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Depression/anxiety symptoms in axial spondyloarthritis and psoriatic arthritis patients in Serbia: a pilot study

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Abstract

To assess prevalence and change of depression/anxiety symptoms in spondyloarthritis patients and feasibility of depression/anxiety questionnaires. 43 Patients with axial spondyloarthritis (axSpA) and 27 patients with psoriatic arthritis (PsA) were consecutively recruited. There were 34 patients on biologics and 36 patients on nonbiologics. Patients were not previously treated for depression. The demographic variables, pain, patient global assessment, laboratory, clinical findings, diseases activity scores, Beck Depression Inventory (BDI) and Depression Anxiety and Stress Scale—short version (DASS-21) were collected. The study visits were at the beginning, after 1 month, after 3 and after 6 months. In axSpA and PsA patients on biologics, BDI and DASS-21 were significantly lower compared to nonbiologics group during time. The axSpA patients on biologics had significantly lower BDI and depression severity by BDI at each time point and lower DASS-21 after 1, 3 and 6 months. BDI in PsA patients who received biological therapy was significantly lower after 3 and 6 months. In biologics groups, BDI significantly decreased after 3 months in axSpA patients and after 1 month in PsA patients. In axSpA patients, there was a medium correlation between BDI and axial pain, patient global assessment and disease activity scores. The biological therapy significantly affected the depression/anxiety symptoms in axSpA and PsA during time. BDI moderately correlated with pain and disease activity in axSpA. BDI and DASS-21 are easy to use in daily practice.

Keywords Depression/anxiety symptoms · Spondyloarthritis · BDI · DASS-21 · Biological therapy

Introduction

Spondyloarthritis (SpA) is a chronic inflammatory entity that includes axial, articular and extra-spinal/articular manifestations, such as spondylitis, sacroillitis, arthritis, enthesitis, dactylitis, uveitis, psoriasis, inflammatory bowel disease (IBD), with a common family background [1]. In 2009 and 2011, the Assessment of the Spondyloarthritis International Society (ASAS) proposed a new set of classification criteria for SpA. The axial spondyloarthritis (axSpA) criteria allow the classification of patients with predominantly axial skeletal involvement (either on radiographs or MRI) and, for the first time, patients with a non-radiographic form of the disease. Another classification set relates to patients with predominantly peripheral manifestations (e.g., peripheral arthritis, enthesitis, and dactylitis) [2, 3]. Non-biologic drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are recommended as the first-line and the second-line treatment options for SpA. The new biologic treatment includes anti-tumor necrosis factor (anti-TNF) therapies for axSpA and PsA, anti-IL-17 therapy for AS and PsA and anti-IL-12/23 therapy for PsA [4]. Because of the heterogeneity of the disease, the definition of the treatment targets for SpA is challenging. New recommendations on general treat-to-target (T2T) strategy in SpA were developed by an international task force in 2017. At the beginning of the consensus process, the task force planned a single set of recommendations for axial (including AS and non-radiographic axial SpA) and peripheral SpA (pSpA), including psoriatic arthritis. However, due to lack of data on investigated targeted treatment in other pSpA (including reactive arthritis and IBD), the principal activity focused on axial SpA and PsA [5]. Recommendations are summarized in 11 key points on the treatment target and on validated measure

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of disease activity in axSpA and PsA. The major overarching principle was related to the treatment target as shared decision between the patient and the rheumatologist. This statement is clear if we know that axSpA and PsA are long/standing diseases with progressive structural axial/articular damage. Both conditions lead to significant functional impairment, decrease in a working capacity, unsatisfactory emotional and social life [6, 7]. The physician's traditional focus on clinical outcome and patient's priorities on psychological impact of SpA and quality of life should be part of the new approach to the management and treatment options. This can be achieved through improved communication between rheumatologist and their patients. The importance of co-operation between rheumatologists and other specialists was also recognized as one of the overarching principles in the treatment of SpA, due to a numerous extra-articular manifestations and associated diseases [5].

Experts consider depression as one of the six most frequent comorbidities in chronic inflammatory rheumatic diseases besides ischemic cardiovascular diseases, malignancies, infections, diverticulitis and osteoporosis [8, 9]. Depression includes the following heterogeneous symptoms present most of the day or nearly every day by DSM-5 diagnostic criteria: depressed mood, markedly diminished interest or pleasure in almost all activities, significant weight loss when not dieting or weight gain, or disturbance in appetite, slowing down of thought and a reduction of physical movement, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, diminished ability to think or concentrate, recurrent thoughts of death, suicidal thoughts or attempts. The individual must be experiencing five or more symptoms during the 2 weeks period and at least one of the symptoms should be either depressed mood or loss of interest or pleasure [10]. Lately, it has been found that the role of inflammation is important in understanding pathophysiology of the depression. The periodical and gradual elevations of the inflammatory markers and cytokines could likely influence the neuroplasticity in SpA patients [11]. However, the mechanisms linking inflammation to depression are still not well known and require further researches. The hallmarks of anxiety are excessive anxiety and worry. Difficulties in controlling worries are associated with three (or more) of the following six symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance [12].

The nationally representative study provides evidence that in a sample of non-institutionalized civilians, there was a strong association of depression and rheumatoid arthritis (RA) [13]. Relationship between psychiatric symptoms and self-reported outcome measures, clinical parameters and diseases activity in patients with ankylosing spondylitis (AS) was also explored recently [14]. AS might increase the risk of a newly diagnosed depressive and anxiety disorder, but not schizophrenia or bipolar disorder [15].

