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Concise report

Determinants of the patient global assessment of well-being in early axial spondyloarthritis: 5-year longitudinal data from the DESIR cohort

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Abstract

Objectives. To investigate the determinants of patient well-being over time, and the influence of age, gender and education in patients with early axial spondyloarthritis (axSpA).

Methods. Five-year data from DESIR, a cohort of early axSpA, were analysed. The outcome was the BAS-G over 5 years. Generalized estimating equations (GEE) were used to test the relationship between potential explanatory variables from five outcome domains (disease activity, physical function, spinal mobility, structural damage and axial inflammation) and BAS-G over time. Longitudinal relationships were analysed using an autoregressive GEE model. Age, gender and educational level were tested as effect modifiers or confounders.

Results. A total of 708 patients were included. Higher BASDAI questions on fatigue [β (95% CI): 0.17 (0.13, 0.22)], back pain [0.51 (0.46, 0.56)], peripheral joint pain [0.08 (0.04, 0.12)] and severity of morning stiffness [0.08 (0.03–0.13)], and higher BASFI [0.14 (0.08, 0.19)] were associated with a higher BAS-G. In the autoregressive model, the same variables except for morning stiffness were associated with a worsening in BAS-G. Age, gender and educational level were neither effect modifiers nor confounders.

Conclusion. A higher level of back pain is associated with a worsening of patient well-being, as are, though to a lesser extent, higher levels of fatigue, peripheral joint pain and physical disability. Age, gender and educational level do not have an impact on these relationships.

Key words: outcome measures, quality of life, spondyloarthritis, disability evaluation, patient attitude to health

CLINICAL SCIENCE

Introduction

Quality of life (QoL) and well-being are highly relevant outcomes for patients with axial spondyloarthritis (axSpA). Understanding how QoL or well-being is determined by other outcomes will help us achieve better QoL or well-being for the patient.

Machado *et al.* [1] proposed a framework of how the disease outcomes impact health-related QoL (HRQoL) in patients with ankylosing spondylitis, currently known as radiographic axial SpA (r-axSpA) [2]: spinal damage and inflammation together explain spinal mobility impairment; this in turn, together with disease activity, explains functional disability; the latter, again together with disease activity, explains HRQoL. This framework was based on cross-sectional analyses and did not investigate a longitudinal association between the determinants and QoL within a patient. In addition, the framework was defined in patients with established r-axSpA, leaving the question unanswered of whether the proposed framework also applies to patients in the early stages of the disease.

When tailoring patient-specific care, it is important to consider contextual factors. Contextual factors are not outcomes, but may have influence on outcomes as effect modifiers or confounders [3]. This is a relatively new concept not considered in the development of Machado's model. Personal factors that frequently are relevant contextual factors are age, gender and the patient's educational level.

In this study, we investigated the determinants of patient well-being over time and the influence of age, gender and patient's educational level on these relationships in patients with early axSpA.

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Rheumatology key messages

- The previously developed framework of outcomes in ankylosing spondylitis applies to patients with early axSpA.
- The level of back pain has the largest impact on axSpA patient well-being.
- axSpA patient's educational level, gender and age do not influence the determinants of well-being.

Methods

Study design and population

DESIR is a cohort of patients with early inflammatory back pain highly suggestive of axSpA, previously extensively described [4]. Briefly, the inclusion criteria were patients aged 18–50 years, with inflammatory back pain of >3 months and <3 years duration, and symptoms highly suggestive of axSpA according to the rheumatologist. A total of 708 patients were included and prospectively followed with clinical data collected every 6 months up to 2 years and thereafter annually up to 5 years. Radiographs of the spine and sacroiliac joints (SIJ) were performed at baseline, 2 years and 5 years. MRI of the spine and SIJ was performed in all patients at baseline and at 2 and 5 years only in patients from the nine centres in Paris. All patients with the BAS-G assessed at least once during the 5-year follow-up were included in the current study. The database used for this analysis was locked in June 2016. DESIR has been approved by the appropriate ethical committees and all patients signed the informed consent before participation.

Outcome: BAS-G

The BAS-G is a self-administered measure for the assessment of well-being [5], the construct defined as 'a person's cognitive and affective evaluation of his or her life as a whole' [6]. BAS-G was collected as a 0–10 numerical scale by asking 'how do you evaluate the effect of your disease on your general condition' with 'none' and 'very severe' as anchors (a higher BAS-G means worse well-being). BAS-G is an average of two questions regarding the previous week and the previous 6 months. For this study, only the question on the previous week was used because it represents well-being at the time of the assessment and the other patient-reported outcomes included were based on the same time frame.

