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 is lacking about the relationship between disease activity and health-related quality of life (HRQoL). In early axSpA, we assessed and quantified the association between change in Ankylosing Spondylitis Disease Activity Score (ASDAS) and HRQoL over time.

Methods: Baseline and one-year data of axSpA patients fulfilling the ASAS classification criteria from the SPACE-cohort were analyzed. Associations between change in ASDAS and in physical (PCS) or mental component summary (MCS) of the 36-item Short Form (SF-36) were tested by linear regression models. Age, gender, ASAS criteria arm, and blue- vs. white-collar work were tested for effect modification. Subsequently, these factors and medication were tested for confounding.

Results: 161 axSpA patients (53% male, mean (SD) age 29.7 (7.5) years, mean symptom duration 13.6 (7.2) months, HLA-B27+ 91%, radiographic sacroiliitis 22%) had a mean (SD) 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 one year, respectively. Per unit increase in ASDAS between baseline and one year, PCS worsened by 9.5 points. The same level of disease activity had less adverse impact on physical HRQoL in women and white-collar workers.

Conclusion: Our data are the first to show that in a broad group of patients with early axSpA increasing ASDAS is associated with worsening in physical HRQoL, but not mental HRQoL, over time.

Key Indexing Terms: Spondyloarthritis, Severity of Illness Index, Quality of Life, Longitudinal Studies

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Running head: Disease activity-HRQoL in early axSpA

Introduction

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 being to maximize long-term health-related quality of life (HRQoL) and social participation. In order to achieve these outcomes, the proposed treatment target is inactive disease or, alternatively, low disease activity by Ankylosing Spondylitis Disease Activity Score (ASDAS) (1).

It is well-known that ankylosing spondylitis (AS, radiographic axSpA) has a substantial impact on HRQoL and that increased disease activity influences HRQoL adversely (2-4). Similar data of patients with early axSpA is 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 gender distribution is similar, while patients with severe AS are more often male (5, 6).

But also in early axSpA patients changes in disease activity over time seem to be associated with changes in HRQoL. In the ABILITY-1 trial in patients with non-radiographic axSpA an improvement in disease activity as measured by the ASDAS was associated with an improvement in HRQoL (7). However, patients in the ABILITY-1 trial had a relatively long symptom duration (8-10 years), had exclusively non-radiographic axSpA, and a high level of disease activity necessitating treatment with a tumor necrosis factor (TNF)-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 if 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 vs. physically demanding ones. For example, physically demanding jobs are associated

with greater functional limitations in AS patients and have been reported to have a negative impact on HRQoL (8, 9). Further, women have a higher disease activity and worse physical functioning compared to men (10).

In order 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 this 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 one-year data from the SPondyloArthritis Caught Early (SPACE) cohort, which has been described in detail previously (5), were analyzed. In brief, the SPACE cohort is an ongoing inception cohort that includes patients above 16 years of age with chronic back pain (CBP; persisting ≥3 months and ≤2 years, and onset <45 years). For the 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 (LUMC, P08.105). Informed consent forms from all study participants had been obtained beforehand.

All study participants underwent a full work-up as part of the study protocol at baseline and one year consisting of medical history, physical examination, laboratory assessments (C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR)), and questionnaires. At baseline, human leukocyte antigen (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 three readers per imaging modality. Images were considered to be positive for sacroiliitis when ≥2 readers agreed using the modified New York criteria (mNY) 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 + 2 SpA features) if patients fulfilled the clinical arm exclusively and to the imaging arm (sacroiliitis + 1 SpA feature) if patients fulfilled either the imaging arm alone or both arms.

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

HRQoL was assessed by the 36-item Short-Form Health Survey (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 gender, age, and country (18, 19). As no Italian age- and gender-matched scores were available, Dutch age- and gender-matched scores were used for all Italian patients (n=26). The adjusted scores were used to calculate two summary measures, the physical (PCS) and mental component summary (MSC). In rare cases (n=6) of a negative PCS scores were set to zero. The PCS and MCS were transformed in order to compare the scores to the general population mean of 50. Higher scores indicate 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 (engineer, teacher, nurse practitioner, systems analyst),

3. Commercial profession (representative, agent, clerk, sales person),

4. Technical support (lab technician, legal officer, IT),

5. Administrative support (secretary, invoice administration),

6. Service profession (security officer, janitor), and

7. Operator or labourer (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 non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biological DMARDs (bDMARDs) were each separately categorized as '*no medication*', '*stopped using medication*', '*started using medication*', and '*continued use of medication*' between baseline and one year. Twelve patients were already treated with csDMARDs and one patient with bDMARDs 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 and standard deviations (SD). Linear regression models were built with ΔASDAS as independent variable and ΔPCS or ΔMCS as dependent variable between baseline and one year. Age at baseline, gender, ASAS axSpA subclassification (imaging vs. clinical arm), and job-type (white-collar vs. blue-collar) at baseline were tested for effect modification one by one 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 due to small sample sizes, stratification was only performed if each subgroup consisted of at least 15 patients. Subsequently, these factors and in addition treatment were tested for confounding (crude regression coefficient changed by >10% after adding each factor) and models were adjusted for each confounder. Data were analysed using STATA SE V.14 (Statacorp, College Station, Texas, USA). P-values of <0.05 were considered to be statistically significant.