Association between depression and SpA may present diagnostic and treatment dilemmas, because some SpA symptoms (e.g., refractory pain, fatigue, stiffness, and tenderness) can be also found in depression/anxiety. In our opinion, depression and anxiety are insufficiently recognized by both clinicians and patients in a daily practice. Detection of depression and anxiety is time-consuming and requires some education to be registered. We have conducted this pilot study as an introduction to the main future study. The aims of the pilot study were: (a) assessing the prevalence and change of depression/anxiety symptoms in SpA patients on biological and nonbiological therapy; (b) testing the feasibility of patient self-report questionnaires for depression/anxiety in daily rheumatology practice.

Methods

Patients

This is an observational, real-life study of 76 adult patients with spondyloarthritis according to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria [2, 3]. Patients were consecutively recruited. Only SpA patients who were not previously treated for depression and who did not consider themselves to be depressed were included. All patients agreed to meet all longitudinal participation requirements for study visits—at the beginning, after a month, after three and after 6 months. There were 43 patients with axSpA (including AS and non-radiographic axSpA), 27 patients with PsA and 6 patients with reactive arthritis. Taking into account a small number of patients with reactive arthritis, their findings were not presented in the results. Of the remaining 70 patients, a total of 34 patients received biological therapy (anti-TNF-α drugs) and 36 patients received nonbiological therapy. In axSpA group, there were 23 patients on biologics, 11 patients treated with csDMARD and nine patients treated with NSAID. In PsA group, 11 patients have been treated with biologics, 12 patients with csDMARD and 4 patients have been treated with NSAID.

AxSpA patients received biological therapy if: (a) disease was active ≥ 4 weeks (BASDAI ≥ 4.0 and ASDAS-CRP ≥ 2.1), (b) they were previously treated with at least two NSAIDs at the maximum recommended dose (except in the case of unreliability) for at least 3 months. The criteria for receiving biological therapy in PsA patients were: (a) active peripheral arthritis (≥ 3 painful/swollen joints) for which methotrexate (or other csDMARDs) has been administered, at an optimal dose, for at least 6 months (except in the case of insufficiency), but no improvement has been achieved,

(b) clinical Disease Activity in Psoriatic Arthritis Score (cDAPSA) > 27, (c) elements of intolerance on csDMARD.

Study design

Demographic data were collected: gender, age, disease duration, and study treatment (non-biological or biological drugs). The axial and peripheral pain intensity by visual analogue scale VAS (0–10 mm), patient general disease assessment (PGA) by VAS (0–10 mm), swollen joints count (SWJC) (0–66), tender joints count (TJC) (0–68), erythrocyte sedimentation rate (ESR), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [16], Bath Ankylosing Spondylitis Functional Index (BASFI) [17], Bath Ankylosing Spondylitis Metrology Index (BASMI) [18], Ankylosing Spondylitis Disease Activity Score-ESR (ASDAS-ESR) [19] and cDAPSA [20] were registered at every study visit.

C-reactive protein (CRP), ASDAS-CRP [19] and Disease Activity in Psoriatic Arthritis Score (DAPSA) [20] were done only at the beginning, because of the high costs of CRP test.

Instruments for assessing depression/anxiety symptoms

The participants completed the Beck Depression Inventory (BDI) and Depression Anxiety and Stress Scale—short version (DASS-21) at every study visit. It takes a total of 5–10 min to complete BDI and DASS-21 questionnaires.

The BDI [21] is the most well-researched depression self-report inventory. It comprises of 21 items designed to assess cognitive, behavioral and somatic symptoms of depression. Each item scores between 0 and 3, according to the severity of the symptoms during the past week. Total score ranges from 0 to 63. The conventional cut-off scores of BDI are: 0–13 minimal, 14–19 mild, 20–28 moderate and 29–63 severe depression [22].

The original 42-item DASS was modified into a shorter 21-item version [23, 24]. Both versions are instruments often used to assess subjective depressive, anxiety and stress complaints in clinical groups and a community sample [25]. The DASS-21 questionnaire is a 21-item short version of the DASS with three scales: depression (D), anxiety (A) and stress (S). The DASS21–depression (DASS21-D) scale focuses on mood, motivation, and self-confidence. DASS21-anxiety (DASS21-A) scale focuses on physiological excitation, panic and fear and DASS21-stress (DASS21-S) scale focuses on tension and irritability. Each of the three DASS-21 scales contains seven items, where e*ach item* is rated *from 0 to 3.* Final score on each scale ranges from 0 to 42, with higher scores indicating more severe level of depression, anxiety, and stress. To calculate DASS-21, final scores on each scale are summed and multiplied by two.

No research has been done on the possible performance of the DASS-21 as a screening instrument for depression disorders in rheumatology patients. Because of that, we used DASS-21 total score of 60 and higher as indicator of severe depression according to the literature [26, 27].

Statistical analysis

Descriptive statistics was calculated for patient characteristics, BDI, DASS-21 and severity of depression/anxiety symptoms (mean and standard deviation for symmetric variables, median and interquartile range for asymmetric variables, frequencies and percentages for categorical variables). Non-normality of distribution of numerical variables was assessed with Lilliefors–Kolmogorov, Shapiro–Wilk and Anderson–Darling tests [28]. Asymmetry of distribution was assessed with Miao, Gel and Gastwirth bootstrap symmetry test [29], combined with histogram and boxplot graphical representation. Baseline characteristics of axSpA and PsA patients, as well as patients treated with biological and nonbiological therapy, were compared with exact Wilcoxon sum rank test [30] and two-sample χ^2 test of proportions, as appropriate.

