in nonradiographic axial SpA have detected these objective signs of inflammation as strong predictive factors for the effectiveness of anti-TNF treatment (12,15).

However, the long-term natural history of patients with nonradiographic axial SpA is not well known. In particular, the rate of radiographic progression (i.e., the percentage of patients who will switch from having nonradiographic axial SpA to having radiographic axial SpA over time), the predisposing factors for such a switch, and whether the presence of objective signs of inflammation might predict this SI joint radiographic progression are not known. Moreover, categorization of the structural damage observed at the level of the SI joint (sacroiliitis according to the modified New York criteria [yes/no]) might not be the optimal way to evaluate the natural history of the disease, and other potential scoring systems of radiographic structural damage of the SI joint might be more appropriate.

The Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort, a French multicenter longitudinal observational study of patients with recent-onset inflammatory low back pain suggestive of axial SpA according to the treating rheumatologist (16), offered a unique opportunity to answer these questions. In the DESIR cohort, concomitantly with a clinical evaluation performed every 6 months, plain radiographs have been collected systematically at baseline and at the 2-year follow-up visit. Moreover, MRIs of the pelvis were obtained at baseline, so this could be evaluated as a possible predictive factor for progression.

## PATIENTS AND METHODS

**Patients.** For this analysis, the data collected during the first 2 years of follow-up in the DESIR cohort were used. The DESIR cohort has been described extensively (16). Briefly, consecutive patients ages 18–50 from 25 centers in France were included. Patients had inflammatory back pain in the thoracic spine, lumbar spine, and/or buttocks area based on either the Calin (17) or Berlin (18) criteria with a duration of  $\geq 3$  months but  $< 3$  years. They were included in the study if the treating rheumatologist considered the symptoms to be suggestive of axial SpA, with a score of  $\geq 5$  on a scale of 0–10, where 0 was not suggestive of axial SpA and 10 was very suggestive of axial SpA. Between December 2007 and April 2010, 708 patients were included.

The study was conducted according to good clinical practice guidelines and was approved by the appropriate medical ethics committee. A detailed description of the study protocol is available online at <http://www.lacohortedesir.fr/desir-english/>. The research proposal for this particular analysis was approved by the scientific committee of the DESIR cohort.

**Data collection.** A database was built using a standardized case report form that included data from questionnaires, findings of physical examinations, ongoing treatments,

comorbidities, and laboratory test results according to the DESIR protocol. The database used for this analysis was locked in October 2014.

**Demographic and disease characteristics.** At baseline, the following information was collected: age, sex, smoking status, HLA-B27 status, and duration of axial symptoms. At baseline and at the 6-month intermediate visits during the first 2 years of follow-up, the following parameters were also collected: Bath AS Disease Activity Index (BASDAI) (19), Bath AS Functional Index (BASFI) (20), CRP level, TNF therapy intake, and nonsteroidal antiinflammatory drug (NSAID) intake according to the ASAS NSAID score (21).

**Radiographs of the pelvis.** The radiographs of the pelvis obtained at baseline and after 2 years of follow-up were centrally stored in a specific software program after anonymization and blinding of the date of collection according to a prespecified list of randomization with 7 different letters (from A to G). For example, for a specific patient, the baseline radiograph could be coded as C and the 2-year radiograph as A.

The radiographs were evaluated by 2 central readers (RvdB and VVH; reader 1 and reader 2, respectively). A detailed description of the central reading has been published previously (22). Briefly, each reader evaluated each SI joint according to the modified New York method. In this method, the joint is graded on a scale of 0–4, where 0 = a normal SI joint, 1 = suspicious changes, 2 = minimal abnormality, 3 = unequivocal abnormality, and 4 = severe abnormality (e.g., complete ankylosis of the SI joint). The 2 radiographs for each individual patient were evaluated at the same time. Readers were aware that the 2 radiographs were of the same patient but were unaware of the chronology of the radiographs. The readers were blinded with regard to all clinical and laboratory data and the other imaging modality (i.e., MRI). Agreement between the 2 readers with regard to fulfillment of the modified New York criteria for sacroiliitis at the patient level (i.e., at least unilateral grade 3 or bilateral grade 2 and/or a progression of at least 1 grade for each SI joint) was calculated. In cases in which the readers disagreed, a radiologist (MR) or a rheumatologist (PC) experienced in the field of SpA served as adjudicator. The adjudicator scored the pelvic radiograph as yes or no according to the modified New York criteria by assigning a grade for each SI joint based on the scale described above, and was blinded with regard to the assessment of the primary readers. An image was marked as positive if 2 of the 3 readers agreed.

