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The effect of anti-inflammatory treatment on depressive symptoms in spondyloarthritis: does the type of drug matter?

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Abstract

Objective: To investigate the effect of pharmacological treatment of SpA on depressive symptoms and explore whether this effect differs between drug classes.

Methods: Data from the observational Assessment of SpondyloArthritis international Society Health Index Validation Study were used. Patients were assessed at baseline and after initiation of NSAIDs/conventional synthetic DMARDs (csDMARDs)/TNF inhibitors (TNFis). Depressive symptoms were assessed with the Hospital Anxiety and Depression Scale depression subscale [HADS-D; 0–21 (best–worst)]. Covariables included demographics and disease characteristics, including disease activity [Ankylosing Spondylitis Disease Activity Score (ASDAS)/BASDAI]. The change in HADS-D from baseline was compared between treatments (NSAIDs/csDMARDs/TNFis) with analysis of variance and multivariable regression analysis.

Results: A total of 304 patients were included; 102/45/157 initiated NSAIDs/csDMARDs/TNFis and 260 (85%) / 44 (15%) had axial/peripheral SpA. At baseline, the mean HADS-D was 6.9 (s.d. 4.2); 126 (42%) were possibly depressed (HADS-D $\geq$8) and 66 (22%) were probably depressed (HADS-D $\geq$11). At follow-up, depressive symptoms significantly improved in all treatment groups. In multivariable regression without disease activity measures, initiating TNFis compared with NSAIDs was associated with greater improvement in depressive symptoms [$\beta = -1.27$ (95% CI −2.23, −0.32)] and lower odds of possible depression at follow-up [odds ratio 0.47 (95% CI 0.23, 0.94)]. This association was attenuated after additional adjustment for disease activity (ASDAS/BASDAI) but not CRP. csDMARDs did not differ from NSAIDs regarding their effect on HADS-D. Between-drug class results were confirmed in axial SpA (axSpA), although less clear in peripheral SpA.

Conclusion: Treatment of active SpA also improves depressive symptoms. Especially in axSpA, TNFis have a greater effect than NSAIDs, which is mainly explained by a stronger effect on disease activity. We found no evidence for a direct link between CRP-mediated inflammation and depressive symptoms in SpA.

Keywords: spondyloarthritis, depression, treatment, drugs, TNF inhibitor, NSAID, DMARD

Rheumatology key messages

- Pharmacological treatment of SpA with NSAIDs, csDMARDs or TNFis improves depressive symptoms.
- Especially in axSpA, TNFis have a greater effect than NSAIDs on these comorbid depressive symptoms.
- No evidence was found for a link between (CRP-mediated) inflammation and depression.

Introduction

SpA is a chronic inflammatory disease that can affect the sacroiliac joints, spine, peripheral joints and entheses. Depending on the predominant location of its manifestations, the disease is considered axial (axSpA) or peripheral (pSpA) [1, 2]. Complaints commonly involve physical health and include pain, stiffness and impaired physical functioning. However, mental health might also be affected. The prevalence of mental health disorders, such as depression and anxiety, is increased in SpA compared with the general population [3, 4]. EULAR recommends screening for depression in patients with chronic inflammatory rheumatic diseases [5].

Depression is a complex disorder, with multifactorial aetiology [6, 7]. Currently it is unknown why depressive symptoms

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and depression are more prevalent in SpA. One explanation might be that the symptoms and impact of SpA on daily life, as well as stigmatization (e.g. due to physical disability, psoriasis) and worries about future prospects, negatively affect mental health (depression secondary to SpA). Alternatively, SpA and depression could share a common pathophysiological pathway. Previous studies have demonstrated inflammatory biomarkers, such as TNF-α and CRP, are increased in people with depression (but without SpA) [8, 9]. These observations contributed to the inflammatory hypothesis of depression, which suggests that (subclinical) inflammation is a direct cause of depression [10]. Most studies on this topic were conducted in healthy individuals without SpA or other inflammatory rheumatic disease. In SpA, the evidence on inflammatory depression is limited and conflicting. Patients with axSpA and possible depression have higher CRP and ESR [11]. Studies investigating correlations between these inflammatory markers and depressive symptoms led to conflicting results [12–15]. Finally, a recent ancillary analysis of a randomized controlled trial (RCT) in axSpA found that the severity of depressive symptoms decreased significantly when treated with a TNF inhibitor (TNFi) compared with placebo. This effect was mainly attributed to improvement in axSpA-related symptoms, not to (CRP-mediated) inflammation [16]. In PsA, similar associations between depressive symptoms and patient-reported disease activity were observed [17].