The difference between BDI in patients treated with biological and BDI of patients treated with non-biological therapy was estimated with Hodges-Lehmann statistic (median of all possible differences). 95% confidence interval of median of these differences was calculated, based on Wilcoxon rank sum test [31].

Spearman's correlation coefficient was calculated between BDI or DASS-21 and following baseline characteristics: age, duration of disease, VAS-axial pain, VAS-peripheral pain, SJC, TJC, PGA, ESR and CRP in axSpA and PsA, as well as for correlation with BASFI, BASDAI, BASMI, ASDAS-ESR, ASDAS-CRP in axSpA patients and for correlation with cDAPSA, DAPSA in PsA patients.

Test of strength of correlation and 95% confidence interval for the correlation coefficient were carried out using Fisher's transformation of the sample correlation coefficient [32]. The correlation is considered to be weak if the absolute value of the population correlation coefficient is between 0 and 0.3 and of medium strength if it is between 0.3 and 0.7.

The correlation of baseline characteristics with BDI or DASS-21 was analysed during time, separately in axSpA and PsA patients. In multiple comparisons, difference between correlation coefficients at any two time points was tested using battery of five tests for comparison of two non-overlapping dependent correlations (Pearson and Filon test, Dunn and Clark test, Steiger test, Raghunathan, Rosenthal, and Rubin test, Silver, Hittner, and May test [33]).

Brunner-Langer mixed nonparametric ANOVA [34] was used for testing the effects of diagnosis (axSpA, PsA) and its interaction with time on BDI and DASS-21, as well as

on severity of depression/anxiety symptoms. Further, effects of biological therapy, time, as well as their interaction, separately in axSpA and PsA patients, were tested using Brunner-Langer mixed nonparametric ANOVA. In post hoc analysis, exact Wilcoxon sum rank test was used for comparisons between groups of patients and exact Wilcoxon signed rank test was used for comparisons at each two time points. Following significant interaction effect of time with biological therapy, the following hypotheses were tested: (a) BDI/DASS-21 in patients on biologics is lower than in patients on nonbiological therapy, (b) BDI/DASS-21 within each group decreased during time. Decrease during time was tested by comparing values at each two time points.

In multiple comparisons, false discovery rate was controlled using Benjamini-Hochberg's method [35].

The level of significance was set at 0.05. Statistical analysis was performed in statistical software R, version 4.3.2 (using R packages *stats*, *nortest, lawstat, exactRankTests, cocor, nparLD*).

Results

Patient characteristics

The baseline characteristics measured at the beginning are presented in Table 1. There were statistically significant differences between axSpA and PsA patients with respect to age ($W=215.5$, $p<0.001$), SWJC ($W=242.5$, $p<0.001$) and TJC ($W=351$, $p=0.004$).

DASS-21 were not available (not fully completed questionnaires or more answers chosen for an item) in 8 (11.4%) of SpA patients. Descriptive statistics of BDI, DASS-21 and severity of depression by BDI and DASS-21 at the beginning is presented in Table 2.

Changes of BDI and DASS-21 during time in total of all axSpA and PsA patients

PsA patients had higher BDI and DASS-21 than axSpA patients after three months (BDI: $p=0.010$, DASS-21: $p=0.007$) and after six months (BDI: $p=0.005$, DASS-21: $p=0.003$) (Fig. 1).

Changes of BDI and DASS-21 during time in axSpA patients on biological and nonbiological therapy

BDI was significantly lower in axSpA patients who received biologics compared to axSpA patients who received nonbiological therapy, at each time point (beginning, after 3 months and after 6 months: $p<0.001$, after one month: $p=0.003$). Estimate of median of differences between these two groups was 7.5 with 95% CI = (2,12) at the beginning, 4.5 with 95% CI = (1,9) after 1 month, 7.5 with 95% CI = (3,13) after 3 months and 7.5 with 95% CI = (3,14) after 6 months. In axSpA group of patients treated with biological therapy, BDI significantly decreased after 3 months and remained unchanged after 6 month (Fig. 2).

DASS-21 was significantly lower in axSpA patients treated with biologics compared to axSpA patients treated with nonbiological therapy after 1 month ($p=0.027$), after 3 months ($p=0.009$) and after 6 months ($p=0.016$) (Fig. 2).

In axSpA patients who received nonbiological therapy, BDI and DASS-21 did not significantly change during time.

Changes of BDI and DASS-21 during time in PsA patients on biological and nonbiological therapy

BDI in PsA patients on biologics was significantly lower compared to PsA patients on nonbiological therapy after 3 months ($p=0.004$) and after 6 months ($p=0.003$). In PsA patients on biologics, BDI significantly decreased after 1 month and remained the same until the end (Fig. 2).

There were no statistically significant effects on DASS-21 in PsA patients on biologics. BDI and DASS-21 did not significantly change during time in PsA patients who received nonbiological therapy.

The severity of depression/anxiety by BDI and DASS-21

Severity of depression by BDI was significantly lower in axSpA patients who received biologics at each time point (beginning: $p=0.030$, after 1 month: $p=0.047$, after 3 months: $p=0.007$, after 6 months $p=0.003$), compared to axSpA patients on nonbiological therapy (Table 3).

Correlation analysis

In axSpA patients, there was a weak correlation between BDI and peripheral pain-VAS, TJC and ESR and a medium correlation between BDI and axial pain-VAS, PGA, BASFI, BASDAI, ASDAS-ESR and ASDAS-CRP. BDI did not correlate with any of the baseline characteristics in PsA patients (Table 4).