**MRI of the pelvis.** The MRIs collected at baseline were stored centrally after anonymization. The images were evaluated by 2 central readers (RvdB and FT). A detailed description of the central reading has been published previously (23). Briefly, findings of MRI of the SI joint were considered positive according to the ASAS definition if bone marrow edema lesions highly suggestive of SpA were present (either  $\geq 1$  bone marrow edema lesion on  $\geq 2$  consecutive slices or severe bone marrow edema lesions on a single slice) (24). All available baseline MRIs of the SI joint were read independently by the 2 readers, who were blinded with regard to all clinical and laboratory data and the other imaging modality (i.e., pelvic radiographs). Agreement on whether MRI findings were positive was calculated. In the case of disagreement, a senior radiologist (MR) served as adjudicator. The adjudicator scored the MRI of the SI joint according to the ASAS definition and was blinded with regard to the assessment of the primary readers. An image was marked as positive if 2 of the 3 readers agreed.

**Statistical analysis.** Since the primary objective of this study was to examine SI joint radiographic progression over the first 2 years, only patients with available radiographs at baseline and 2-year follow-up were analyzed. The first step of the analysis consisted of a descriptive comparison of the patients enrolled in the DESIR cohort and the patients who completed the first 2 years of the study.

With regard to the rate of radiographic progression, the main analysis was the evaluation of the percentage of patients who were classified at baseline as having nonradiographic axial SpA and subsequently developed radiographic axial SpA after 2 years (based on the modified New York criteria). Similarly, we evaluated the percentage of patients who were classified at baseline as having radiographic axial SpA and were subsequently classified as having nonradiographic SpA after 2 years. Radiographic progression was also evaluated in the entire population, considering the radiographic score as a continuous variable with a range of 0–8 (4 possible grades for each SI joint). This analysis was conducted separately for reader 1 and for reader 2 but was also done for the mean score of the 2 readers.

The final analysis evaluating radiographic progression consisted of the evaluation of the percentage of patients considered to be progressors based on additional definitions. The first proposed definition was a change of at least 1 grade in at least 1 SI joint after 2 years of follow-up. For this analysis, we were able to calculate the percentage of “progressors” (worsening) and similarly the percentage of “regressors” (improving). The second proposed definition was a change of at least 1 grade in at least 1 SI joint after 2 years of follow-up and an absolute score of the “worsened” joint at year 2 of at least 2 (i.e., at least minimal abnormality). The third definition was the percentage of patients with a change other than 0 in the total score of the 2 SI joints (mean of the 2 readers); for this analysis, we defined a “progressor” as a patient with a change in the total score of  $>0$  and “regressor” as a patient with a change in the total score of  $<0$ . These analyses were performed on the whole set of patients for whom pelvic radiographs were available but by presenting the data with regard to the presence or absence of baseline radiographic structural damage according to the modified New York criteria.

Possible predisposing factors for structural progression were evaluated according to different definitions of the dependent variable and to a similar list of potential independent variables. The potential independent variables included selected variables collected at baseline (i.e. age, sex, smoking status, HLA-B27 positivity, CRP level, presence of inflammation on MRI of the SI joints, BASDAI, and SI joint radiographic structural damage according to the modified New York criteria). The different definitions of the dependent variable were as follows: 1) switch from nonradiographic to radiographic axial SpA after 2 years of follow-up, 2) switch from radiographic to nonradiographic axial SpA after 2 years of follow-up, 3) changes (worsening) in at least 1 grade in at least 1 SI joint after 2 years of follow-up, 4) changes (improvement) in at least 1 grade in at least 1 SI joint after 2 years of follow-up, and 5) changes (worsening) in at least 1 grade in at least 1 SI joint after 2 years of follow-up and an absolute score for the “worsened” SI joint of at least 2 at year 2.

