In Early Axial Spondyloarthritis, Increasing Disease Activity Is Associated with Worsening of Health-related Quality of Life over Time

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ABSTRACT. ***Objective.*** In early axial spondyloarthritis (axSpA), data are lacking about the relationship between disease activity and health-related quality of life (HRQOL). We assessed and quantified the association between change in Ankylosing Spondylitis Disease Activity Score (ASDAS) and HRQOL over time in early axSpA.

Methods. Baseline and 1-year data of patients with axSpA fulfilling the Assessment of Spondyloarthritis international Society (ASAS) classification criteria from the SPondyloArthritis Caught Early (SPACE) cohort were analyzed. Associations between change in ASDAS and in physical (PCS) or mental component summary (MCS) of the Medical Outcomes Study Short Form-36 were tested by linear regression models. Age, sex, ASAS criteria arm, and blue- versus white-collar work were tested for effect modification. Subsequently, these factors and medication were tested for confounding.

Results. There were 161 patients with axSpA [53% male, mean (± SD) age 29.7 (± 7.5) yrs, symptom duration 13.6 (± 7.2) months, HLA-B27–positive 91%, radiographic sacroiliitis 22%] who had ASDAS of 2.5 (± 1.0) and 2.0 (± 0.8), PCS of 28.4 (± 14.3) and 36.9 (± 13.1), and MCS of 48.2 (± 13.8) and 49.3 (± 12.0) at baseline and 1 year, respectively. Per unit increase in ASDAS between baseline and 1 year, PCS worsened by 9.5 points. The same level of disease activity had fewer adverse effects on physical HRQOL in women and white-collar workers.

Conclusion. To our knowledge, our data are the first to show that in a broad group of patients with early axSpA, increasing ASDAS is associated with worsening of physical HRQOL, but not mental HRQOL, over time. (J Rheumatol First Release March 15 2018; doi:10.3899/jrheum.170796)

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A task force of international experts recently published recommendations for treat-to-target (T2T) in axial spondyloarthritis (axSpA) and formulated the primary goal of T2T as maximizing longterm health-related quality of life (HRQOL) and social participation[1]. To achieve these outcomes, the proposed treatment target is inactive disease, or alternatively, low disease activity by Ankylosing Spondylitis Disease Activity Score (ASDAS)[1].

Ankylosing spondylitis (AS, radiographic axSpA) has a substantial effect on HRQOL, and increased disease activity influences HRQOL adversely[2,3,4]. Similar data of patients with early axSpA are lacking.

Data from patients with AS cannot be extrapolated to patients with early axSpA. For instance, most patients with early axSpA do not have radiographic sacroiliitis, and sex distribution is similar, whereas patients with severe AS are more often male[5,6].

Also in early axSpA, patient changes in disease activity over time seem to be associated with changes in HRQOL. In

the ABILITY-1 trial in patients with nonradiographic axSpA, an improvement in disease activity as measured by ASDAS was associated with an improvement in HRQOL[7]. However, patients in the ABILITY-1 trial had a relatively long symptom duration (8-10 yrs), had exclusively nonradiographic axSpA, and a high level of disease activity necessitating treatment with a tumor necrosis factor inhibitor.

It is rational to assume that the association between changes in disease activity and changes in HRQOL found in AS also extends to patients with early axSpA. However, it is unclear whether this association is of similar magnitude in relevant subgroups of axSpA. The association may, for instance, be different in males and females, or in those with sedentary jobs versus physically demanding ones. For example, physically demanding jobs are associated with greater functional limitations in patients with AS and have been reported to reduce HRQOL[8,9]. Further, women have higher disease activity and worse physical functioning compared to men[10].

To implement T2T strategies in patients with early axSpA, more information is needed about the association between disease activity and HRQOL in these patients and relevant subgroups in daily clinical practice. Therefore, the objective of our study was to assess and quantify the association between the change in disease activity and in HRQOL in a broad patient population with early axSpA, and in relevant subgroups over time.

MATERIALS AND METHODS

Baseline and 1-year data were analyzed from the SPondyloArthritis Caught Early (SPACE) cohort, which has been described in detail previously[5]. In brief, the SPACE cohort is an ongoing inception cohort that includes patients > 16 years of age with chronic back pain (persisting ≥ 3 mos and ≤ 2 yrs, and onset < 45 yrs). For our current study, the database was locked on March 31, 2017. Patients were recruited from multiple European sites in the Netherlands, Norway, Italy, and Sweden. The SPACE cohort has been approved by the medical ethical committee of the Leiden University Medical Center (P08.105). Informed consent forms from all study participants had been obtained beforehand.