Several studies have shown that TNFis can improve depressive symptoms in SpA [16, 18–21]. The effects of other drugs used in SpA, such as NSAIDs and conventional synthetic DMARDs (csDMARDs), on depressive symptoms in patients with SpA is unknown. For clinical practice, it is relevant to know whether these drug classes also improve comorbid depression in SpA. Knowledge on differences between drugs regarding their effects on depressive symptoms in SpA would help set proper expectations for both rheumatologists and patients. In addition, it could help guide treatment decisions regarding depression, such as referral to a psychologist or psychiatrist for clinical evaluation. Furthermore, if there are differences between these drug types (with different mechanisms of action), this could potentially provide insights into the potential role of inflammatory pathways involved in comorbid depression in SpA. The objective of the current study was to investigate the effect of pharmacological treatment of SpA on depressive symptoms in daily practice and to explore whether this effect differs between drug types.

Methods

Study design and population

Data from the Assessment of SpondyloArthritis international Society Health Index (ASAS HI) Validation Study were used. This study has been described before [22]. In short, the ASAS HI Validation Study was a cross-sectional international observational study with a longitudinal component. Patients were eligible if they fulfilled the ASAS classification criteria for axSpA or pSpA [23, 24]. All patients were assessed at baseline and subgroups of stable patients (reliability arm) or patients who required a therapeutic change due to active disease (responsiveness arm) were later re-assessed. For the current study, only patients from the responsiveness arm were included, regardless of whether they had experienced improvement at follow-up.

All participating centres received approval from their local ethics committee (Supplementary Data S1, available at *Rheumatology* online) to conduct the study and investigate the collected outcomes and all participants provided written informed consent.

Treatment

Change in drug treatment was the main exposure and included initiation of an NSAID, csDMARD or TNFi. Patients were allowed to have received similar drugs before. The timing of follow-up depended on the type of drug started at baseline: 2–24 weeks after initiation for NSAIDs and 12–24 weeks after initiation for csDMARDs/TNFis. Information on drug treatment was physician reported.

Depressive symptoms

The presence and extent of depressive symptoms was the main outcome and was assessed with the Hospital Anxiety and Depression Scale depression subscale (HADS-D) [25]. The HADS-D contains seven items, each scored on a scale of 0–3, resulting in a sum score of 0–21 (best–worst). Thresholds for 'possible depression' (HADS-possible) and 'probable depression' (HADS-probable) are scores of $\geq$8 and $\geq$11, respectively. HADS-D was completed at baseline and follow-up.

Demographics and disease characteristics

Demographic and disease characteristics were collected at baseline with questionnaires completed by patients and their physicians and included age, gender, SpA subtype, human leucocyte antigen B27 (HLA-B27) status, symptom duration, history of extra-musculoskeletal manifestations (EMMs: uveitis, psoriasis, IBD), education level, employment, CRP (measured $<$3 weeks ago) and current medication.

The following outcomes were collected at baseline: disease activity was assessed with the CRP-based Ankylosing Spondylitis Disease Activity Score (ASDAS), the BASDAI [26, 27] and a single global patient-reported item concerning last week's disease activity (PtGA); pain and well-being were assessed by single global items; physical function was measured with the BASFI [28]; overall function and health were assessed with the ASAS HI and the 36-item Short Form [SF-36; summarized as the Physical Component Summary (PCS) and the Mental Component Summary (MCS) [29, 30]. For all these measures, except the PCS/MCS, lower scores indicate a better outcome.

At follow-up, all outcome measurements described above were repeated. In addition, patients were asked to indicate whether they experienced improvements in disease impact when compared with baseline.

Statistical analysis

Baseline characteristics were described and compared between treatment groups (based on the treatment initiated at baseline: NSAID, csDMARD, TNFi) using analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables and the chi-squared test for categorical variables.

Pre–post comparisons (follow-up *vs* baseline) were conducted within each treatment group for depressive symptoms (HADS-D, both absolute score and proportion of patients with HADS-possible or HADS-probable) and for other outcomes (including disease activity, physical function and inflammation) using paired *t*-tests or Wilcoxon matched-pairs

signed-rank tests for continuous variables and McNemar's test for categorical variables. Next, change from baseline in these outcomes was compared between treatment groups using ANOVA. Effect size (Cohen's d_z = mean change/pooled SD.; 0.20–0.49 small effect, 0.50–0.79 moderate effect, ≥0.8 large effect [31]) was calculated for the change in depressive symptoms in the overall population and for each treatment group. Post hoc tests were adjusted for multiple testing using Tukey's (ANOVA) or Dunn's test (Kruskal–Wallis).