All of the analyses were performed using a multiple regression model that included all of the independent variables for which the univariate analysis revealed a statistical significance at a *P* level of at least  $<0.20$ . Only the independent variables that had a *P* value of less than 0.05 in the multivariate analysis were considered to be statistically significant. No correction was performed because of the multiplicity of the tests,

**Table 1.** Baseline characteristics of the SpA patients\*

	Entire DESIR cohort (n = 708)	2-year completers (n = 595)	2-year completers with available imaging data (n = 449)	Radiographic status according to the modified New York criteria†					
				Positive at baseline			Negative at baseline		
				Positive at 2 years (n = 116)	Negative at 2 years (n = 7)	All (n = 123)	Positive at 2 years (n = 16)	Negative at 2 years (n = 310)	All (n = 326)
Age, mean ± SD years	34 ± 8	34 ± 9	34 ± 9	34 ± 9	30 ± 7	33 ± 9	30 ± 10	35 ± 9	34 ± 9
Sex, % female	54	52	53	36	29	36	62	59	59
B27 positive, %	58	60	61	72	86	72	94	55	57
Duration of symptoms, mean ± SD months	18 ± 10	18 ± 11	18 ± 11	20 ± 10	17 ± 9	20 ± 10	18 ± 10	18 ± 11	18 ± 11
Symptoms, %‡									
Arthritis	21	21	21	17	29	18	6	24	23
Enthesitis	49	49	49	41	57	41	31	52	51
Uveitis	9	8	7	7	14	7	13	7	7
IBD	4	4	4	3	0	3	6	4	4
BASDAI (0–100 scale), mean ± SD	45 ± 20	44 ± 20	44 ± 19	40 ± 19	39 ± 20	40 ± 19	43 ± 18	45 ± 19	45 ± 19
BASDAI ≥40, %	60	60	59	48	57	49	50	64	63
BASFI (0–100 scale), mean ± SD	30 ± 23	30 ± 23	30 ± 22	29 ± 22	27 ± 21	29 ± 22	19 ± 21	31 ± 22	30 ± 22
CRP, mean ± SD mg/liter	8 ± 14	8 ± 14	8 ± 15	12 ± 17	24 ± 29	13 ± 18	8 ± 11	6 ± 13	6 ± 13
Inflammation of the SI joints on MRI, %§	35.5	36.8	37.2	64.8	85.7	66.1	93.3	22.9	26.4
ASDAS-CRP, mean ± SD	2.7 ± 1.0	2.7 ± 1.0	3.0 ± 1.0	3.0 ± 1.0	3.0 ± 1.0	3.0 ± 1.0	2.7 ± 1.0	2.7 ± 1.0	2.7 ± 1.0
ASDAS-CRP, %									
>3.5	19	20	19	22	40	23	14	17	17
≤3.5 to ≥2.1	52	50	51	52	60	52	64	50	50
<2.1 to ≥1.3	22	21	21	19	0	18	14	22	22
<1.3	8	8	9	7	0	7	7	11	10
ASAS NSAID index, mean ± SD#	56 ± 53	58 ± 53	59 ± 53	58 ± 51	33 ± 47	57 ± 51	70 ± 61	59 ± 53	59 ± 53
Patients taking NSAIDs during the week preceding baseline, %	70	71	72	75	57	74	62	72	71
Patients taking a DMARD during the 6 months preceding baseline, %	13	13	14	11	14	11	12	16	16

\* SpA = spondyloarthritis; DESIR = Devenir des Spondyloarthropathies Indifférenciées Récentes; IBD = inflammatory bowel disease; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; CRP = C-reactive protein; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score using the CRP; DMARD = disease-modifying antirheumatic drug.

† Presence of radiographic sacroiliitis at baseline was defined as at least a unilateral grade 3 or a bilateral grade 2, as determined by the central readers.

‡ Presence or history of the symptoms listed.

§ According to the Assessment of SpondyloArthritis international Society (ASAS) definition.

# The ASAS nonsteroidal antiinflammatory drug (NSAID) index was determined according to the ASAS proposal (ref. 21) and calculated based on the NSAID intake during the week preceding the baseline visit.