All study participants underwent a full examination as part of the study protocol at baseline and 1 year, consisting of medical history, physical examination, laboratory assessments [C-reactive protein (CRP), erythrocyte sedimentation rate], and questionnaires. At baseline, HLA-B27 was tested, and magnetic resonance imaging (MRI) and radiography of the sacroiliac joints and spine were obtained. The treating rheumatologist provided the diagnosis using local reading of imaging and indicated the level of confidence regarding the diagnosis on a numerical scale (0, not confident at all; 10, very confident). For classification, central reading was performed by 3 readers per imaging modality. Images were considered to be positive for sacroiliitis when ≥ 2 readers agreed using the modified New York criteria for radiographs[11] and Assessment of Spondyloarthritis international Society (ASAS) definition for a positive MRI of the sacroiliac joints[12]. Patients diagnosed with axSpA were classified according to the ASAS axSpA criteria[13] to the clinical arm (HLA-B27 plus 2 SpA features) if patients fulfilled the clinical arm exclusively, and to the imaging arm (sacroiliitis plus 1 SpA feature) if patients fulfilled either the imaging arm alone or both arms.

Disease activity had been assessed by ASDAS (CRP-based)[14,15]. The ASDAS level was categorized as inactive disease (< 1.3), moderate disease activity (< 2.1), high disease activity (≤ 3.5), and very high disease activity (> 3.5)[16].

HRQOL was assessed by the Medical Outcomes Study Short Form-36 (SF-36)[17]. Eight subscales were calculated and transformed into scale scores, with numeric scales ranging from 0 (worst health) to 100 (best health) after recoding and recalibration. These scale scores were weighted according to sex, age, and country[18,19]. Because no Italian age- and sex-matched scores were available, Dutch age- and sex-matched scores were used for all Italian patients (n = 26). The adjusted scores were used to calculate 2 summary measures, the physical (PCS) and mental component summary (MCS). In rare cases (n = 6) of a negative PCS, scores were set to 0. The PCS and MCS were transformed to compare the scores to the general population mean of 50. Higher scores indicated better HRQOL[20].

The patient's job type was determined using a multiple-choice question with the following options: (1) management position (e.g., director, manager, member of the board of directors); (2) professional specialist (e.g., engineer, teacher, nurse practitioner, systems analyst); (3) commercial profession (e.g., representative, agent, clerk, salesperson); (4) technical support (e.g., laboratory technician, legal officer, information technology); (5) administrative support (e.g., secretary, invoice administration); (6) service profession (e.g., security officer, janitor); and (7) operator or laborer (e.g., assembler, mechanic, carpenter, builder). Answer options 1, 2, 3, 4, and 5 were considered to reflect "white-collar workers," and answer options 6 and 7 were considered to reflect "blue-collar workers."

The use of nonsteroidal antiinflammatory drugs, conventional synthetic disease-modifying antirheumatic drugs (csDMARD), and biological (b-) DMARD were separately categorized as "no medication," "stopped using medication," "started using medication," and "continued use of medication" between baseline and 1 year. Twelve patients were already treated with csDMARD and 1 patient with bDMARD at baseline because of inflammatory bowel disease, uveitis, dactylitis, peripheral arthritis, psoriasis, or a combination thereof.

Analysis. Patients diagnosed with axSpA and fulfilling the ASAS classification were included in the analysis. Categorical variables were described as frequencies (proportions) and continuous variables as means (± SD). Linear regression models were built with change in ASDAS (ΔASDAS) as the independent variable and ΔPCS or ΔMCS as dependent variables between baseline and 1 year. Age at baseline, sex, ASAS axSpA subclassification (imaging vs clinical arm), and job type (white vs blue collar) at baseline were tested for effect modification 1 by 1 in each model, and stratification of the models was conducted if effect modification was found (p value for the interaction term < 0.10). To prevent spurious effects because of small sample sizes, stratification was only performed if each subgroup consisted of ≥ 15 patients. Subsequently, these factors and treatments were tested for confounding (crude regression coefficient changed by > 10% after adding each factor) and models were adjusted for each confounder. Data were analyzed using STATA SE V.14 (Statacorp). P values < 0.05 were considered statistically significant.