Potential explanatory variables

As our interest was a framework of the disease outcomes determining the patient well-being, variables from the five outcome domains of Machado's framework (disease activity, physical function, spinal mobility, structural damage and axial inflammation) were tested as potential explanatory variables of BAS-G: (i) from the disease activity domain: the BASDAI (0–10) and its individual questions (Q1 fatigue, Q2 back pain, Q3 peripheral joint pain, Q4 enthesitis, Q5 severity of morning stiffness, Q6 duration of morning stiffness, 0–10 each), swollen joint count in 28 joints (SJC28, 0–28), tender joint count in 53 joints (TJC53, 0–159, with each joint graded 0–3; no tenderness = 0, tenderness = 1, tenderness and grimace = 2, tenderness, grimace and withdrawal = 3), enthesitis measured with the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES, 0–39) [7], CRP level (mg/l), presence of any extra-musculoskeletal manifestations (i.e. cumulative presence of any of uveitis, psoriasis or inflammatory bowel disease); (ii) the BASFI (0–10) [8] from the physical function domain; (iii) the BASMI linear definition (BASMI Linear, 0–10) [9] from the spinal mobility domain; (iv) modified New York grading (mNY grading, sum of the bilateral SIJ; 0–8) and modified Stoke Ankylosing Spondylitis Spine Score (mSASSS, 0–72) [10] from the structural damage domain; (v) Spondyloarthritis Research Consortium of Canada MRI indices for the spine (SPARCC-spine, 0–414) and SPARCC for SIJ (SPARCC-SIJ, 0–72) from the axial inflammation domain. For all imaging scores, the mean scores of three central readers blinded for chronological order and clinical information were used [11].

Contextual factors

The patient's age, gender and educational level were tested as potential effect modifiers or confounders of the relationship between determinants of BAS-G and BAS-G. Educational level was the highest educational level achieved at baseline and was used as a binary variable (university level or not). If stratification for age was necessary, the population was dichotomized by the median age at baseline (33.3 years old).

Treatment variables

Because of their potential confounding effect, the following treatment variables were tested: use of non-steroidal anti-inflammatory drugs, corticosteroids, conventional synthetic disease-modifying anti-rheumatic drugs, and TNF inhibitors in the previous 6 months.

Statistical analysis

Generalized estimating equations (GEE) were used to analyse the relationship between the potential explanatory variables of BAS-G and BAS-G itself. By using this method in the presence of repeated measurements, we

can make best use of all available data and obtain a population-averaged parameter that takes within-patient correlations into account. As the outcome was continuous, we used a linear GEE model with an exchangeable correlation matrix that fitted the data best. Whether to include BASDAI as a total composite score or its six individual component questions was decided upon goodness-of-fit of the models [quasi-likelihood under the independence model criterion (QIC), the lower the better] [12].

Contextual factors were first tested as effect modifiers by means of an interaction; when significant (*P*-value <0.15) and clinically relevant, models were stratified. When effect modification was excluded, contextual factors were tested as confounders: when the addition of the contextual factor to a univariable GEE model led to a relevant change in the regression coefficient of the potential explanatory variable, it was kept in the final model.

To identify the determinants of BAS-G, we ran univariable and multivariable GEE models with forced entry of all potential explanatory variables. Treatment variables were tested as possible confounders. Since associations found in a GEE model reflect both a cross-sectional and longitudinal effect, we used an autoregressive GEE model [i.e. adjusted for the outcome (BAS-G) at the previous time point] to disentangle whether the determinants have a true longitudinal association with BAS-G. For this we made use only of data from yearly assessments, so that the intervals between the time points were identical (i.e. 1 year).

Analyses were repeated in the subgroup of patients with MRI available at follow-up and additionally including the MRI scores as potential explanatory variables. *P*-values <0.05 were considered significant unless specified otherwise and all statistical analyses were conducted using Stata version 14.

Results

A total of 708 patients were included. The subgroup of patients with repeated MRI results available consisted of 220 patients. Baseline characteristics are shown in Supplementary Table S1, available at *Rheumatology* online, without important differences between the groups. BASDAI was included in the models split in its individual questions, as this has shown the best fit (QIC: 8659.140 *vs* 10133.570).

Contextual factors were neither effect modifiers nor confounders of the relationship between the identified determinants of BAS-G and BAS-G (Supplementary Tables S2–S5, available at *Rheumatology* online). In the multivariable model, fatigue score (BASDAI Q1), back pain score (Q2), peripheral joint pain score (Q3) and severity of morning stiffness score (Q5), as well as BASFI were positively associated with BAS-G (Table 1). This effect was independent of age, gender, educational level or treatment.

The autoregressive GEE model showed that increases in BASDAI individual question scores on fatigue (Q1), back pain (Q2) and peripheral joint pain (Q3), or BASFI and the mNY grading resulted in a worsening of BAS-G (Table 2) (all independently).