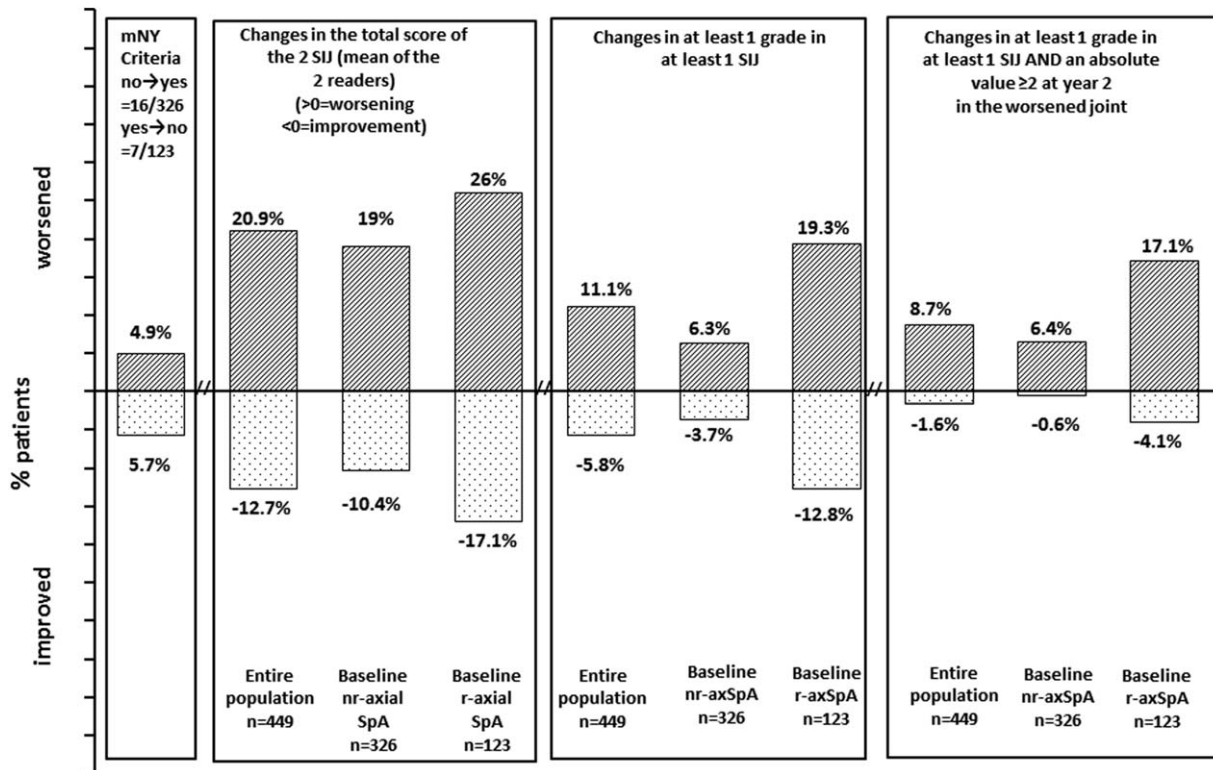
but the first analysis (i.e., the evaluation of the factors predicting the switch from nonradiographic to radiographic axial SpA) was considered the primary one.

## RESULTS

**Patients and study course.** Of the 708 patients enrolled, 595 completed the first 2 years of follow-up. Radiographs of the pelvis at baseline and at 2 years were available for 449 patients. Table 1 summarizes the baseline characteristics of the patients with regard to

the completion of the study and the baseline SI joint radiographic status. There was no significant difference between the whole population of the cohort and the patients evaluated in this study.

**Radiographic progression at year 2.** Figure 1 summarizes the main findings of the different analyses performed. Of the 326 patients who did not fulfill the modified New York criteria at baseline, 16 (4.9%) became positive after 2 years of follow-up. At the same time, of the 123 patients who did fulfill the modified



**Figure 1.** Radiographic progression in the sacroiliac joint (SIJ) over a 2-year follow-up period in patients with recent-onset ( $<3$  years) nonradiographic axial spondyloarthritis (nr-axial SpA) and patients with radiographic axial SpA (r-axial SpA). mNY = modified New York.

New York criteria at baseline, 7 (5.7%) no longer fulfilled the modified New York criteria at year 2.