Next, linear regression analyses were conducted to assess any association between treatment group [categorical: NSAIDs [reference], csDMARDs, TNFis) and the outcome (change in depressive symptoms according to HADS-D) while adjusting for other variables. First, potential confounders (SpA subtype, HLA-B27 status, symptom duration, history of EMMs, education, employment) that were associated with the outcome ($P < 0.10$ in univariable analysis) were added to the treatment group in a multivariable model ('base model') and retained if statistically significant upon inclusion ($P < 0.05$). Age and gender were always included in multivariable analysis. In a next step, measures of disease activity (change in ASDAS/BASDAI/CRP) or physical function (change in BASFI) were each added in separate models (because of collinearity) to see if any association between treatment group and outcome would remain after taking improvement of SpA into account. Similar regression analyses were conducted using logistic regression, with possible depression (HADS-D ≥8, yes/no) and probable depression (HADS-D ≥11, yes/no) at follow-up as the outcome, while adjusting for potential confounders as well as baseline HADS-D status.

Sensitivity analyses were conducted by (1) only including the subgroup of patients with elevated CRP (≥5 mg/l) at baseline; (2) using the absolute HADS-D at follow-up as the outcome instead of the change in HADS-D in a negative binomial regression with adjustment for baseline HADS-D (negative binomial regression was chosen due to the skewed distribution of absolute HADS-D scores); (3) adjusting for time between baseline and follow-up assessment; and (4) stratifying by SpA subtype (axSpA/pSpA), even if there were no signs of confounding or effect modification (stratification by SpA subtype was a pre-planned analysis). Before any analyses, collinearity and interactions between variables were checked for. In case of a relevant interaction, analyses were stratified. Missing data were not imputed. *P*-values <0.05 were considered statistically significant. Analyses were conducted in Stata SE version 14.0 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

In total, 1548 patients were assessed at baseline. Of these, 304 had a therapeutic change and were included in the current study: 102 patients received an NSAID, 45 a csDMARD and 157 a TNFi. At baseline, the mean age was 37.3 years (SD. 12.6), 190 (63%) were male, 260 (85%) had axSpA and the mean ASDAS was 3.3 (SD. 1.1) (Table 1). The mean HADS-D was 6.9 (SD. 4.2), with 126 (42%) having possible depression and 66 (22%) probable depression. Twenty patients (6.6%) indicated they received treatment for depression.

Baseline characteristics were largely similar across the different treatment groups, with some minor differences (Table 1). As expected, newly initiated treatment was related to current treatment (e.g. those who were already on a TNFi at baseline were more likely to receive another TNFi instead of a csDMARD or NSAID). Also, patients in which a csDMARD was initiated less often had the axial subtype. Depressive symptoms (HADS-D) were numerically higher in the TNFi group (7.4) compared with the NSAID (6.6) and csDMARD (5.9) groups. Of note, disease activity, physical function and inflammation did not differ significantly between treatment groups at baseline.

Pre–post comparison and change from baseline

The mean time between the baseline and follow-up assessment was 6.3 weeks (SD. 4.0) for NSAIDs, 15.0 weeks (SD. 2.5) for csDMARDs and 15.6 weeks (SD. 5.1) for TNFis. At follow-up, all outcomes had improved significantly compared with baseline, both in the overall population and in the treatment subgroups (Fig. 1, Supplementary Table S1, available at *Rheumatology* online). Most patients [$n = 244$ (80.8%)] indicated that the impact of their disease had improved compared with baseline. The mean HADS-D decreased from 6.9 (SD. 4.2) to 5.1 (SD. 4.2) in the overall population [$\Delta = -1.9$ (SD. 3.8), Cohen's $d_z = -0.45$; $P < 0.01$ pre–post comparison). The change in HADS-D was larger for those who received a TNFi [$\Delta = -2.4$ (SD. 3.9), Cohen's $d_z = -0.56$] compared with those who received an NSAID [$\Delta = -1.3$ (SD. 3.8), Cohen's $d_z = -0.32$; $P < 0.05$ *vs* TNFi] or csDMARD [$\Delta = -1.2$ (SD. 3.4), Cohen's $d_z = -0.32$; $P = 0.15$ *vs* TNFi]. Similar differences between treatment groups were seen for other outcomes, such as ASDAS, BASDAI and ASAS HI (Fig. 1). Improvement in the HADS-D was comparable between patients with axSpA and pSpA [NSAIDs/csDMARDs/TNFis: $\Delta = -1.3/-0.9/-2.4$ (axSpA) *vs* $\Delta = -1.4/-1.6/-2.3$ (pSpA)].

At follow-up, 85 (28%) and 31 (10%) patients had possible and probable depression, respectively, compared with 126 (42%) and 66 (22%) at baseline ($P < 0.01$ for both). Proportions of possibly and probably depressed patients decreased most in those who received a TNFi (Table 2). Patients without (self-reported) improvement following the therapeutic change were more likely to have probable depression at follow-up (23.7% *vs* 7.0%).

