Axial Psoriatic Arthritis: Update on a Longterm Prospective Study

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ABSTRACT. ***Objective.*** To evaluate changes in symptoms, spinal mobility, and radiographic features in patients with axial psoriatic arthritis (AxPsA).

Methods. Patients with AxPsA were identified from the University of Toronto Psoriatic Arthritis clinic database. Axial symptoms, metrology, and radiographic features at study entry were compared to 5-year and 10-year followup assessments. Data were analyzed using continuity adjusted McNemar's test, an exact binomial test, or logistic regression.

Results. Of 297 patients (mean age 42.5 yrs, PsA duration 8 yrs) in the study, 56% had axial symptoms, 43% had radiographic evidence of sacroiliitis, and 13% had syndesmophytes at entry. The number of patients with neck/back pain, neck/back stiffness, and clinical sacroiliitis declined significantly at both 5- and 10-year followup periods. There was a significant increase in the number of patients with restricted cervical spinal mobility at both 5- and 10-year visits and significant reduction in lateral flexion at both timepoints. At 5 (10) years, of those without sacroiliitis at baseline, 36.6% (51.7%) developed at least grade 2 sacroiliitis; 46.5% (52.0%) of those who presented with grade 2 progressed to a higher grade; and 15.6% (25.0%) with grade 3 progressed to grade 4 sacroiliitis. Of the patients without cervical/thoracic/lumbar syndesmophytes at study entry, 11%/16%/14% (14%/21%/20%) developed syndesmophytes in these regions at 5 (10) year followup. Similar results were obtained when analyses were restricted to patients satisfying radiographic criteria alone.

Conclusion. Over a 10-year period, patients with AxPsA had improvement in neck and back pain, but lateral spinal flexion and cervical mobility deteriorated. (First Release Nov 1 2009; J Rheumatol 2009;36:2744–50; doi:10.3899/jrheum.090412)

Key Indexing Terms:
PSORIASIS PSORIATIC ARTHRITIS SPONDYLITIS
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Psoriatic arthritis (PsA) affects both peripheral and axial joints. Depending on the definition used 25%–70% of patients with PsA have axial involvement (AxPsA)[1]. However, there are few longterm studies on the course of spondylitis in general, and AxPsA in particular[2]. Two decades ago, we reported a prospective study on AxPsA[3]. Based on that study, we concluded that although patients with AxPsA have radiographic progression of their disease, this remains clinically silent and does not compromise spinal mobility[3]. However, that study was conducted on only 52 subjects who were followed for a mean duration of only 57 months. We therefore sought to investigate the progression of spinal disease in a larger cohort of subjects with longer followup enrolled at the University of Toronto PsA clinic. Specifically, we aimed to determine if on longterm followup there are changes in symptoms, spinal mobility measures, and radiographic signs in patients with AxPsA.

MATERIALS AND METHODS

The study was conducted at the University of Toronto PsA clinic. This open dynamic cohort was established in 1978. Patients are entered into the cohort if they have an inflammatory arthritis (peripheral or axial) in the presence of psoriasis[4]. Patients are assessed every 6–12 months according to a standard protocol that includes a complete history, physical examination (including detailed assessment of peripheral joints and spine), laboratory evaluation, radiographic evaluation of hands, feet, pelvis, cervical, thoracic and lumbar spine (every 2 years), and patient questionnaires on function, fatigue and quality of life[4]. The metrologic indices and questionnaires have been modified periodically as new validated methods have become available. Data are tracked on a computerized Oracle® database. The study

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For the purposes of this study, AxPsA was defined according to 2 criteria:

1. Clinical AND/OR radiographic evidence of AxPsA (AxPsA-CR): (a) Presence of psoriasis, and (b) Clinical criteria: (i) inflammatory neck/back pain and/or stiffness, or (ii) clinical sacroiliitis, and (c) Radiographic criteria: (i) presence of (possibly unilateral) sacroiliitis (as defined by grades 2–4 of the New York criteria on pelvic radiographs), and/or (ii) marginal or paramarginal syndesmophytes (cervical, thoracic, or lumbar)[5].
2. Radiographic evidence of AxPsA (AxPsA-R): (a) Presence of psoriasis, and (b) Radiographic criteria as above.