A higher percentage of progressors, both in terms of absolute value and in terms of differences between the progressors and the regressors, was observed for the other definitions of progressors, in particular the definition of a progressor as a patient in whom a change in at least 1 grade in at least 1 SI joint was observed. According to this definition, 11.1% of the patients were defined as progressors and only 5.8% as regressors. If we define the "true" percentage of progression as the percentage of patients who experienced worsening minus the percentage of patients who experienced improvement, the progression can be estimated as  $-0.8\%$  according to the modified New York criteria,  $+8.2\%$  for changes in the total score of the 2 SI joints of  $>0$ ,  $+5.3\%$  for changes in at least 1 grade in at least 1 SI joint, and  $+7.1\%$  for changes in at least 1 grade in at least 1 SI joint and an absolute score of  $\geq 2$  at year 2 in the worsened joint. The magnitude of true progression was always higher in the subgroup of patients with baseline radiographic structural damage.

Moreover, the evaluation of the changes in the mean total score (of the scores assigned by the 2 readers) of the 2 SI joints showed a minimal but significant worsening, with a mean  $\pm$  SD of  $0.1 \pm 0.8$  in the whole population ( $P < 0.001$ ). Possible scores ranged from  $-8$  (total disappearance at 2 years of a baseline bilateral grade 4) to  $+8$  (appearance at 2 years of a bilateral grade 4 in a patient with baseline normal joints [bilateral grade 0]). This worsening was more pronounced in the patients with nonradiographic axial SpA at baseline (mean  $\pm$  SD  $0.2 \pm 0.7$ ;  $P < 0.001$ ) than in the patients with radiographic axial SpA at baseline (mean  $\pm$  SD  $0.0 \pm 0.8$ ;  $P = 0.10$ ). Because of the previously demonstrated poor interreader reliability (22), we performed this analysis separately for each reader. The observed changes for reader 1 versus reader 2 were  $+0.2 \pm 0.9$  versus  $+0.1 \pm 0.9$ ,  $+0.2 \pm 0.9$  versus  $+0.1 \pm 0.9$ , and  $+0.0 \pm 1.1$  versus  $-0.1 \pm 0.9$  in the entire population, the patients with nonradiographic axial SpA at baseline, and the patients with radiographic axial SpA at baseline, respectively.

**Predisposing factors for structural progression.** The main analysis was of the switch from nonradiographic to radiographic axial SpA based on the

**Table 2.** Radiographic progression during the 2-year follow-up period with regard to baseline and 2-year characteristics in patients with recent-onset (<3 years) axial SpA\*

	Radiographic progression		P†
	Yes (n = 16)	No (n = 310)	
<b>Baseline characteristics</b>			
Age, mean ± SD	30.0 ± 10.2	34.8 ± 8.6	0.02
Sex, % male	38	41	0.98
Smokers, %	56	32	0.08
HLA-B27 positive, %	94	56	0.006
CRP, mg/liter	8.3 ± 11.5	6.2 ± 13.5	0.04
Inflammation of the SI joints on MRI, %	94	23	<0.001
BASDAI, mean ± SD	43.4 ± 18.5	45.0 ± 19.5	0.66
<b>2-year characteristics</b>			
BASDAI AUC, mean ± SD	37 ± 21	39 ± 18	0.57
ASAS NSAID index AUC, mean ± SD	35 ± 22	40 ± 34	0.93
Months of anti-TNF therapy, mean ± SD	3.3 ± 6.7	4.9 ± 8.3	0.49

\* Radiographic progression was defined as a switch from nonradiographic axial spondyloarthritis (SpA) (not fulfilling the modified New York criteria for structural damage) at baseline to radiographic axial SpA (fulfilling the modified New York criteria for structural damage) at 2 years. CRP = C-reactive protein; SI = sacroiliac; MRI = magnetic resonance imaging; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASAS = Assessment of SpondyloArthritis international Society; NSAID = nonsteroidal antiinflammatory drug; AUC = area under the curve; anti-TNF = anti-tumor necrosis factor.

† By chi-square test for binary variables and Student's *t*-test or Mann-Whitney Wilcoxon test for continuous variables.