Regression analyses

There were no relevant interactions in the regression analyses. In univariable linear regression analyses, treatment with a TNFi was associated with a greater improvement in depressive symptoms [$\beta_{\text{TNFi } vs \text{ NSAID}} = -1.17$ (95% CI −2.13, −0.20)]. This association remained when adjusting for age, gender and HLA-B27 status in multivariable analysis [$\beta_{\text{TNFi } vs \text{ NSAID}} = -1.27$ (95% CI −2.23, −0.32)] (Table 3). However, when the change in disease activity (ASDAS or BASDAI) was added to the model, this association largely disappeared [ASDAS model: $\beta_{\text{TNFi } vs \text{ NSAID}} = -0.51$ (95% CI −1.58, 0.55); a similar observation was seen in the BASDAI model], suggesting that disease activity mediated this relationship. In contrast, adjustment for CRP did not have a similar effect on the association between treatment and the change in depressive symptoms (Table 3). Additionally, a greater improvement in ASDAS, BASDAI or BASFI was itself associated with a greater improvement in depressive symptoms, while this was not seen for CRP (Table 3; Supplementary Table S2, available at *Rheumatology* online).

Observations in logistic regression analyses were similar (Table 4). Adjusted odds of having 'possible depression'

Table 1. Baseline characteristics of the overall study population and by treatment initiated

Characteristics	All ($N = 304$)	Treatment initiated at baseline		
		NSAID ($n = 102$)	csDMARD ($n = 45$)	TNFi ($n = 157$)
Age, years, mean (S.D.)	37.3 (12.6)	35.0 (12.3)	38.4 (13.9)	38.5 (12.4)
Male, *n* (%)	190 (62.9)	69 (67.6)	21 (46.7)[a]	100 (64.5)
High education, *n* (%)	140 (46.4)	50 (49.0)	20 (44.4)	70 (45.2)
Employed, *n* (%)	191 (63.2)	67 (65.7)	30 (66.7)	94 (60.6)
axSpA, *n* (%)	259 (85.8)	96 (94.1)	26 (57.8)[a]	137 (88.4)[b]
Symptom duration, years, mean (S.D.)	11.4 (10.0)	10.9 (10.2)	7.7 (6.6)	12.9 (10.4)[b]
HLA-B27 positive, *n* (%)	200 (66.2)	71 (69.6)	27 (60.0)	102 (65.8)
History of uveitis, *n* (%)	65 (21.8)	12 (11.9)	5 (11.1)	48 (31.6)[a,b]
History of psoriasis, *n* (%)	33 (11.1)	6 (5.9)	10 (22.7)[a]	17 (11.2)
History of IBD, *n* (%)	22 (7.5)	5 (5.2)	1 (2.2)	16 (10.7)
Current medication[c], *n* (%)				
NSAID	224 (74.2)	66 (64.7)	39 (86.7)[a]	119 (76.8)
csDMARD	75 (24.8)	22 (21.6)	12 (26.7)	41 (26.5)
TNFi	48 (15.9)	5 (5.0)	1 (2.2)	42 (27.1)[a,b]
ASDAS, mean (S.D.)	3.3 (1.1)	3.3 (1.0)	3.2 (1.1)	3.4 (1.1)
CRP, mg/L, mean (S.D.)	16.8 (23.2)	14.6 (21.5)	15.8 (23.4)	18.5 (24.2)
Elevated CRP (≥5 mg/L), *n* (%)	179 (63.0)	55 (59.8)	28 (62.2)	94 (64.8)
BASDAI (0–10), mean (S.D.)	5.5 (2.2)	5.3 (2.3)	5.3 (2.3)	5.7 (2.1)
BASFI (0–10), mean (S.D.)	4.1 (2.7)	3.6 (2.7)	4.3 (2.8)	4.4 (2.7)
PtGA (0–10), mean (S.D.)	6.2 (2.4)	5.9 (2.7)	6.0 (2.6)	6.4 (2.2)
Well-being (last week) (0–10), mean (S.D.)	6.1 (2.5)	5.7 (2.7)	5.9 (2.8)	6.5 (2.2)[a]
Pain (0–10), mean (S.D.)	5.9 (2.5)	5.5 (2.6)	6.0 (2.6)	6.2 (2.5)
ASAS-HI (0–17), mean (S.D.)	8.3 (4.0)	7.8 (4.0)	7.8 (4.1)	8.8 (3.9)
HADS-D (0–21), mean (S.D.)	6.9 (4.2)	6.6 (4.0)	5.9 (3.8)	7.4 (4.3)
SF-36 PCS (0–100), mean (S.D.)	35.8 (9.8)	38.3 (10.2)	34.3 (9.7)	34.6 (9.4)[a]
SF-36 MCS (0–100), mean (S.D.)	40.7 (10.1)	40.7 (10.4)	42.7 (10.0)	40.1 (9.8)

[a] $P < 0.05$ compared with NSAIDs (adjusted for multiple testing).
[b] $P < 0.05$ compared with csDMARDs (adjusted for multiple testing).
[c] Medication at baseline, before therapeutic change.