In axSpA patients, DASS-21 correlated weakly with axial pain-VAS, PGA, BASFI and ASDAS-ESR in axSpA patients, and with axial pain -VAS and CRP in PsA patients (Table 4).

In PsA patients, only correlation between BDI score and peripheral pain-VAS significantly changed with time (from − 0.05 at the beginning to 0.53 after 1 month).

Table 1 Baseline characteristics of the patients

Baseline characteristics	axSpA			*p* value	PsA			*p*-value
	Total (*N* = 43)	Bio (*N* = 23)	Non-bio (*N* = 20)		Total (*N* = 27)	Bio (*N* = 11)	Non-bio (*N* = 16)	
Sex, female	12 (27.9%)	3 (13.0%)	9 (45.0%)	**0.047**	12 (44.4%)	4 (36.4%)	8 (50.0%)	0.759
Age, years	41.7 (10.3)	37.8 (10.0)	46.0 (8.9)	**0.012**	53.9 (9.3)	52.5 (4.2)	54.8 (11.7)	0.137
Disease duration, years*	10 (13.5)	10 (10.5)	10 (13.5)	0.177	8 (11)	10 (8.5)	4 (9)	**0.028**
Peripheral pain-VAS	3.8 (2.8)	2.2 (2.1)	5.7 (2.3)	**< 0.001**	5.6 (2.1)	4.4 (2.2)	5.9 (1.8)	0.106
Axial pain-VAS	3.9 (2.8)	2.8 (2.4)	5.2 (2.6)	**0.003**	4.6 (2.6)	4.5 (1.3)	4.6 (3.3)	0.597
SWJC*	0 (1)	0 (0.5)	0 (2)	0.238	3 (3)	3 (3)	3 (3.2)	0.737
TJC*	2 (4)	1 (4)	3.5 (5.2)	0.157	4 (6.5)	4 (7)	4.5 (5.5)	0.836
ESR (mmHg/h) *	16 (24.5)	10 (11.0)	25.5 (30.2)	**< 0.001**	15 (26.5)	6 (3.5)	30 (30.5)	**< 0.001**
CRP (mg/L) *	5 (7.05)	4.1 (8.11)	5 (4.65)	0.625	5.4 (7.84)	4 (6.01)	6.5 (8.45)	0.182
PGA	4.3 (2.3)	3.0 (1.9)	6.0 (1.6)	**< 0.001**	5.0 (1.3)	4.6 (1.0)	5.2 (1.4)	0.402
DAPSA -CRP				–				0.300
Remission (≤ 4)	–	–	–	–	0 (0%)	0 (0%)	0 (0%)	
Low (> 4 and ≤ 14)	–	–	–	–	4 (14.8%)	2 (18.2%)	2 (12.5%)	
Moderate (> 14 and ≤ 28)	–	–	–	–	8 (51.9%)	7 (63.6%)	7 (43.8%)	
High (> 28)	–	–	–	–	9 (33.3%)	2 (18.2%)	7 (43.8%)	
cDAPSA								0.817
Remission (≤ 4)	–	–	–	–	1 (3.7%)	1 (9.1%)	0 (0%)	
Low (> 4 and ≤ 13)	–	–	–	–	5 (18.5%)	2 (18.2%)	3 (18.8%)	
Moderate (> 13 and ≤ 27)	–	–	–	–	19 (70.4%)	7 (63.6%)	12 (75%)	
High (> 27)	–	–	–	–	2 (7.4%)	1 (9.1%)	1 (6.2%)	
BASFI	3.78 (2.62)	2.40 (1.86)	5.38 (2.49)	**< 0.001**	–	–	–	–
BASDAI	4.31 (2.95)	2.27 (1.94)	6.66 (2.00)	**< 0.001**	–	–	–	–
BASMI	5.3 (3.3)	4.4 (3.3)	6.3 (3.1)	0.071	–	–	–	–
ASDAS-ESR	2.69 (1.28)	1.87 (1.05)	3.63 (0.79)	**< 0.001**	–	–	–	–
ASDAS-CRP	2.48 (1.05)	1.89 (0.95)	3.15 (0.68)	**< 0.001**	–	–	–	–

Statistically significant difference: p-value is smaller than 0.05

All results are presented as mean (sd) for symmetric variables, median (IQR—interquartile range) for asymmetric variables and number (%) for categorical variables. Asymmetric variables are noted with *

axSpA axial spondyloarthritis, *PsA* psoriathic spondyloarthritis, *VAS* visual analogue scale, *SWJC* swollen joint counts, *TJC* tender joint counts, *ESR* erythrocyte sedimentation rate, *CRP* Creactive protein, *PGA* patient global assessment, *cDAPSA* clinical Disease Activity in Psoriatic Arthritis Score, *DAPSA* Disease Activity in Psoriatic Arthritis Score, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index *ASDAS* Ankylosing Spondylitis Disease Activity Score, *bio* biological therapy, *non-bio* nonbiological therapy