Inflammatory neck/back pain was defined as neck/back pain that is made worse with inactivity and improves with exercise. Morning stiffness was defined as the presence of stiffness in the neck/back lasting at least 30 minutes following periods of prolonged inactivity. Clinical sacroiliitis was recorded by either the Gaenslen test or the Patrick-FABER test or by direct pelvic compression[6]. Marginal syndesmophytes were recorded if the vertebral ossifications arose from the edge of the vertebral body and formed a fine vertical bridge, and paramarginal syndesmophytes were described when the ossification arose away from the edge of the vertebra and was broad and coarse[7-9]. Presence of either classical and/or paramarginal syndesmophytes at cervical/thoracic/lumbar vertebrae was considered to represent the presence of "syndesmophytes" at these regions of the spine. Syndesmophytes were distinguished from osteophytes in that the latter, which originate from the cartilaginous endplate in response to degeneration of the disc, are wider, horizontally oriented, and are associated with narrowed disc spaces[8]. Paramarginal syndesmophytes were also distinguished from diffuse idiopathic skeletal hyperostosis (DISH) in that the latter condition occurs in 4 or more consecutive vertebrae, involves primarily the right side of the thoracic spine, and is associated with normal sacroiliac joints[10]. All radiographs were read by consensus of at least 2 rheumatologists.

The first criteria (AxPsA-CR) were used to mirror the work carried out in our previous study[3]. The second criteria (AxPsA-R) were used because we wanted to investigate whether the results remain unchanged if clinical symptoms and signs are ignored, given the poor sensitivity and specificity of the clinical criteria[11,12]. We thus carried out 2 analyses. The first analysis included patients satisfying AxPsA-CR at their initial assessment. For the second study we selected patients satisfying AxPsA-R at their initial assessment as well as those satisfying the criteria at a later assessment, taking the first assessment with radiographic features of spinal disease to be the baseline assessment. Thus, the first study is a followup report on our previous study and used clinical symptoms/signs as described[3]. The second was a similar study using radiographic criteria alone. Here, the currently used definition of inflammatory axial pain requiring pain and stiffness is used. Pain and stiffness are not reported separately.

The following features of spinal disease were recorded at each assessment: presence of inflammatory pain and stiffness involving the cervical or thoracolumbar spine, qualitative restriction in cervical mobility defined as restriction to less than 70% on lateral flexion, measurement of thoracolumbar mobility, clinical sacroiliitis by one of 3 maneuvers described above, and radiographs of the cervical, thoracic and lumbar spine (anteroposterior and lateral views) and sacroiliac joints (anteroposterior view of the pelvis)[6]. Thoracolumbar mobility was measured by finger-to-floor distance, 10 centimeter segments test, finger-to-fibula distance, and chest expansion[13].

Statistical analysis. Data obtained at assessment at study entry were compared to a 5-year and 10-year followup assessment. However, time between assessments in the dataset is variable. Therefore, as the 5-year (10-year) followup we took the first assessment after 5 (10) years, with a cutoff at 10 (20) years. For the analysis of radiographic features we used the first assessment after 5 (10) years with complete radiographic data, with a cutoff at 10 (20) years, since radiographs are not taken at every assessment. For binary data the number of patients with and without the feature in question at study entry was tabulated against the number of patients with and without the feature at the followup assessment. For continuous data the mean values were calculated at study entry and at the followup assessment. For binary data we used an asymptotic chi-squared version of McNemar's test with a continuity correction to calculate p values, whenever the counts were all greater than 10. For smaller numbers an exact binomial test was used. For continuous data, p values were calculated using the score tests from conditional logistic regression. For the study using AxPsA-R, an additional regression analysis was performed for each feature of spondylitis to investigate differences in disease progression between patients who were diagnosed with radiographic spinal disease at their initial assessment, and those who developed the disease at a later stage. We found no evidence to suggest any differences between the 2 groups of patients, and so did not distinguish between them in the final model.