Results

In total, 361 patients had baseline and one-year data. Of the 361 patients, 107 did not have an axSpA diagnosis, the diagnosis was missing (n=7), or did not fulfill the classification criteria after diagnosis (n=73). The 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% was 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 (SD 2). Patients had a mean (SD) ASDAS of 2.5 (1.0) at baseline and 2.0 (0.8) at one

year. At baseline, 11% of the patients had inactive disease, 27% moderate disease activity, 48% 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 one year (***Table 2***). The MCS remained constant between baseline and one year (mean (SD) 48.2 (13.8) at baseline, 49.3 (12.0) at one year) 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 one year, one unit change in ASDAS (ΔASDAS) led on average to 9.5 points change in PCS (ΔPCS, ***Figure 1***). The SF-36 subscales role physical, bodily pain, and physical functioning changed the most compared to other subscales between baseline and one year per unit change of the ASDAS (see ***Table 3***, β=-24.5, 95%CI -30.1; -18.8, β=-17.2, 95%CI -19.9; -14.5, and β=-12.6, 95%CI -15.2;-10.1, respectively).

The association between ΔASDAS and ΔPCS was modified by gender (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 patients who worked at baseline (61.2%). The association between ΔASDAS and ΔPCS was less strong in women (β=-7.7, 95%CI -9.9; -5.5) than in men (β=-11.0, 95%CI -13.7; -8.4) and in white-collar workers (β=-9.6, 95%CI -12.3; -7.0) than in blue-collar workers (β=-15.6, 95%CI -23.0; -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, two-year data were also available. Similar results were found for ASDAS, PCS, and MCS at both baseline and one year for these patients as compared to patients with one year data only. Over two years ASDAS (1.9 (SD 0.9)) and PCS (39.1 (SD 12.2)) improved slightly and MCS remained stable (50.1 (SD 11.2)). Most importantly, the association between ΔASDAS and ΔPCS was similar between baseline and one-year (β=-9.8, 95%CI -12.2;-7.5), and one-year and two-year follow-up (β=-8.9, 95%CI -11.1;-6.7).

Discussion

Compared to the general population, patients with early axSpA are limited in physical HRQoL, but not in mental HRQoL. Furthermore, 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 treat-to-target that it is important to aim for lower disease activity in early axSpA patients in order to improve HRQoL.

The most important finding of this study is that the strength of the association between disease activity and HRQoL is gender-specific and job-type-specific. Knowledge is limited regarding the association in these subgroups of patients. A similar level of disease activity seems to impact 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 gender. A similar proportion of males and females had a white-collar job (49% vs. 51%, respectively). But 61% of blue-collar workers was male. Unfortunately, no separate effects for subgroups stratified

on both gender and job-type could be evaluated due to the small patient number 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 as 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 a surprising correlation as both ASDAS and SF-36 do contain several questions that appear similar. For instance the 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 this study is the high diagnostic certainty of axSpA after a thorough diagnostic work-up in all patients. In addition, the mean values of ASDAS (baseline 2.5, one year 2.0) and PCS (baseline 28.4, one year 36.9) in our cohort are comparable to other axSpA cohorts. For example, in the Devenir des Spondyloarthrites Indifférenciées Récentes (DESIR) cohort, early axSpA patients (symptom duration <3 years) had a mean ASDAS of 2.6 and PCS of 41 (23) and in the Herne (24) and Swiss Clinical Quality Management (SCQM) cohorts (25) (non-

radiographic axSpA with a symptom duration >5 years) 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. As two different outcome measurements were used, no direct comparisons between this cohort and the SPACE cohort were possible (26).

In summary, mental functioning of patients with early axSpA is comparable to the general population. However, even in the earliest phase of disease, axSpA patients are already impaired in their physical HRQoL. Moreover, for the first time we show 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 also in early axSpA patients inactive disease or low disease activity should be the treatment target.

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Figure legends

Figure 1: Scatterplot of the correlation between change in ASDAS (ΔASDAS) and change in PCS (ΔPCS) between baseline and one year with the disease state at baseline indicated.