Discussion

Detection of depression/anxiety symptoms in SpA patients is challenging due to the overlapping of somatic symptoms. No data were available on the prevalence of depression/anxiety in SpA patients in Serbia. To properly create a plan for a large prospective study, we conducted this smaller-sized pilot study in accordance with the definition of a pilot study in clinical trials [36]. There are many possible causes of depression, including faulty neurotransmmiter systems, genetic vulnerability, stressful life events, medications and medical problems. Depression is also associated with significant morbidity, disability, increased comorbidities and mortality [37]. Due to lack of time and numerous duties in everyday clinical work, association of axSpA/PsA with depression/anxiety is often overlooked. Both conditions negatively affect quality of life, emotional and social functioning, and work productivity. Ward and Kuzis have reported that from 234 patients with AS, 31 patients (13.2%) developed permanent work disability and 57 patients (24.3%) had received disability payments [38]. The work disability in AS was associated with being older, longer disease duration, lower educational standard, comorbidity, greater physical impairment, pain, fatigue, stiffness, anxious and depressed mood [39]. The work disability of our SpA patients was not the object

Table 2 BDI, DASS-21 and severity of depression by BDI and DASS-21 in study patients at the beginning

Variable	axSpA			pSpA		
	Total ($N=43$)	Bio ($N=23$)	Non-bio ($N=20$)	Total ($N=27$)	Bio ($N=11$)	Non-bio ($N=16$)
BDI median (IQR)	6 (10.5)	4 (5.5)	12 (10)	10 (13)	10 (12)	10 (13.5)
DASS-21 median (IQR)	29 (36.5)	28 (30)	36 (42)	44 (25.5)	42 (23)	45 (27)
BDI depression severity number (%)						
Minimal 0–13	34 (79.1%)	21 (91.3%)	13 (65.0%)	17 (63.0%)	7 (63.6%)	10 (62.5%)
Mild 14–19	4 (9.3%)	1 (4.3%)	3 (15.0%)	7 (25.9%)	4 (36.4%)	3 (18.8%)
Moderate 20–28	4 (9.3%)	0 (0%)	4 (20.0%)	0 (0%)	0 (0%)	0 (0%)
Severe 29–63	1 (2.3%)	1 (4.3%)	0 (0%)	3 (11.1%)	0 (0%)	3 (18.8%)
Total	43 (100%)	23 (100%)	20 (100%)	27 (100%)	11 (100%)	16 (100%)
DASS-21 severe depression number (%)						
No < 60	32 (80.0%)	21 (91.3%)	11 (64.7%)	17 (77.3%)	8 (80.0%)	9 (75.0%)
Yes ≥ 60	8 (20.0%)	2 (8.7%)	6 (35.3%)	5 (22.7%)	2 (20.0%)	3 (25.0%)
Total	40 (100%)	23 (100%)	17 (100%)	22 (100%)	10 (100%)	12 (100%)

IQR interquartile range, *axSpA* axial spondyloarthritis, *PsA* psoriatic spondyloarthritis, *BDI* beck depression inventory, *DASS-21* Depression anxiety and stress scale short version, *bio* biological therapy, *non-bio* nonbiological therapy

DASS-21 is calculated for 40 axpA and 22 pSpA patients

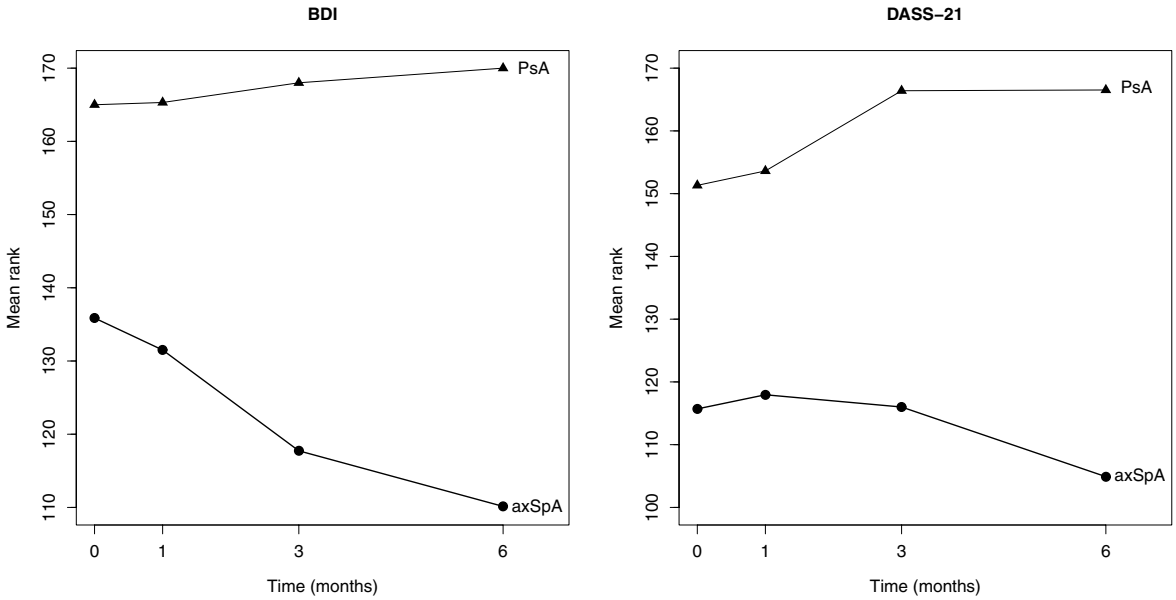

Fig. 1 The change of BDI and DASS-21 during time in axSpA and PsA patients

of this study. However, it is worth exploring this issue in the future, especially in our lower-income economy.