(HADS-D ≥8) at follow-up were reduced by >50% for those receiving TNFis compared with those on NSAIDs [odds ratio $(OR)_{TNFi\ vs\ NSAID} = 0.47$ (95% CI 0.23, 0.94)]. After additional adjustment for disease activity (ASDAS/BASDAI) or physical function (BASFI), this association between treatment and depressive state was attenuated. Disease activity or physical function itself was associated with the outcome, with a greater improvement being associated with lower odds of possible depression at follow-up (Table 4; Supplementary Table S3, available at *Rheumatology* online). For CRP, no such effect was observed. Baseline HADS-D status was a very strong predictor for follow-up HADS-D status in all analyses (OR range 16.31–25.15 in various models). Similar analyses with 'probable depression' (HADS-D ≥11) at follow-up were conducted as well, with mostly similar results, but these should be interpreted with caution due to the small number of patients having 'probable depression' at follow-up ($n = 31$) (Supplementary Table S4, available at *Rheumatology* online).

Sensitivity analyses

The sensitivity analyses showed similar results. Compared with initiation of NSAIDs, initiation of TNFis was associated with a lower absolute HADS-D at follow-up (sensitivity analysis 1), with a greater improvement in HADS-D from baseline in those with an elevated baseline CRP (sensitivity analysis 2) or after adjustment for time between the baseline and follow-up assessment (sensitivity analysis 3), and this association was attenuated when adjusted for ASDAS/BASDAI but not CRP (Supplementary Tables S5–S7, available at *Rheumatology* online).

There were no signs that the subtype of SpA (axSpA/pSpA) acted as a potential confounder or effect modifier in the analyses. Nonetheless, pre-planned analyses by SpA subtype (sensitivity analysis 4) were conducted to see if results from the main analysis would also be observed in diagnostic subgroups. In the axSpA subgroup ($n = 95/26/136$ for initiation of NSAIDs/csDMARDs/TNFis, respectively), results were similar to those of the main analysis: mean HADS-D improved significantly from baseline [$\Delta = -1.9$ (S.D. 3.5)] and TNFis had a greater effect than NSAIDs. Furthermore, results suggested no difference between csDMARDs and NSAIDs in axSpA, or even a smaller effect for csDMARDs, although only a few patients with axSpA received a csDMARD (Supplementary Table S8, available at *Rheumatology* online). In the much smaller pSpA subgroup, improvement in the HADS-D was similar [$\Delta = -2.0$ (S.D. 3.9)]. However, results from the main regression analysis could not be reproduced. Of note, in addition to the small sample size for pSpA ($n = 6/19/19$ for initiation of NSAIDs/csDMARDs/TNFis, respectively), the effect sizes for the drug types were substantially smaller or even close to zero when compared with those in the axSpA subgroup (Supplementary Table S8, available at *Rheumatology* online). Additional adjustment for current depression treatment at baseline (yes/no) yielded similar results (post hoc analysis, results not shown).

Discussion

In this prospective observational study in daily practice, pharmacological treatment of active SpA resulted in a significant reduction of depressive symptoms and odds of