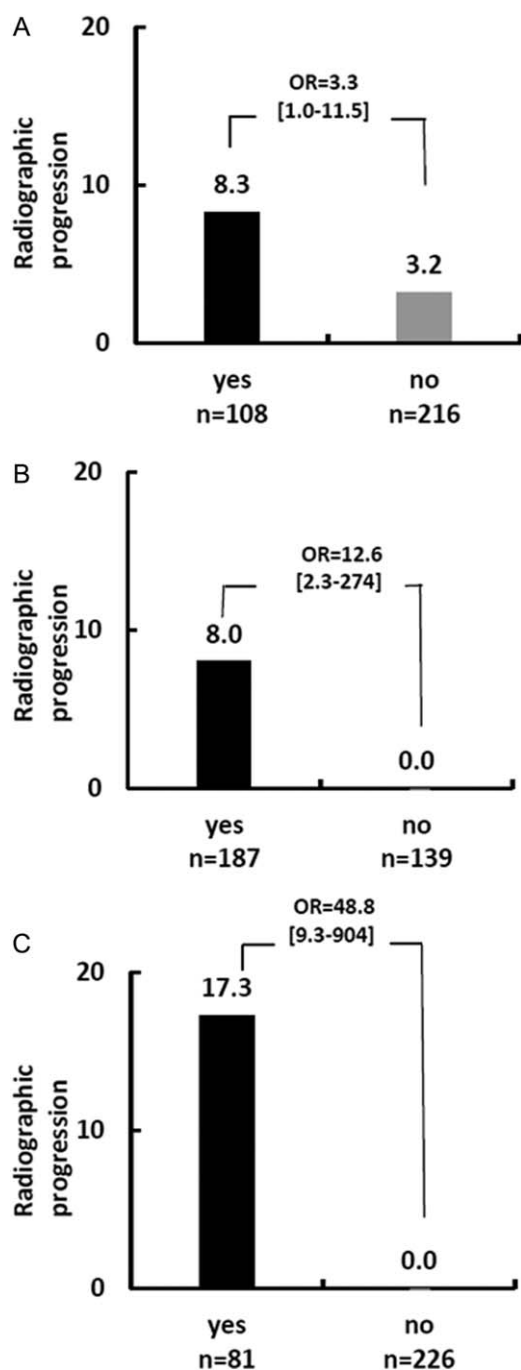
modified New York criteria. Table 2 summarizes the findings of the univariate analyses. Multiple logistic regression identified 3 variables: smoking status, HLA-B27 positivity, and inflammation observed on MRI of the SI joint (Figure 2). The percentage of patients who switched from nonradiographic axial SpA to radiographic axial SpA was 8.3% versus 3.2% for smokers at baseline versus nonsmokers at baseline (odds ratio [OR] 3.3 [95% confidence interval (95% CI) 1.0–11.5]), 8.0% versus 0.0% for HLA-B27-positive patients versus HLA-B27-negative patients (OR 12.6 [95% CI 2.3–274]), and 17.3% versus 0.0% for patients with inflammation of the SI joints on MRI at baseline versus those without inflammation of the SI joints on MRI at baseline OR 48.8 (95% CI 9.3–904).

In order to check the validity of the observed results, we planned to perform a similar analysis defining the dependent variable as the switch from radiographic axial SpA to nonradiographic axial SpA. This analysis was not performed, however, because the number of patients was too small (only 7 of 123 patients experienced improvement).

The analysis defining radiographic progression as a worsening of at least 1 grade in at least 1 SI joint identified HLA-B27 positivity, positive findings on MRI, and the presence of baseline structural damage of the SI joint on radiographs of the pelvis as predisposing factors for radiographic progression (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web

site at <http://onlinelibrary.wiley.com/doi/10.1002/art.39666/abstract>). It should be noted that in the univariate analysis, there was a trend toward statistical significance for the variable “current smoker at baseline” ( $P = 0.057$ ). The percentage of progressors was 14.1% versus 6.9% for HLA-B27-positive patients versus HLA-B27-negative patients, 20.4% versus 6.4% for patients with positive findings on MRI versus those without positive findings on MRI, and 21.9% versus 7.4% for patients with radiographic structural damage versus those without radiographic structural damage according to the modified New York criteria. For this definition of change, we also performed an analysis defining radiographic regression as an improvement of at least 1 grade in at least 1 SI joint. According to this analysis, 26 of the 449 patients were considered regressors. This analysis identified only the variable “baseline structural damage of the SI joint on pelvic radiograph” as a predisposing factor, with an OR of 2.5 (95% CI 1.03–6.16) ( $P = 0.043$ ). The percentage of regressors was 11.4% versus 3.7% in the group with abnormal radiographic structural damage at baseline versus the group without abnormal radiographic structural damage at baseline.