Durmus et al. [40] have shown that BDI was significantly higher in AS group compared to control group. Depression/anxiety was minimal by BDI and it was not severe by DASS-21 in the most of our patients. However, severe depression/anxiety based on DASS-21 in one-fifth of patients, which was not recognized by physicians, requires our full attention. In the main study, we need to plan an additional education about depression for physicians and patients in rheumatology clinic. It should also be taken into account that we used cut-off of DASS-21 for severe depression/anxiety related to patients with substance use disorder, according to the current literature [26, 27]. This study indicates the need to set DASS21 cut-off value specifically in rheumatology patients. It has been noticed that psychiatric symptoms were significantly correlated with BASDAI, BASFI, pain-VAS, disease activity, functional capacity and fatigue, but were not correlated with self-esteem [40]. It has also been reported that depression/anxiety was positively associated

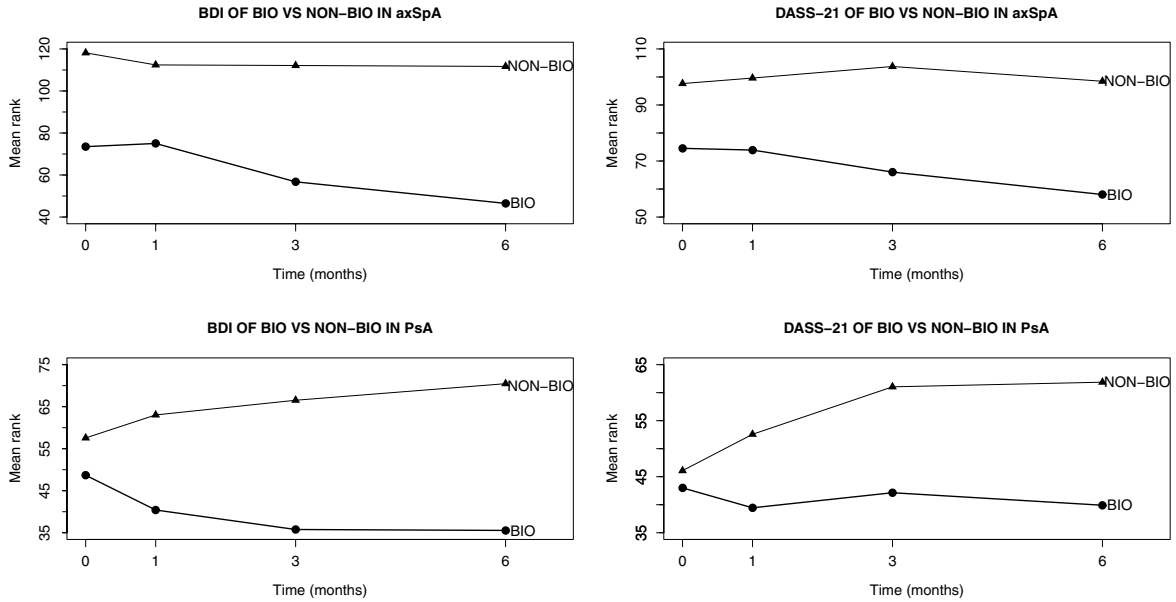

Fig. 2 The change of BDI and DASS-21 during time in axSpA and PsA patients treated with biological and nonbiological therapy

with BASFI, but not associated with BASMI [41]. In another study, depression symptoms were significantly associated with BASFI and BASDAI, but not with age, sex, ASDAS-ESR/CRP and VAS in patients with axSpA [42]. Another study has shown similar results on positive correlation between risks of depression and anxiety and VAS-pain, BASDAI, BASFI, and ASDAS-CRP in patients with axSpA [43]. In our axSpA and PsA patients, the depression/anxiety symptoms were higher for patients with higher scores in pain, PGA, tender joints count, increased laboratory parameters of inflammation, BASDAI, BASFI, ASDAS-ESR and ASDAS-CRP. Depression was not associated with age, disease duration or sex in our patients. One possible explanation is that patients with long disease duration have grown accustomed to it and, therefore, are able to better cope with its consequences in daily activities. It seems that BDI is more convenient than DASS-21 to detect the relationship between clinical features and depression symptoms in spondyloarthritis patients.

Biological therapy era has opened many questions. We have answered some of them, but many questions still remain unanswered. The relationship between biological therapy and depression and the role of TNF-α agents as possible neuromodulators are insufficiently studied. It has been published that treatment with infliximab in the depressed patients with increased CRP resulted in a significant decrease in depressive symptoms [44]. Arisoy et al. [45] concluded that TNF-α antagonism may have a potential antidepressant effect, besides its established anti-inflammatory effect in AS patients. Our axSpA and PsA patients were treated by nonbiologic or biologic drugs. There was no change of depression/anxiety symptoms during the time in our patients with nonbiological therapy. Patients with axSpA treated with nonbiologics were more depressed from the beginning. Their basic characteristics (they were older, with worse axial and peripheral pain, with higher values of ESR, PGA, BASFI, BASDAI, ASDAS-CRP and ASDAS-ESR than patients on biologics) contributed to this, in addition to under-efficient therapy. The values of BDI and DASS-21 significantly decreased in our patients on biologics compared to patients on nonbiologics during the time. However, when we analyzed the changes in severity of depression/anxiety, we noticed that significant decrease in the degree of the depressive symptoms severity was influenced by biologic treatment only in our axSpA study patients, but not in our PsA patients. The reason for this probably lies in basic characteristics of our patients with PsA. They were older with more painful, tender and swollen joints than patients with axSpA. Another reason for this finding could be the insufficient duration of biologics in these patients. This result also showed us the necessity of co-operation with the neuropsychiatrists, to determine whether the observed differences within defined degrees of depression severity have clinical value.