RESULTS

The number of patients and their demographic and disease characteristics are given in Table 1. In Table 1, axial symptoms require pain *and* stiffness; therefore the numbers reported are lower than if "and/or" definitions are used. If "and/or" definitions are used, of the 297 patients with AxPsA-CR 225 (75%) had axial symptoms, 167 of whom had neck pain or stiffness (56%) and 154 had back pain or stiffness (52%)[3].

We first examined changes in symptoms and signs of spinal disease between study entry and 5-year and 10-year followup assessments in patients with AxPsA-CR. Table 2 presents the data for the clinical symptoms and signs at baseline and followup for those with and without each symptom/sign at the assessment time. The number of patients with neck pain, back pain, neck stiffness, and back stiffness declined significantly at both followup periods. Similarly, the number of patients with clinical sacroiliitis declined significantly. We then examined the presence of inflammatory neck and back pain in those with AxPsA-R. At both timepoints, there was a significant decline in the number of patients with inflammatory neck pain, but not in inflammatory back pain (Table 3).

We then examined changes in spinal mobility between study entry and at 5-year and 10-year endpoints. Table 4 displays results of the change in spinal mobility in patients with AxPsA-CR. At both 5- and 10-year followup visits, the number of patients with limitation in mobility of cervical spine increased significantly. The finger-to-floor distance and three 10-cm segments did not change significantly at followup. However, finger-to-fibula distance (indicating restriction in lateral spinal flexion) and chest expansion increased significantly. In patients with AxPsA-R (212 patients) the results were similar (data not shown). At 5-year followup, there was an increase in finger-to-fibula distance (mean 2.1 cm at baseline, 2.9 cm at 5-years; $p < 0.01$) and a trend towards restriction of cervical mobility ($p = 0.07$). At 10 years, we could observe a significant increase in the finger-to-fibula distance (mean 1.9 cm at baseline, 3.5 cm at 10 years; $p < 0.001$) and a higher proportion of patients had restriction of cervical mobility ($p < 0.0001$). There was no change in chest expansion.

Table 1. Demographic and disease characteristics of patients with AxPsA at study entry. AxPsA-CR was defined by clinical AND/OR radiographic evidence of AxPsA, and AxPsA-R was defined by the presence of radiographic criteria alone (for details of criteria see text). Data are number (%) of patients or mean (standard deviation), unless specified.

Characteristics	AxPsA-CR	AxPsA-R
No. patients	297	244
Male/female	169/128	156/88
Age, yrs	42.5	43.8
Duration of psoriasis, yrs	14	16
Duration of PsA, yrs	8	9
Median (range) duration of followup, yrs	10.9 (5.1–32.7)	10.3 (5.0–28.4)
No. of actively inflamed (tender and/or swollen) joints	10.5 (9.8)	9.7 (10.0)
No. of swollen joints	3.3 (4.3)	3.4 (4.3)
No. of clinically damaged joints	4.2 (9.1)	5.1 (9.7)
No. of radiographically damaged joints	5.7 (9.4)	7.3 (9.9)
Axial symptoms	166/297 (56)	110/244 (45)
Inflammatory neck pain	122/297 (41)	92/244 (38)
Inflammatory back pain	114/297 (38)	66/244 (27)
Clinical sacroiliitis	54/282 (19)	27/227 (12)
Syndesmophytes (classical and/or paramarginal)		
Cervical	29/284 (10)	38/239 (16)
Thoracic	36/250 (14)	52/223 (23)
Lumbar	28/250 (11)	36/222 (16)
Radiographic sacroiliitis*		
Grade 2	63/285 (22)	125/240 (52)
Grade 3	47/285 (16)	55/240 (23)
Grade 4	13/285 (5)	14/240 (6)

* When asymmetric, number indicates the higher grade of sacroiliitis.

Table 2. Changes in symptoms of spinal disease between study entry and 5-year and 10-year followup for patients with AxPsA-CR at initial assessment.