The analysis defining radiographic progression as a worsening of at least 1 grade in at least 1 SI joint and a final absolute grade of at least 2 in the worsened joint identified the same predisposing factors (HLA-B27, inflammation of the SI joints on MRI, and baseline



**Figure 2.** Risk of radiographic progression in the sacroiliac joint (SIJ) after a 2-year follow-up period in patients with recent-onset axial spondyloarthritis (SpA) with regard to baseline parameters. Radiographic progression was defined as a switch from nonradiographic axial SpA to radiographic axial SpA according to the modified New York criteria. **A**, Smoking status at baseline. **B**, HLA-B27 positivity. **C**, Inflammation (subchondral bone edema according to the Assessment of SpondyloArthritis international Society/Outcome Measures in Rheumatology recommendations) of the SI joints on magnetic resonance imaging (MRI) at baseline, determined by a central reading procedure. Bars show the percent of patients. OR = odds ratio (with 95% confidence interval shown in brackets).

structural damage) (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.39666/abstract>). The percentage of progressors was 11.6% versus 5.2% for HLA-B27-positive patients versus HLA-B27-negative patients, 17.8% versus 4.2% for patients with inflammation of the SI joints on MRI versus patients without inflammation of the SI joints on MRI at baseline, and 20.3% versus 4.9% for patients with structural damage versus patients without structural damage at baseline.

Finally, the multivariate analysis of the mean changes in the total score (of the scores assigned by the 2 readers) of the 2 SI joints identified only 2 variables as predisposing factors to radiographic progression: HLA-B27 positivity and baseline MRI positivity. HLA-B27 positivity was associated with an increase of 0.41 in the total score ( $P = 0.014$ ), and inflammation of the SI joints observed on MRI was associated with an increase of 1.03 in the total score ( $P < 0.001$ ).

## DISCUSSION

This study suggests that structural progression does occur during 2 years of follow-up in early axial SpA, but it is quite small and is only observed in a small number of patients. Our findings indicate that the total SI joint score and/or a change of at least 1 grade are the most sensitive definitions of progression. Moreover, this study also suggests that genetic factors (e.g., HLA-B27 positivity), environmental factors (e.g., smoking status), and inflammation (e.g., inflammation of the SI joints observed on MRI) are independent predictors of radiographic progression in the SI joint in early axial SpA.

The results regarding the percentage of patients switching from nonradiographic axial SpA to radiographic axial SpA (4.9%) and from radiographic axial SpA to nonradiographic axial SpA (5.7%) could suggest that the observed changes were related to a measurement error due to the poor intra- and interreliability of this outcome measure (22) and not to true structural progression of the disease. However, our findings provide evidence of a true progression rate. The results found using the other definitions of progression support the notion of real progression (e.g., worsening in total SI joint score [in 20.9% of patients] versus improvement in total SI joint score [in 12.7% of patients] and changes of at least 1 grade in at least 1 SI joint [11.1% progressors versus 5.8% regressors]). In addition, the difference in mean change in total score was highly significant (mean  $\pm$  SD  $0.1 \pm 0.8$ ;  $P < 0.001$ ). Moreover, similar findings have been reported in other cohorts (24). In

the German Spondyloarthritis Inception Cohort (GESPIC), the percentage of patients with a change in at least 1 grade in at least 1 SI joint was 16.8% and 6.3% for the progressors and regressors, respectively (25).

It should be noted that the rate of progression observed in the DESIR cohort was very low. For example, 300 of the 449 patients evaluated had no change at all in the total SI joint score. Despite the fact that we have seen that there are several arguments in favor of the existence of true progression, it has to be recognized that the relatively high number of regressors makes the evaluation of the true rate of progression challenging. Our findings suggest that progression is a true phenomenon and that regression might reflect measurement error.

The results of the present study indicate that genetic factors (HLA-B27 positivity), environmental factors (smoking status), and inflammation (positive findings on MRI) could be considered independent factors for subsequent structural progression. Moreover, the analyses conducted in the entire baseline population (including patients with radiographic structural damage and those with nonradiographic structural damage) suggest that the presence of baseline structural damage is also a predisposing factor of structural progression.