The evaluation of the disease activity and treatment effect might be challenging in SpA patients with depression/anxiety symptoms. Depression is frequently present in SpA patients with higher disease activity score and may affect the intensity of the patient's symptoms in disease activity scores that are included in the evaluation criteria for receiving biological therapy. It might lead to unnecessary initiation of a anti-TNF therapy, dose escalations or switches.

Table 3 BDI, DASS-21 and severity of depression by BDI in patients on biological and nonbiological therapy during time

Variable	Sign. effect	ANOVA test	Multiple comparisons	
			Groups	Test in time points
BDI				
axSpA, PsA	Group	$F = 6.231, df_1 = 1, df_2 = 61.35, p = 0.015$	axSpA, pSA	$t_3 : W = 368.5, p = 0.010$
			axSpA, PsA	$t_6 : W = 352.5, p = 0.005$
axSpA	Bio	$F = 17.465, df_1 = 1, df_2 = 37.72, p < 0.001$	axSpA bio	$t_0 > t_3 : V = 164, p = 0.002$
	Time	$F = 7.669, df_1 = 2.65, df_2 = \infty, p < 0.001$	axSpA bio	$t_0 > t_6 : V = 136, p < 0.001$
	Bio×time	$F = 4.599, df_1 = 2.65, df_2 = \infty, p = 0.005$	axSpA bio	$t_1 > t_3 : V = 152, p = 0.010$
			axSpA bio	$t_1 > t_6 : V = 161, p < 0.001$
			axSpA bio, non-bio	$t_0 : W = 359, p < 0.001$
			axSpA bio, non-bio	$t_1 : W = 340, p = 0.003$
			axSpA bio, non-bio	$t_3 : W = 375.5, p < 0.001$
			axSpA bio, non-bio	$t_6 : W = 386, p < 0.001$
PsA	Bio	$F = 5.260, df_1 = 1, df_2 = 20.68, p = 0.032$	PsA bio	$t_0 > t_1 : V = 34, p = 0.016$
	Bio×time	$F = 5.435, df_1 = 2.16, df_2 = \infty, p = 0.003$	PsA bio	$t_0 > t_3 : V = 60.5, p = 0.006$
			PsA bio	$t_0 > t_6 : V = 43, p = 0.008$
			PsA bio, non-bio	$t_3 : W = 36.5, p = 0.004$
			PsA bio, non-bio	$t_6 : W = 33.5, p = 0.003$
DASS-21				
axSpA, PsA	Group	$F = 8.114, df = 1, df_2 = 62.33, p = 0.006$	axSpA, PsA	$t_3 : W = 319.5, p = 0.007$
			axSpA, PsA	$t_6 : W = 293.5, p = 0.003$
axSpA	Bio	$F = 5.707, df_1 = 1, df_2 = 38.61, p = 0.021$	axSpA bio, non-bio	$t_1 : W = 280, p = 0.027$
			axSpA bio, non-bio	$t_3 : W = 320, p = 0.009$
			axSpA bio, non-bio	$t_6 : W = 282.5, p = 0.016$
Depression severity by BDI				
axSpA	Bio	$F = 6.589, df_1 = 1, df_2 = 26.59, p = 0.016$	axSpA bio, non-bio	$t_0 : W = 289, p = 0.030$
			axSpA bio, non-bio	$t_1 : W = 271.5, p = 0.047$
			axSpA bio, non-bio	$t_3 : W = 302.5, p = 0.007$
			axSpA bio, non-bio	$t_6 : W = 314.5, p = 0.003$

t_0—beginning, t_1—after 1 month, t_3—after 3 months, t_6—after 6 months, *bio* biological therapy, *non-bio* nonbiological therapy

No significant changes of depression/anxiety symptoms were found in SpA patients treated with NSAIDs and cDMARDs. There is a paucity of data on impact of nonbiological therapy on quality of life and depression in rheumatology, as opposed to numerous data on impact of biological therapy. The explanation for this can be sought, on the one hand, in the high expectations and beliefs of rheumatologists in the biologics and, on the other hand, in the demands of the authorities due to high price of biologic therapy.

Our results on the significant effect of biological therapy on depression and, in particular, on the effect of biological therapy on depression that lasts over time, is our small, but hopefully valuable contribution in this field. We believe this will be the subject of future long-term researches.

Our study is limited by its small sample size. In our pilot study, we wanted to pre-test patient-related questionnaires BDI and DASS-21 in spondyloarthritis patients. This study is the first phase in the design of a main study for detecting and monitoring depression in rheumatology patients in Serbia. Another reason for small sample size lies in one of the inclusion criteria, i.e. the absence of previously diagnosed depression. Depression is not a diagnosis that is screened in rheumatology daily practice, unlike cardiovascular or gastrointestinal diseases. The majority of depression diagnosis in SpA patients has been set up without consultation with a rheumatologist. Even in large national studies in much richer countries with a more extensive registry and bigger funds than Serbia, there is a lack of well-documented epidemiological data on the presence of depression in a relatively uncommon disease such as SpA. In addition, there is a limited number of studies that deal with this topic [46, 47]. The second limitation of our study is the lack of evaluation of other risk factors (comorbidities or sociological data) in the development of depression in our patients.