RESULTS

In total, 361 patients had baseline and 1-year data. Of the 361 patients, 107 either did not have an axSpA diagnosis, the diagnosis was missing (n = 7), or they did not fulfill the classification criteria after diagnosis (n = 73). ASDAS could not be calculated in 12 patients, and 1 patient did not fill out the SF-36.

Of the 161 patients with axSpA, 53% were male, mean (SD) age was of 29.7 (7.5) years, and mean symptom duration was 13.6 (7.2) months (Table 1). Patients had on average 5 SpA features, including imaging and HLA-B27 carriership. Mean level of confidence in diagnosis was 8 (± 2). Patients had a mean ASDAS of 2.5 (± 1.0) at baseline and 2.0 (± 0.8) at 1 year. At baseline, 11% of the patients had inactive disease, 27% moderate disease activity, 48%

Table 1. Baseline characteristics of patients with axSpA in the SPACE cohort included in the analysis. Values are mean ± SD or n (%) unless otherwise specified.

Characteristics	n = 161
Age at inclusion, yrs	29.7 ± 7.5
Male	86 (53)
Symptom duration, mos	13.6 ± 7.2
IBP	135 (84)
Positive family history	84 (52)
Enthesitis[a]	44 (27)
Dactylitis[a]	14 (9)
Peripheral arthritis[a]	36 (22)
Good response to NSAID[b]	99 (62)
Uveitis[a]	28 (17)
Psoriasis[a]	25 (16)
IBD[a]	8 (5)
HLA-B27–positive	146 (91)
Elevated ESR, mm/CRP, mg/l	73 (45)
X-SI–positive	36 (22)
MRI-SI–positive	69 (43)
No. SpA features[c]	5.0 ± 1.7
Confidence in axSpA diagnosis by rheumatologist	8.1 ± 2.0
ASAS classification	
Clinical arm only	76 (47)
Imaging arm only	22 (14)
Both arms	63 (39)
Use of NSAID	127 (79)
Use of csDMARD	12 (8)
Use of bDMARD	1 (1)

[a] Past or present condition, either diagnosed or confirmed by a physician. [b] Back pain not present or was much better 24–48 hours after a full dose of NSAID. [c] Included HLA-B27 testing and imaging. axSpA: axial spondyloarthritis; SPACE: SPondyloArthritis Caught Early; IBP: inflammatory back pain; NSAID: nonsteroidal antiinflammatory drugs; IBD: inflammatory bowel disease; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; X-SI: radiograph of sacroiliac joints; MRI-SI: magnetic resonance imaging of sacroiliac joints; ASAS: Assessment of Spondyloarthritis international Society; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; bDMARD: biological DMARD.

high disease activity, and 14% very high disease activity (Table 2).

The mean (± SD) PCS was 28.4 (± 14.3) at baseline and increased to 36.9 (± 13.1) at 1 year (Table 2). The MCS remained constant between baseline and 1 year [48.2 (± 13.8) and 49.3 (± 12.0), respectively] and was comparable to the general population (MCS = 50). No correlation was found between the change in ASDAS and the change in MCS ($r = –0.05$, $p = 0.54$). Therefore, the regression analyses focused on PCS only.

Between baseline and 1 year, 1 unit ΔASDAS led on average to a 9.5-point change in PCS (Figure 1). The SF-36 subscales role physical, bodily pain, and physical functioning changed the most compared to other subscales between baseline and 1 year per unit change of the ASDAS (Table 3; $\beta = –24.5$, 95% CI –30.1 to –18.8; $\beta = –17.2$, 95% CI –19.9 to –14.5; and $\beta = –12.6$, 95% CI –15.2 to –10.1, respectively).

Table 2. Characteristics of patients with axSpA at baseline and 1 year (n = 161). Values are mean ± SD unless otherwise specified.