Disease Characteristic	5-year Followup, n = 287				10-year Followup, n = 165			
	Entry	Followup		p	Entry	Followup		p
		Without	With			Without	With	
Neck pain	Without	125	31	< 0.001	Without	67	17	< 0.0001
	With	68	63		With	50	31	
Neck stiffness	Without	121	22	< 0.0001	Without	61	17	< 0.0001
	With	72	72		With	51	36	
Back pain	Without	138	27	< 0.0001	Without	70	19	< 0.001
	With	78	44		With	51	25	
Back stiffness	Without	130	27	< 0.0001	Without	69	16	< 0.0001
	With	80	50		With	50	30	
Clinical sacroiliitis	Without	174	10	< 0.0001	Without	105	7	< 0.01
	With	39	11		With	25	5	

Next, progression in radiographic signs of spondylitis (sacroiliitis, syndesmophytes) was examined. Table 5 shows the progression in sacroiliitis, and Table 6 progression in syndesmophytes in patients with AxPsA-CR. Of 101 patients who had no sacroiliitis, 37 (36.6%) developed either grade 2 or grade 3 sacroiliitis at 5-year followup. Of 43 patients with grade 2 sacroiliitis, 20 (46.5%) progressed to grade 3 or 4, and of 32 with grade 3 sacroiliitis, 5 (15.6%) progressed to grade 4 sacroiliitis. After 10 years of followup, of 60 patients without sacroiliitis, 31 (51.7%) developed grade 2 or 3 sacroiliitis; 13 of 25 (52%) with grade 2 sacroiliitis developed grade 3 or 4 sacroiliitis; and 4 out of 16 (25%) with grade 3 sacroiliitis progressed to grade 4 sacroiliitis. With regard to syndesmophytes, 11/16/14 patients without cervical/thoracic/lumbar syndesmophytes, respectively, at study entry developed syndesmophytes in these regions at 5-year followup (N = 183). After 10 years, 14/21/20 patients without cervical/thoracic/lumbar syndesmophytes at study entry developed syndesmophytes in these regions (N = 103). In patients with AxPsA-R, 35% of

Table 3. Changes in symptoms of spinal disease between study entry and 5-year and 10-year followup for patients with AxPsA-R at initial assessment.

Disease Characteristic	5-year Followup, n = 237				10-year Followup, n = 130			
	Entry	Followup		p	Entry	Followup		p
		Without	With			Without	With	
Inflammatory neck pain	Without	129	19	< 0.001	Without	61	13	0.04
	With	50	39		With	27	28	
Inflammatory back pain	Without	148	28	0.268	Without	69	21	1.0
	With	38	23		With	21	19	

Table 4. Changes in spinal mobility between study entry and 5-year and 10-year followup for patients with AxPsA-CR at initial assessment.

Mobility Measure	5-year Followup, n = 245				10-year Followup, n = 146			
	Entry	Followup		p	Entry	Followup		p
		Without	With			Without	With	
Cervical spine limitation	Without	134	38	0.007	Without	72	34	< 0.0001
	With	17	56		With	6	34	
	Entry	Followup			Entry	Followup		
Finger-to-floor*	9.5	9.3		0.73	8.7	9.0		0.73
10-cm segments*								
Upper	2.1	2.1		0.85	2.2	2.11		0.55
Middle	3.1	3.2		0.52	3.2	3.2		0.69
Lower	3.8	3.8		0.92	3.9	3.8		0.11
Finger-to-fibula*†	1.8	2.7		0.003	1.2	2.7		< 0.0001
Chest expansion*	5.1	5.5		0.03	5.1	5.5		0.06

* Mean (in cm); † mean of right and left.

Table 5. Changes in the right and left sacroiliac joints between study entry and 5-year and 10-year followup periods in patients with AxPsA-CR.

Radiographic Sacroiliitis	Study Entry No. Patients	5-year Followup			Study Entry No. Patients	10-year Followup		
		Grade 2	Grade 3	Grade 4		Grade 2	Grade 3	Grade 4
R sacroiliitis								
Grade 0/1	106	26	8	0	65	21	8	0
Grade 2	45	23	20	2	23	10	10	3
Grade 3	26	—	23	3	13	—	11	2
Grade 4	6	—	—	6	2	—	—	2
L sacroiliitis								
Grade 0/1	116	25	10	0	67	20	9	2
Grade 2	35	22	13	0	21	11	8	2
Grade 3	29	—	24	5	13	—	10	3
Grade 4	3	—	—	3	2	—	—	2

Table 6. Number of patients with AxPsA-CR with syndesmophytes on spinal radiographs at study entry and 5-year and 10-year followup periods.