The presence of objective signs of inflammation (either an abnormal CRP level or the presence of subchondral bone edema at the SI joint observed on MRI) have previously been reported as predisposing factors for subsequent radiographic progression in the SI joint (26). Our study failed to show a clear relationship between an abnormal CRP level at baseline and radiographic progression. Such a relationship was previously reported in the German cohort, where MRIs of the SI joint were not available (25). In our study, the relationship between the presence of inflammation on MRI and radiographic progression was very high, suggesting a very low risk of radiographic structural progression when no subchondral bone edema was observed on MRI of the SI joint.

A cross-sectional study of the DESIR cohort has previously emphasized the link between HLA-B27, radiographic structural damage, and the presence of subchondral bone edema observed on MRI of the SI joints (27). Moreover, the risk of structural progression has been reported to be particularly high in the case of the coexistence of HLA-B27 positivity and inflammatory lesions of the SI joint in the Leeds cohort (26). The findings of the present study support this link, since HLA-B27 positivity and inflammatory lesions of the SI joint on MRI were considered to be independent factors for structural progression. Objective signs of inflamma-

tion in SpA have also been reported as predisposing factors for anti-TNF treatment response, especially in patients with nonradiographic axial SpA (12,14,15).

Our study also indicates that smoking might be an independent factor predisposing to subsequent structural progression. In the DESIR cohort, the cross-sectional analysis performed on the baseline data suggested a link between smoking status and both the activity and severity of the disease (28). Smoking has also been reported to be related to the risk of structural progression at the level of the spine in the GESPIC cohort, with a potential dose-related effect (29) (i.e., the percentage of progressors defined by a change in the modified Stoke AS Spine Score of at least 2 points was 10.1%, 18.6%, and 28.6% in nonsmokers, those who smoked  $\leq 10$  cigarettes a day, and those who smoked  $> 10$  cigarettes a day, respectively). It should be noted that in the field of axial SpA, smoking has also been found to be related to a high incidence of the disease (30) and a poor response to biologic agents (31).

Findings related to the baseline factors predisposing to subsequent structural progression should be interpreted with caution, since they were determined in a very small number of patients. For example, only 16 patients switched from a nonradiographic to a radiographic status according to the modified New York criteria.

Finally, the presence of baseline structural damage was identified as an important predisposing factor of subsequent structural progression when analyses were performed in the entire population (i.e., in patients with baseline radiographic or nonradiographic structural damage) (see Supplementary Tables 1 and 2, available on the *Arthritis & Rheumatology* web site at <http://onlinelibrary.wiley.com/doi/10.1002/art.39666/abstract>). Such findings are consistent with previous data in rheumatology. For example, the presence of syndesmophytes is an important predisposing factor of subsequent radiographic structural progression at the level of the spine in axial SpA (32); similarly, the presence of baseline erosion in rheumatoid arthritis is a strong predictor of subsequent radiographic progression (33). Our study has some limitations. The relatively short duration of follow-up (2 years) could be considered a weakness of this study, since longer follow-up might be required to detect structural progression (34). However, the short duration could be also seen as a strength, since despite this short time period, this study demonstrated a small but true structural progression.

The findings of the present study (a low rate of progression after a 2-year follow-up period) do not confirm the usual 10% rate (i.e., 10% of patients with non-



radiographic structural damage will switch to radiographic structural damage after 2 years of follow-up) that is frequently mentioned in reviews (35). The low rate of progression observed in the present study has recently been confirmed in a population-based cohort study, with 6.4%, 17.3%, and 26.4% of patients switching from nonradiographic to radiographic disease after 5, 10, and 15 years of follow-up, respectively (36).

The relatively high number of missing values could also be considered a limitation. In our study, only 449 of the 708 patients enrolled were evaluated, mainly due to missing images. However, the similarity in the baseline clinical presentation between the 2 groups (the ones for whom we had a complete data image set and the ones for whom images were missing) is evidence that our results are valid and interpretable.

Our study also has many strengths, especially the high number of patients evaluated and the quality of the reading performed by 2 independent, trained readers. Additional studies with a longer follow-up period and studies in other cohorts of patients are needed to confirm these findings. Our findings also indicate the need for translational research studies to investigate the underlying mechanisms of radiographic progression in SpA.

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