Characteristics	Baseline	1 Year
BASDAI	4.0 ± 2.1	3.1 ± 2.0
CRP	7.5 ± 10.5	4.7 ± 6.6
ASDAS	2.5 ± 1.0	2.0 ± 0.8
ASDAS, n (%)		
Inactive disease, < 1.3	17 (11)	37 (23)
Moderate disease activity, < 1.2	44 (27)	64 (40)
High disease activity, ≤ 3.5	78 (48)	50 (31)
Very high disease activity, > 3.5	22 (14)	10 (6)
SF-36		
PCS	28.4 ± 14.3	36.9 ± 13.1
MCS	48.2 ± 13.8	49.3 ± 12.0
BASFI	2.3 ± 2.2	1.6 ± 2.0

axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; ASDAS: Ankylosing Spondylitis Disease Activity Score; SF-36: Medical Outcomes Study Short Form-36; PCS: physical component summary; MCS: mental component summary; BASFI: Bath Ankylosing Spondylitis Functional Index.

The association between ΔASDAS and ΔPCS was modified by sex ($p = 0.056$ for the interaction term) and job type ($p = 0.077$; Table 4). Information about profession was provided by 79 patients out of 129 who worked at baseline (61.2%). The association between ΔASDAS and ΔPCS was less strong in women ($\beta = –7.7$, 95% CI –9.9 to –5.5) than in men ($\beta = –11.0$, 95% CI –13.7 to –8.4), and in white-collar workers ($\beta = –9.6$, 95% CI –12.3 to –7.0) than in blue-collar workers ($\beta = –15.6$, 95% CI –23.0 to –8.3). No effect modification or confounding was found by age or ASAS classification arm (clinical or imaging arm). Also, no confounding by treatment was found.

In 102 out of 161 patients, 2-year data were also available. Similar results were found for ASDAS, PCS, and MCS at both baseline and 1 year for these patients as compared to patients with 1-year data only. Over 2 years, ASDAS (1.9 ± 0.9) and PCS (39.1 ± 12.2) improved slightly, and MCS remained stable (50.1 ± 11.2). Most importantly, the association between ΔASDAS and ΔPCS was similar between baseline and 1 year ($\beta = –9.8$, 95% CI –12.2 to –7.5), and 1-year and 2-year followup ($\beta = –8.9$, 95% CI –11.1 to –6.7).

DISCUSSION

Compared to the general population, patients with early axSpA are limited in physical HRQOL, but not in mental HRQOL. Further, our data indeed confirm that in a broad group of patients with early axSpA in clinical care, an increase in disease activity is associated with a decline in physical HRQOL over time. Moreover, to our knowledge, we have quantified for the first time the association between ASDAS and HRQOL. Our results confirm the hypothesis used for T2T, in that it is important to aim for lower disease activity in patients with early axSpA to improve HRQOL.

The most important finding of our study is that the

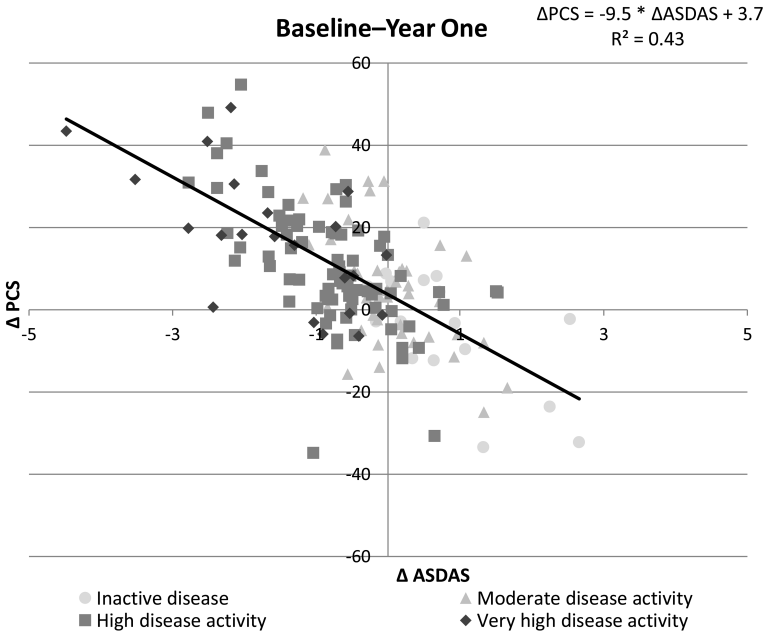

Figure 1. Scatterplot of the correlation between change in ASDAS (ΔASDAS) and change in PCS (ΔPCS) between baseline and 1 year, with the disease state at baseline indicated. ASDAS: Ankylosing Spondylitis Disease Activity Score; PCS: physical component summary.