Syndesmophytes	Study Entry, N = 183 (%)	5-year Followup, N = 183 (%)	Study Entry, N = 103 (%)	10-year Followup, N = 103 (%)
Cervical	19 (10.4)	30 (16.4)	8 (7.7)	22 (21.4)
Thoracic	26 (14.2)	42 (23)	11 (10.7)	32 (31.1)
Lumbar	18 (9.8)	32 (17.5)	7 (6.8)	27 (26.2)

those without sacroiliitis developed at least grade 2 sacroiliitis, 36% of those who presented with grade 2 progressed to a higher grade, and 13% with grade 3 progressed to grade 4 at 5 years. Of patients without cervical/thoracic/lumbar syndesmophytes, 7.8%/13.5%/11.9% developed syndesmophytes at these locations over the followup period. At 10 years, 61% (N = 85) of those without sacroiliitis developed at least grade 2 sacroiliitis, 50% of those who presented with grade 2 progressed to a higher grade, and 19% with grade 3 progressed to grade 4 sacroiliitis. As well, 16%/31%/26% of patients without cervical/thoracic/lumbar syndesmophytes developed syndesmophytes at these locations.

Further analyses in both studies showed no association between HLA-B*27 status and progression of clinical variables of spinal disease. The only suggestive association was that, of 34 patients who were HLA-B*27-positive, 6 developed lumbar syndesmophytes, whereas only 3 of the 110 patients who were HLA-B*27-negative did so ($p = 0.006$, unadjusted for multiple comparisons). There was no association between use of disease-modifying antirheumatic drugs (DMARD) and progression of clinical variables. There was also no significant difference in spinal mobility measurements in those who developed new syndesmophytes compared to those who did not.

DISCUSSION

There are few prospective longterm studies on spondyloarthritis in general and AxPsA in particular. Our previous prospective study in AxPsA on patients enrolled in the University of Toronto PsA clinic showed that although patients with AxPsA have radiological progression of their disease, it remained clinically silent and did not compromise spinal mobility[3]. However, that study was limited to only 52 patients followed for an average of 57 months. We therefore updated the information to the current study, where followup for at least 5 years was available on 297 patients and 10 years on 165 patients with a median followup duration of 10.9 years. We now show that patients develop new radiographic features on followup, but in contrast to our previous report, there is significant improvement in symptoms and signs in these patients[3]. The number of patients with inflammatory neck pain, back pain, neck stiffness, and back stiffness, and the number of patients with clinical sacroiliitis declined significantly, suggesting that, over time, symptoms related to spondylitis improve, likely due to therapeutic interventions. There was significant deterioration in the mobility of cervical spine and lateral spinal flexion, although there was improvement in chest expansion. The other measurements (finger-to-floor distance, three 10-cm segments) remained unchanged. It should be noted, however, that the finger-to-floor distance and the 10-cm segment measurements were not severely affected in these patients to begin with. We also examined patients with AxPsA defined purely on radiographic criteria, for whom similar followup was available. There were 244 patients with 5-year followup visit and 130 with 10-year followup, and the median duration of followup was 10.3 years. As noted by Queiro, *et al*, there was a high prevalence of asymptomatic axial involvement in PsA[14]. Only 45% of patients thus defined had inflammatory back/neck symptoms. Although the entry criteria are different, the results showed the same general trends, with improvement in inflammatory neck symptoms, but not in back symptoms. With regard to mobility measures, there was significant deterioration in the mobility of cervical spine and lateral spinal flexion, but not in chest expansion, finger-to-floor distance, and three 10-cm segments. Radiographic progression was also detected. There was some suggestion that HLA-B*27 may be associated with development of new lumbar syndesmophytes. Therapy with DMARD as well as presence of syndesmophytes did not affect spinal disease progression. However, very few patients experienced progression in syndesmophytes. In general, the rate of progression in the second 5-year period was not much different from that in the first, except for cervical spine mobility; the presence of cervical spine limitation at both earlier timepoints indicated that cervical spine limitation would generally be present after 10 years as well. For the finger-to-fibula distance the trend was for patients who progressed in the first time period to remain more stable in the second.