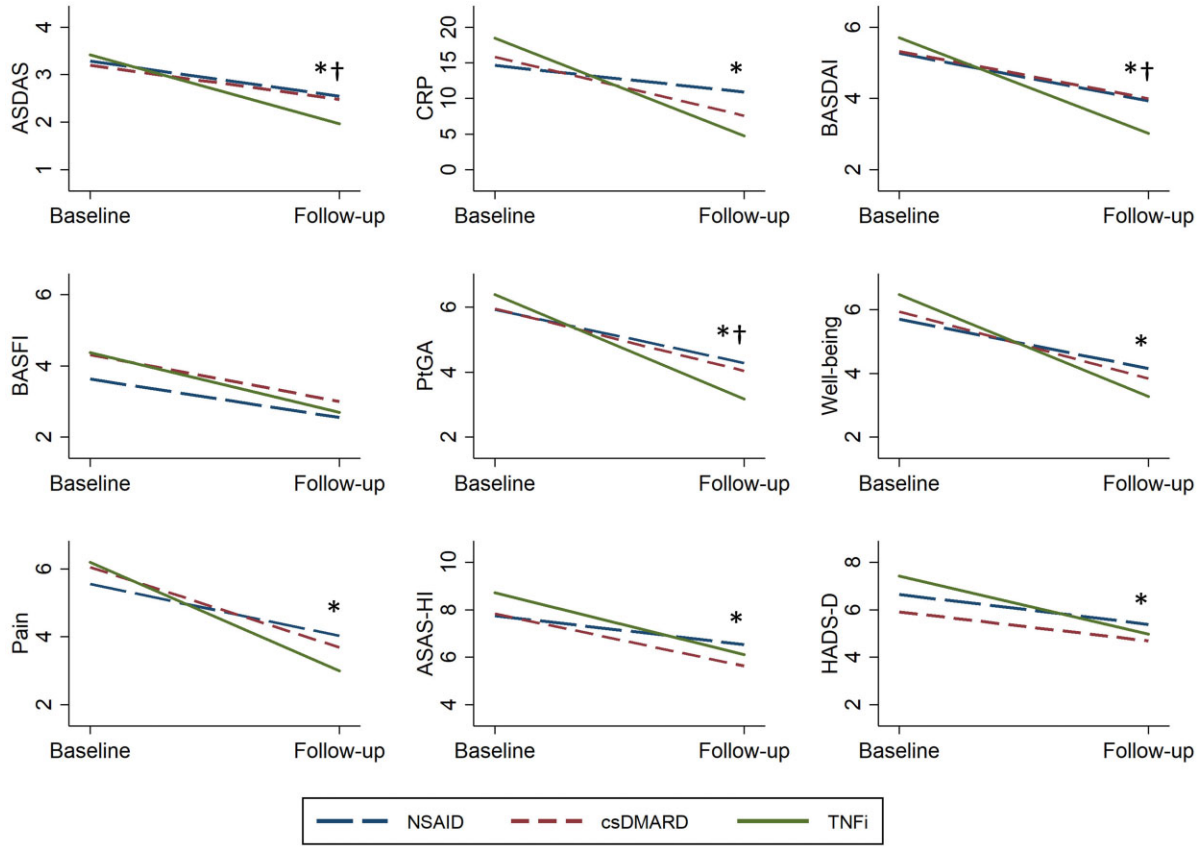

Figure 1. Change from baseline in outcomes by treatment initiated at baseline. The scale of the *y*-axis for each outcome was adjusted to best fit the data. For all outcomes, values had significantly improved at follow-up compared with baseline in the overall population and in each of the treatment subgroups. Numerical values (means and S.D.s) are presented in Supplementary Table S1, available at *Rheumatology* online. *Significant difference between TNFi *vs* NSAID in change from baseline (adjusted for multiple testing). †Significant difference between TNFi *vs* csDMARD in change from baseline (adjusted for multiple testing). For none of the outcomes was there a significant difference in change from baseline between csDMARD *vs* NSAID

Table 2. Depression classification according to the HADS-D score at baseline and follow-up

Classification	Baseline, *n* (%)	Follow-up, *n* (%)	*P*-value[a]
Possible depression (HADS-D ≥8)			
All patients ($N = 303/300$)[b]	126 (42)	85 (28)	<0.01
By drug type			
NSAID ($n = 101$)	38 (38)	32 (32)	
csDMARD ($n = 45$)	13 (29)	9 (20)	
TNFi ($n = 157/154$)[b]	75 (48)	44 (29)	
Probable depression (HADS-D ≥11)			
All patients ($N = 303/300$)[b]	66 (22)	31 (10)	<0.01
By drug type			
NSAID ($n = 101$)	20 (20)	13 (13)	
csDMARD ($n = 45$)	5 (11)	3 (7)	
TNFi ($n = 157/154$)[b]	41 (26)	15 (10)	

[a] For comparison of proportion with possible/probable depression before (baseline) and after treatment (follow-up).
[b] Number of patients at baseline/number of patients at follow-up with non-missing outcome.

(possible/probable) depression. Treatment with TNFis was associated with a greater improvement of depressive symptoms and lower odds of depression compared with treatment with NSAIDs. This effect could largely be explained through improvement of disease activity and/or physical function, while CRP-mediated inflammation did not seem to contribute directly. Of note, it is unclear whether these results apply to axSpA only or also to pSpA.