Table 3. Association between change in disease activity and change in the subscales of the SF-36 between baseline and 1 year (n = 161).

ΔSubscales	ΔASDAS		
	β	95% CI	Adjusted R^2
Physical functioning	–12.6	–15.2 to –10.1	0.375
Role physical	–24.5	–30.1 to –18.8	0.313
Bodily pain	–17.2	–19.9 to –14.5	0.498
General health	–5.7	–8.2 to –3.3	0.113
Vitality	–7.8	–10.6 to –4.9	0.148
Social functioning	–7.3	–10.4 to –4.2	0.112
Role emotional	–9.4	–15.7 to –3.0	0.044
Mental health	–4.9	–7.0 to –2.8	0.113

SF-36: Medical Outcomes Study Short Form-36; ASDAS: Ankylosing Spondylitis Disease Activity Score.

Table 4. Association between change in disease activity and change in PCS between baseline and 1 year (n = 161).

ΔASDAS	ΔPCS			
	n	β	95% CI	p
Model stratified for sex, p = 0.056 for the interaction				
Male	86	–11.0	–13.7 to –8.4	< 0.001
Female	75	–7.7	–9.9 to –5.5	< 0.001
Model stratified for job type, p = 0.077 for the interaction[a]				
White collar	61	–9.6	–12.3 to –7.0	< 0.001
Blue collar	18	–15.6	–23.0 to –8.3	< 0.001

[a] 79 of 129 working patients provided information about profession. Results are corrected for age and stratified in case of effect modification (p < 0.10). PCS: physical component summary; ASDAS: Ankylosing Spondylitis Disease Activity Score.

strength of the association between disease activity and HRQOL is sex-specific and job type–specific. Knowledge is limited regarding the association in these subgroups of patients. A similar level of disease activity seems to affect HRQOL more adversely in men than in women. A possible explanation for this difference is that men and women appear to cope differently with the disease[21,22]. In addition, the differences for job type could also be explained by sex. A similar proportion of males and females had white-collar jobs (49% vs 51%, respectively). But 61% of blue-collar workers were male. Unfortunately, no separate effects for subgroups stratified on both sex and job type could be evaluated because of the small patient population in these subgroups. It is possible that physical HRQOL is more important for blue-collar workers than for white-collar workers, because good physical HRQOL enables them to do their work. Our results show that a similar improvement in disease activity is associated with more improvement in HRQOL in blue-collar workers than in white-collar workers. Thus, blue-collar workers may benefit more from decreasing disease activity. However, the observed difference between blue- and white-collar workers should be interpreted with caution because only 61.2% of all working patients provided information about their job type. Consequently, these associations require further study.

The association found between disease activity and

HRQOL may not be surprising because both ASDAS and SF-36 do contain several questions that appear similar. For instance, ASDAS includes spinal and peripheral pain questions and the SF-36 contains questions about bodily pain. However, the ASDAS is a disease-specific composite score developed and validated for axSpA and also contains CRP. The SF-36 is a generic questionnaire aimed at measuring HRQOL and includes measurements of role emotional and social functioning.

A strength of our study is the high diagnostic certainty of axSpA after a thorough diagnostic investigation in all patients. In addition, the mean values of ASDAS (baseline 2.5, 1 yr 2.0) and PCS (baseline 28.4, 1 yr 36.9) in our cohort are comparable to other axSpA cohorts. For example, in the Devenir des Spondyloarthrites Indifférenciées Récentes (DESIR) cohort, patients with early axSpA (symptom duration < 3 yrs) had a mean ASDAS of 2.6 and PCS of 41[23], and in the Herne[24] and Swiss Clinical Quality Management cohorts[25] (nonradiographic axSpA with a symptom duration > 5 yrs), the mean ASDAS ranged from 2.8 to 3.0 and PCS from 20 to 42, respectively. The ESPERANZA cohort has also found an association between the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire[26]. Because 2 different outcome measurements were used, no direct comparisons between this cohort and the SPACE cohort were possible.

Mental functioning of patients with early axSpA is comparable to that of the general population. However, even in the earliest phase of disease, patients with axSpA are already impaired in their physical HRQOL. Moreover, we showed that in a broad group of patients with early axSpA, increasing disease activity is associated with worsening in physical HRQOL over time. This finding supports the recommendation that in patients with early axSpA, inactive disease or low disease activity should be the treatment target.

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