In the subgroup analysis including patients with MRI scores available, the modified NY grading was negatively and significantly associated with well-being (higher mNY grading–lower well-being), in addition to the same determinants identified in the total study population (Supplementary Table S6, available at *Rheumatology* online). SPARCC-spine and SPARCC-SIJ did not contribute to explaining BAS-G.

Discussion

This study showed that a higher level of back pain is associated with a worse well-being, as are, though to a lesser extent, higher levels of fatigue, peripheral joint pain, severity of morning stiffness and physical function. These determinants except for morning stiffness have a true longitudinal association, i.e. they are associated with a worsening of patient well-being. These findings are in line with Machado's framework, according to which HRQoL is independently determined by disease activity and physical function. These results have additionally confirmed that such a framework also applies to patients in early phases of their disease, and that the relationships allow a longitudinal interpretation and not only a cross-sectional one: if disease activity worsens, the same happens to general well-being.

There have been some reports showing disease activity and physical function associated with HRQoL in patients with axSpA [13–16], but most of them are cross-sectional analyses with only one specifically having investigated the association between disease activity and HRQoL at two time points [14]. In our study we have seen that some of the individual patient-reported outcomes (PROs) included in the composite disease activity measures, such as the level of back pain, matter the most for patient well-being. Additionally, the presence of higher levels of PROs determines a worsening in patient well-being. It is therefore important to address patients' complaints to improve well-being. The objective findings that clinicians usually consider relevant, such as CRP, structural damage and inflammation on MRI are of minor relevance for patient well-being. These findings have an implication both in clinical practice and clinical research. In clinical practice, these PROs should be taken into account in treatment decisions, with the knowledge that they determine the patient's well-being, and the physician may be able to optimize the patient well-being by adjusting the therapy. For clinical research, our findings underscore the importance of these PROs as factors contributing to patient well-being, contrasting to the importance of the objective findings in the assessment of disease-modifying effect.

Though not associated with BAS-G in the multivariable analysis, spinal mobility was associated with BAS-

Table 1 Factors associated with BAS-G[a]

Explanatory variable	Coefficient (95% CI)	
	Univariable analysis	Multivariable analysis
BASDAI Q1 (fatigue, 0–10)	0.68 (0.65, 0.70)	0.17 (0.13, 0.22)*
BASDAI Q2 (back pain, 0–10)	0.83 (0.81, 0.85)	0.51 (0.46, 0.56)*
BASDAI Q3 (peripheral joint pain, 0–10)	0.51 (0.48, 0.54)	0.08 (0.04, 0.12)*
BASDAI Q4 (enthesitis, 0–10)	0.60 (0.58, 0.62)	0.03 (−0.01, 0.07)
BASDAI Q5 (severity of morning stiffness, 0–10)	0.66 (0.64, 0.68)	0.08 (0.03, 0.13)*
BASDAI Q6 (duration of morning stiffness, 0–10)	0.50 (0.47, 0.53)	0.03 (−0.01, 0.07)
SJC28 (0–28)	0.14 (0.06, 0.23)	0.01 (−0.11, 0.13)
TJC53 (0–159)[b]	0.08 (0.07, 0.09)	−0.01 (−0.02, 0.01)
MASES (0–39)	0.15 (0.14, 0.17)	0.00 (−0.02, 0.02)
CRP (mg/l)	0.04 (0.03, 0.05)	0.01 (−0.00, 0.01)
Any EMM (presence *vs* absence)	−0.02 (−0.26, 0.22)	−0.05 (−0.21, 0.11)
BASFI (0–10)	0.85 (0.82, 0.88)	0.14 (0.08, 0.19)*
BASMI linear (0–10)	0.69 (0.59, 0.80)	−0.07 (−0.16, 0.02)
mNY grading (0–8)	−0.16 (−0.25, −0.07)	0.01 (−0.03, 0.06)
mSASSS (0–72)	−0.09 (−0.15, −0.03)	−0.01 (−0.04, 0.02)

[a]Associations of the potential explanatory variables of BAS-G and BAS-G are expressed as regression coefficient (95% CI) in generalized estimating equation models with the potential explanatory variables as independent time-varying variables and BAS-G as the dependent time-varying variable. [b]Total score of the 53 joints with each joint graded 0–3 (0 = no tenderness, 1 = tenderness, 2 = tenderness + grimace, 3 = tenderness + grimace + withdrawal). **P*-value <0.05 (multivariable analysis). BASDAI Q1–6: individual component questions of BASDAI; EMM: extra-musculoskeletal manifestations; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; mNY grading: modified New York grading; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; SJC28: swollen joint count in the 28 joints; TJC53: tender joint score in the 53 joints.