Several previous studies in SpA investigated the effect of TNFis on depressive symptoms [18–21]. One RCT did not find a significant difference between etanercept and placebo in non-radiographic axSpA, although both groups improved significantly [19]. Another RCT observed a larger improvement in depressive symptoms with etanercept compared with sulfasalazine in radiographic axSpA (r-axSpA) [18]. More recently, an ancillary analysis of an RCT in r-axSpA found that, compared with placebo, the extent of depressive symptoms and probability of being possibly depressed decreased substantially with infliximab treatment [16]. In pSpA, RCTs of TNFis did not report on depressive symptoms. In one RCT in early pSpA, overall mental health improved significantly with golimumab compared with placebo [32]. Of note, in all of these studies, depression or mental health was investigated as a secondary outcome or part of a post hoc analysis, and using different instruments. In addition to RCTs, several observational studies reported an effect of TNFis on depressive symptoms, but these were typically without a comparator group, of limited duration and included small samples [20, 21, 33]. The current observational study confirms overall the observations described above and demonstrates the effect of TNFis on depressive symptoms in SpA in daily practice. Furthermore, we observed that NSAIDs and csDMARDs also improved depressive symptoms in SpA, but to a lesser extent

Table 3. Multivariable linear regression analysis of the change in HADS-D from baseline

Variable[a]	Base model		ASDAS model		BASDAI model		CRP model		BASDAI+CRP model	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Age, years	**0.04**	**0.00, 0.07**	0.03	−0.01, 0.07	**0.03**	**0.00, 0.06**	**0.04**	**0.00, 0.08**	0.03	−0.01, 0.06
Male	0.23	−0.67, 1.14	0.55	−0.39, 1.49	0.28	−0.54, 1.10	0.27	−0.71, 1.24	0.34	−0.55, 1.23
HLA-B27 (*vs* negative)										
Positive	**1.56**	**0.46, 2.67**	**1.38**	**0.27, 2.49**	**1.17**	**0.17, 2.18**	**1.35**	**0.19, 2.52**	1.07	−0.00, 2.13
Unknown	**1.70**	**0.19, 3.22**	**2.21**	**0.66, 3.75**	**1.41**	**0.04, 2.77**	**2.10**	**0.49, 3.72**	**1.72**	**0.24, 3.20**
Therapy started (*vs* NSAID)										
csDMARD	0.19	−1.16, 1.54	0.02	−1.34, 1.39	0.14	−1.07, 1.36	0.12	−1.30, 1.54	−0.14	−1.44, 1.16
TNFi	**−1.27**	**−2.23, −0.32**	−0.51	−1.58, 0.55	−0.23	−1.13, 0.67	**−1.27**	**−2.34, −0.19**	−0.59	−1.59, 0.42
ASDAS, change from baseline	–	–	**1.27**	**0.84, 1.71**	–[b]	–[b]	–[b]	–[b]	–[b]	–[b]
BASDAI, change from baseline	–	–	–[b]	–[b]	**0.78**	**0.60, 0.96**	–	–	**0.75**	**0.54, 0.95**
CRP, change from baseline	–	–	–[b]	–[b]	–	–	0.02	−0.00, 0.04	0.00	−0.02, 0.02

Statistically significant associations ($P < 0.05$) are in bold. Change from baseline variables were calculated as follow-up score − baseline score. Negative coefficients reflect a greater improvement in HADS-D.

[a] Variables not included in the final multivariable model: education, employment, SpA subtype, symptom duration, history of EMMs [not potentially associated with outcome in univariable analysis ($P \geq 0.10$)].

[b] Due to collinearity, ASDAS was not included in models with BASDAI/CRP and vice versa.

Table 4. Multivariable logistic regression analysis of possible depression (HADS-D ≥8) at follow-up

Variable[a]	Base model		ASDAS model		BASDAI model		CRP model		BASDAI + CRP model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Possible depression at baseline[b]	**17.20**	**8.62, 34.31**	**18.40**	**8.59, 39.39**	**25.15**	**11.67, 54.17**	**16.31**	**7.86, 33.84**	**24.76**	**10.77, 56.88**
Age, years	**1.03**	**1.01, 1.06**	**1.03**	**1.00, 1.06**	1.03	1.00, 1.05	**1.04**	**1.01, 1.07**	1.03	1.00, 1.06
Male	1.39	0.72, 2.69	1.68	0.80, 3.55	1.51	0.73, 3.11	1.36	0.67, 2.74	1.62	0.74, 3.54
Therapy started (*vs* NSAID)										
csDMARD	0.50	0.18, 1.42	0.52	0.18, 1.52	0.61	0.21, 1.73	0.47	0.16, 1.39	0.50	0.17, 1.52
TNFi	**0.47**	**0.23, 0.94**	0.65	0.29, 1.46	0.79	0.36, 1.71	**0.45**	**0.21, 0.99**	0.64	0.27, 1.50
ASDAS, change from baseline	–	–	**0.58**	**0.41, 0.83**	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]
BASDAI, change from baseline	–	–	–[c]	–[c]	**0.65**	**0.55, 0.78**	–	–	**0.63**	**0.52, 0.77**
CRP, change from baseline	–	–	–[c]	–[c]	–	–	1.00	0.99, 1.02	1.01	0.99, 1.03

Statistically significant associations ($P < 0.05$) are in bold.