The positive features of the BDI and DASS-21 are briefness, easy scoring and administering. The response rate, time of filling out the BDI and DASS-21 questionnaires and percentages of missing values were used as indicators of their

Table 4 Correlation between BDI and DASS-21 and baseline parameters

Variable	*axSpA* (*N* = 43)			PsA (*N* = 27)		
	r	Strength	95% CI	*r*	Strength	95% CI
BDI						
Age	0.19	No	(− 0.12, 0.47)	− 0.07	No	(− 0.44, 0.33)
Disease duration	0.08	No	(− 0.23, 0.38)	0.12	No	(− 0.28, 0.49)
Peripheral pain-VAS	0.38	Weak	(0.08, 0.62)	− 0.12	No	(− 0.46, 0.24)
Axial pain-VAS	0.54	Medium	(0.28, 0.73)	0.24	No	(− 0.16, 0.58)
SWJC	0.25	No	(− 0.06, 0.52)	0.04	No	(− 0.36, 0.42)
TJC	0.27	Weak	(− 0.04, 0.53)	0.18	No	(− 0.22, 0.54)
ESR	0.38	Weak	(0.09, 0.62)	0.14	No	(− 0.27, 0.50)
CRP	0.11	No	(− 0.20, 0.41)	0.31	No	(− 0.09, 0.62)
PGA	0.63	Medium	(0.40, 0.78)	0.18	No	(− 0.23, 0.53)
cDAPSA	–	–	–	0.18	No	(− 0.22, 0.53)
DAPSA-CRP	–	–	–	0.20	No	(− 0.20, 0.55)
‘BASFI	0.67	Medium	(0.45, 0.81)	–	–	–
BASDAI	0.56	Medium	(0.30, 0.74)	–	–	–
BASMI	0.24	No	(− 0.07, 0.51)	–	–	–
ASDAS-ESR	0.60	Medium	(0.36, 0.77)	–	–	–
ASDAS-CRP	0.55	Medium	(0.29, 0.74)	–	–	–
DASS-21						
Age	0.09	No	(− 0.24, 0.40)	0.02	No	(− 0.41, 0.45)
Disease duration	− 0.15	No	(− 0.45, 0.18)	0.17	No	(− 0.29, 0.56)
Peripheral pain-VAS	0.14	No	(− 0.19, 0.44)	− 0.08	No	(− 0.50, 0.37)
Axial pain-VAS	0.42	Weak	(0.11, 0.65)	− 0.42	Weak	(− 0.72, 0.02)
SWJC	0.27	No	(− 0.05, 0.54)	0.23	No	(− 0.23, 0.60)
TJC	0.25	No	(− 0.08, 0.53)	0.23	No	(− 0.16, 0.57)
ESR	− 0.01	No	(− 0.33, 0.31)	0.02	No	(− 0.41, 0.45)
CRP	− 0.15	No	(− 0.45, 0.18)	0.37	Weak	(− 0.19, 0.54)
PGA	0.37	Weak	(0.05, 0.61)	− 0.11	No	(− 0.51, 0.34)
cDAPSA	–	–	–	0.16	No	(− 0.30, 0.55)
DAPSA-CRP	–	–	–	0.24	No	(− 0.21, 0.61)
BASFI	0.43	Weak	(0.13, 0.66)	–	–	–
BASDAI	0.27	No	(− 0.06, 0.54)	–	–	–
BASMI	0.05	No	(− 0.27, 0.37)	–	–	–
ASDAS-ESR	0.28	Weak	(− 0.04, 0.55)	–	–	–
ASDAS-CRP	0.26	No	(− 0.06, 0.54)	–	–	–

r Spearman’s correlation coefficient, *95% CI* 95% confidence interval, *axSpA* axial spondyloarthritis, *PsA* psoriatic spondyloarthritis, *VAS* visual analogue scale, *SWJC* swollen joint counts, *TJC* tender joint counts, *ESR* erythrocyte sedimentation rate, *CRP* Creactive protein, *PGA* patient global assessment, *cDAPSA* clinical Disease Activity in Psoriatic Arthritis Score, *DAPSA* disease activity in psoriatic arthritis score, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *ASDAS* Ankylosing Spondylitis Disease Activity Score

feasibility. A total of 90% SpA patients actively participated in the study at each follow-up and all of them completed the questionnaires. In 70 SpA patients, there were no missing values in BDI questionnaires, and in DASS-21 the percentage of missing values ranges from 4 to 11% (over time). The time to fill out both questionnaires is between 5 and 10 min. The structure, clarity and easy application of these questionnaires were crucial for patients to accept using them during the course of the study. Feasibility of these questionnaires should encourage their use in rheumatology daily practice for the identification of depression in SpA patients. In our future full-scale study, we plan to determine which psychiatric questionnaire is the most sensitive one to detect depression/anxiety symptoms in rheumatology patients. The study findings of unrecognized and untreated depression/anxiety in our patients indicate the need to improve co-operation

and active engagement of psychologists or psychiatrists in all stages of monitoring in SpA patients. The results of this pilot study will help us to implement a more comprehensive approach to treatment target in rheumatology patients in our clinics.

Author contributions SM participated in clinical assessment, designed, coordinated and continuously reviewed the study, participated in data management and statistical analysis and prepared the manuscript for publication. KV participated in data management, performed the statistical analysis and prepared the manuscript for publication. MZ participated in clinical assessment and drafting the manuscript. G. R. participated in clinical assessment analysis and interpretation of data, as well as in drafting the manuscript. ND participated in interpretation of data and drafting the manuscript.

Compliance with ethical standards

Conflict of interest Authors S. Milutinovic, K.Veljkovic, M. Zlatanovic, G. Radunovic and N.Damjanov declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was reviewed and approved by the Ethics Committee of the Institute of Rheumatology, Belgrade, Serbia (Protocol Number: 29/1-35/2016).

Informed consent Informed consent was obtained from all individual participants included in the study.

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