Table 2 Factors longitudinally associated with BAS-G[a]

Factor	Coefficient (95% CI)	
	Univariable analysis	Multivariable analysis
BASDAI Q1 (fatigue, 0–10)	0.62 (0.59, 0.66)	0.15 (0.10, 0.20)*
BASDAI Q2 (back pain, 0–10)	0.82 (0.79, 0.84)	0.54 (0.47, 0.60)*
BASDAI Q3 (peripheral joint pain, 0–10)	0.53 (0.50, 0.57)	0.13 (0.08, 0.19)*
BASDAI Q4 (enthesitis, 0–10)	0.62 (0.58, 0.65)	0.02 (−0.04, 0.08)
BASDAI Q5 (severity of morning stiffness, 0–10)	0.66 (0.63, 0.69)	0.06 (−0.01, 0.13)
BASDAI Q6 (duration of morning stiffness, 0–10)	0.50 (0.47, 0.54)	0.05 (−0.01, 0.11)
SJC28 (0–28)	0.09 (−0.02, 0.20)	0.10 (−0.11, 0.31)
TJC53 (0–159)[b]	0.08 (0.07, 0.09)	−0.01 (−0.03, 0.01)
MASES (0–39)	0.15 (0.13, 0.18)	−0.00 (−0.03, 0.02)
CRP (mg/l)	0.03 (0.02, 0.04)	0.00 (−0.01, 0.01)
Any EMM (presence *vs* absence)	0.18 (−0.07, 0.42)	−0.09 (−0.28, 0.10)
BASFI (0–10)	0.83 (0.79, 0.87)	0.08 (0.00, 0.16)*
BASMI linear (0–10)	0.61 (0.48, 0.74)	−0.10 (−0.22, 0.02)
mNY grading (0–8)	−0.01 (−0.10, 0.07)	0.06 (0.01, 0.12)*
mSASSS (0–72)	−0.04 (−0.09, 0.01)	0.00 (−0.03, 0.04)

[a]Longitudinal associations of the potential explanatory variables of BAS-G and BAS-G are expressed as regression coefficient (95% CI) in autoregressive generalized estimating equation models (i.e. models adjusted for BAS-G at the previous time point using data only from baseline, 12, 24, 36, 48 and 60 months) with the potential explanatory variables as independent time-varying variables and BAS-G as the dependent time-varying variable. [b]Total score of the 53 joints with each joint graded 0–3 (0 = no tenderness, 1 = tenderness, 2 = tenderness + grimace, 3 = tenderness + grimace + withdrawal). **P*-value <0.05 (multivariable analysis). BASDAI Q1–6: individual component questions of BASDAI; EMM: extra-musculoskeletal manifestations; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; mNY grading: modified New York grading; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; SJC28: swollen joint count in the 28 joints; TJC53: tender joint score in the 53 joints.

G in the univariable analysis, implying its effect is dependent on physical function as suggested in Machado's model. In contrast to Machado's model, structural damage did not show any association with BAS-G. This may be attributable to the early nature of the cohort, with low levels of structural damage [17].

The contextual factors, namely age, gender and educational level, were neither effect modifiers nor confounders of the relationship between determinants and BAS-G. Therefore, the impact of the determinants on well-being is the same, regardless of these patient characteristics and not explained by them. The contextual factors that we investigated in this study have been previously reported to be independently associated with QoL (over the long-term and in a cohort of established r-axSpA) [18], disease activity measured by BASDAI [18, 19] and functional disability [19, 20] in patients with axSpA. Nevertheless, in patients with early axSpA, the identified PROs seem to capture the impact on well-being in such a way that contextual factors do not influence this relationship and no longer have an independent effect on the outcomes.

This study has several limitations. First, the Ankylosing Spondylitis Disease Activity Score (ASDAS), a validated disease activity measure with a better performance than the BASDAI, was not tested. In DESIR, ASDAS has been calculated using BAS-G as patient global assessment. Therefore, it was considered incorrect to include ASDAS as an explanatory variable of BAS-G. However, we included the individual BASDAI questions and CRP. Second, our cohort may be heterogeneous as it is defined by the rheumatologist's diagnosis, not by the classification criteria, in order to reflect daily clinical practice. Third, this study did not assess the interrelations between the different outcome measures as was the case in Machado's framework. Notwithstanding, we identified the independent determinants of BAS-G and even of a worsening in BAS-G, which is the same as the determinants identified in the longitudinal model. This means a step forward toward the previous existing framework, and the confirmation of its applicability in patients with early axSpA.

In conclusion, patient well-being is determined by disease activity and physical function over time, with the level of back pain having the largest impact. Traditional contextual factors, like age, gender and educational level, do not influence these associations.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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