[a] Variables not included in the final multivariable model: SpA subtype, HLA-B27, symptom duration, history of EMMs [not associated with outcome in univariable analysis ($P \geq 0.10$)], education, employment (associated with outcome in univariable analysis, but not after adjustment for other variables).

[b] Defined as HADS-D ≥8.

[c] Due to collinearity, ASDAS was not included in models with BASDAI/CRP and vice versa.

than TNFis. Of note, patients were not randomized to treatment, as this was an observational study, which means that confounding by indication could occur (a patient's disease state affecting both the drug type initiated and the severity of depressive symptoms). However, baseline values for a range of disease characteristics and outcomes were comparable between treatment groups, suggesting a similar disease state. In addition, we adjusted for relevant confounders, such as disease activity, to take this into account. Also, in addition to the change (improvement) in depressive symptoms, the severity at follow-up (absolute extent) of depressive symptoms was also lower for those who received TNFis compared with NSAIDs.

Previous studies in populations with or without rheumatic disease pointed towards a link between inflammation and depression [10, 34]. Examples include correlations between peripheral inflammatory biomarkers and depression in general populations (CRP, TNF-α, IL-1, IL-6) and in axSpA (ESR) [8, 9]. Although we did observe differences between drug classes regarding depressive symptoms—which might suggest that inflammation in some way contributes to depression in SpA, as these drugs influence the immune system in different ways—this could be mainly attributed to differences between these drug classes regarding improvement of symptoms of SpA. These findings are similar to a previous analysis in axSpA [16]. It is important to emphasize that this does not necessarily indicate that inflammation does not play a role in the pathophysiology of depression in SpA. First, our study focused on the change in depressive symptoms following drug treatment of SpA. It is still possible that inflammation had some role in the pathogenesis of these depressive symptoms. Second, we only used CRP as inflammatory marker. It is unclear whether CRP is an appropriate biomarker to investigate the link between inflammation and depression in SpA. Not all patients with SpA have increased CRP levels. Of note, in depressed populations without rheumatic disease, CRP as a peripheral inflammatory biomarker strongly correlates with central immune activity and is considered a reliable inflammatory marker for depression research [35]. Still, the results of the current study and several others suggest that other biomarkers should be explored in future studies on comorbid depression. On this line, it is of interest that many chemokine changes associated with depression are present in otherwise healthy populations, but not in those with somatic comorbidity [36]. Possibly, background inflammation as present in

inflammatory diseases such as SpA can mask the role of inflammation in depression [37].

The current study has several limitations. First, assessment of (the impact of SpA treatment on) depression was not the primary purpose of this cohort. Although specifically designed to detect depression, the HADS-D is a self-reported screening instrument and not the gold standard to diagnose depression. We did have some information on patient-reported treatment for depression, but not on physician-diagnosed depression or antidepressant use (although likely not all depressed patients were diagnosed as such and not all depressed cases are treated with antidepressants). Second, as discussed above, we limited the impact of confounding by indication but cannot exclude residual confounding. Third, the subgroup of patients with pSpA was rather small, precluding robust conclusions for this subpopulation.

Strengths of the current study include the longitudinal design and the availability of different treatment groups, which helped facilitate interpretation of the observed changes in depressive symptoms. Also, a range of outcomes was included, which were all assessed with validated instruments.

Studies over the last decades have demonstrated that patients with SpA are at increased risk for depression [3, 4]. Our observation that the most used anti-inflammatory treatments in SpA also improve comorbid depressive symptoms should provide a positive outlook for these patients and their care providers. However, it should be noted that, even in those who reported improvement of SpA in our study, a quarter was still possibly depressed at follow-up and 1 in 15 were probably depressed. This highlights an unmet need in patients with SpA in daily practice. Currently it is unknown whether these patients would benefit from a change in disease management, such as additional therapies or referral to a mental health specialist. Future studies should address this issue. Future studies could also address whether the current findings apply to anxiety as well.

In conclusion, anti-inflammatory treatment of active SpA also improves comorbid depressive symptoms. In axSpA, TNFis have a greater effect than NSAIDs on these symptoms, which can be mainly explained by a stronger effect on disease activity and physical function. This could not be confirmed in pSpA. We did not find evidence for a direct link between CRP-mediated inflammation and depressive symptoms in SpA. Comorbid depressive symptoms are present in a relevant proportion of patients with SpA treatment response, highlighting an unmet need in this population that warrants further investigation.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

The data underlying this article are available in the article and in its online supplementary material.

Authors' contributions

C.W. and A.B. conceived the study. C.W. conducted the analyses. All authors interpreted the results, revised the manuscript critically for important intellectual content and approved the final manuscript.

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