A prospective study on war veterans with ankylosing spondylitis (AS) from Toronto, Canada, having symptom duration of 38 years showed that a predictable pattern of AS emerges within the first 10 years of disease, that 74% of patients who had mild spinal restriction after 10 years did not progress to having more restriction, and 81% who had severe restriction were severely restricted within the first 10 years[15]. In another longterm study conducted in Bath, UK, that investigated the natural history of AS defined by radiographic progression, it was shown that AS is linearly progressive with about 35% change every 10 years[16]. Such studies are unavailable in AxPsA; but, given the consensus that AxPsA is milder than AS, we would expect progression of spondylitis to be slower in AxPsA[1]. Our study is in agreement with this conjecture, as there was only mild restriction to begin with and the mean change in finger-to-fibula distance was less than 2 cm over 10 years, and progression in radiographic features (sacroiliitis) was seen in only about 60% of patients even after 10 years of disease. Drug trials in AS have shown that the spinal mobility measures that are sensitive to change are lumbar lateral flexion and cervical rotation[17-19]. Similarly, this study also shows that in AxPsA, cervical rotation and lumbar lateral flexion worsen over time, despite improvement in clinical symptoms. It should be noted that while the treatment for PsA in general is directed at controlling inflammation, the majority of the patients were not treated specifically for axial arthritis.

Our study has a number of limitations. Our definition of AxPsA could be debated, as the definition of AxPsA is unresolved[1]. Since we aimed to update our previous study on AxPsA, we initially restricted the definition to the one used in that study[3]. The definition included the presence of clinical and/or radiographic evidence of spinal disease. Given the uncertainties of the definition of inflammatory back/spinal pain and the poor sensitivity and specificity of clinical signs of sacroiliitis, the inclusion of patients with symptoms and/or signs without radiographic evidence may not be appropriate[11,12]. We therefore repeated the analysis in patients defined by radiographic criteria alone. The results obtained using either set of criteria were very similar, except that when using radiographic criteria alone, an improvement in back pain could not be demonstrated. This could be because those with radiographically defined AxPsA already have more "severe" disease with radiographic damage and therefore the pain might remain persistent. Since the limitation in mobility measures was similar, we believe that for purposes of classifying AxPsA, radiographic criteria alone suffice. The methods used to measure spinal mobility (the presence or absence of limitation to cervical mobility, finger-to-floor distance, three 10-cm segments, and finger-to-fibula distance) are not the ones currently recommended. However, we have been using these measurements since the inception of the cohort in 1978 and therefore used these measures to study outcome. Since 2006, we have been using the measures found to be reliable in the INternational SPondyloarthritis Interobserver Reliability Exercise (INSPIRE) study[20].

Radiographic progression was assessed by the development of new syndesmophytes or sacroiliitis or worsening of the grade of sacroiliitis, since this information has been obtained systematically and is readily available on our database. Spinal radiographic scores, such as the Bath AS Radiographic Index (BASRI) or modified Stokes AS Spinal Score (mSASSS) were not used[21,22]. However, these indices have not been validated for AxPsA. Given the differences in radiographic features between AS and AxPsA, these scoring systems may need further modification before they are used in AxPsA[23].

We have now demonstrated in a longterm prospective study of AxPsA that, regardless of the definition used, patients with AxPsA show improvement in clinical symptoms over time. However, patients satisfying radiographic definition of AxPsA do not show improvement in back symptoms. These patients demonstrate worsening cervical and lumbar mobility and radiographic changes over time. Further studies are necessary to determine what predicts these features, and whether they affect quality of life and function in patients with AxPsA. Moreover, since there is no accepted definition of AxPsA, we propose that a definition based on radiographic criteria alone such as the one we used (AxPsA-R) is sufficient.

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