Treatment of early rheumatoid and undifferentiated arthritis

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CHAPTER 10

THE RELATIONSHIP BETWEEN DISEASE ACTIVITY AND DEPRESSIVE SYMPTOMS SEVERITY AND OPTIMISM – RESULTS FROM THE IMPROVED-STUDY

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ABSTRACT

Objectives: To assess depressive symptoms severity and dispositional optimism in patients with recent onset arthritis both before and after 4 months treatment.

Methods: Two hundred twenty-two patients with recent onset RA and undifferentiated arthritis in the IMPROVED study filled out the Beck Depression Inventory (BDI-II) to assess depressive symptoms severity and the Life Orientation Test Revised (LOT-R) to measure optimism before and after 4 months of treatment. All patients were treated with methotrexate 25 mg/week and prednisone 60 mg/day (tapered to 7.5 mg/day in 7 weeks). Linear regression analysis was used to assess the association between the disease activity score (DAS) and its components (tender joint count, general well-being measured with a visual analogue scale (VAS), swollen joint count, and erythrocyte sedimentation rate) with the BDI-II an LOT-R scores.

Results: In general, depressive symptoms were mild. The DAS was an independent predictor of depressive symptoms scores both at baseline and after 4 months follow-up, in particular tender joint count and VAS global health. Disease activity was not associated with the level of optimism. Nevertheless, patients who achieved clinical remission improved significantly more in both depression score and optimism score than patients who did not.

Conclusion: Patients with early arthritis report improvement in depressive symptoms and optimism with improvement in disease activity and achieving clinical remission. Depression scores are associated with pain and unwell being but not with swollen joint counts and inflammatory parameters.

INTRODUCTION

Depressive symptoms are more common in patients with rheumatoid arthritis (RA) compared to healthy individuals.[1-4] The etiology of the association between RA and depressive symptoms is poorly understood.[2] Pain and disability may negatively affect mood (and vice versa), but inflammatory processes itself may also play a role in inducing depressive symptoms.[5, 6] Suppression of disease activity might improve depressive symptoms.[3] However, anti-rheumatic treatment with oral corticosteroids, in particular in higher dosages, may also induce psychiatric disorders including depression, anxiety, delirium and (hypo)mania.[7-10] To investigate the relationship between disease activity and mood, we assessed levels of depressive symptoms and dispositional optimism[11] in patients with recent onset arthritis who were treated with methotrexate and a high tapered dose of prednisone with the aim to induce clinical remission in the IMPROVED-study.

PATIENTS AND METHODS

The IMPROVED-study is a multicenter investigator driven clinical trial among patients with recent onset arthritis, designed and conducted by rheumatologists in 12 cooperating hospitals in the western part of the Netherlands. The Medical Ethics Committee of each participating center approved the study protocol, and all patients gave written informed consent. Patients with undifferentiated arthritis (UA) and recent onset RA were included. Recent onset RA was defined according to the ACR/EULAR 2010 classification criteria[12] with a duration of symptoms ≤2 years. UA patients had at least one joint clinically assessed as 'arthritis' and at least one other tender joint, in the opinion of the rheumatologist clinically suspected to represent early RA but not fulfilling the 2010 ACR/EULAR criteria. All patients that were recruited between March 2007 and September 2010 were at least 18 years old, disease modifying anti-rheumatic drug naïve, and had a disease activity score (DAS) ≥1.6. Exclusion criteria included pregnancy, malignancy within the last 5 years, bone marrow hypoplasia, elevated liver enzyme levels (AST and/or ALT >3 times normal value), serum creatinine level >150 umol/l or estimated creatinine clearance of <75 %, uncontrolled diabetes mellitus, uncontrolled hypertension, heart failure (NYHA class III/IV), alcohol or drug abuse, serious infections in the previous 3 months or chronic infectious disease, opportunistic infections within previous 2 months, active or latent hepatitis B, HIV infection or AIDS, lymphoproliferative diseases, and multiple sclerosis.

All patients received initial treatment for the first 4 months with methotrexate 25 mg/week and prednisone 60 mg/day, tapered to 7.5 mg/day in 7 weeks.

At baseline and after 4 months, a trained assessor performed a full joint evaluation and calculated a DAS. The patients were asked to fill out a visual analogue scale (VAS) for global well-being, the Health Assessment Questionnaire (HAQ),[13] and questionnaires on educational level, job participation, and productivity. Separate informed consent was

obtained for additional questionnaires, the Beck Depression Inventory II (BDI-II) and the Life Orientation Test Revised (LOT-R).[14, 15]

The BDI-II is a 21-item questionnaire to assess depressive symptoms severity according to the diagnostic criteria as stated by the DSM-IV. It is scored as the sum of scores (0–3). Missing values, e.g., unanswered questions (12 questions in the baseline questionnaire, 15 questions in the 4-month questionnaire) were replaced with zero. This is the neutral answer in all questions; in case of the question about 'sadness', 0 means 'I don't feel sad'. Patients with a total score of 0–13 are defined as having minimal depressive symptoms, a score of 14–19 denotes mild depressive symptoms, 20–28 moderate depressive symptoms, and 29–63 severe depressive symptoms.[14]

Dispositional optimism was assessed by using the LOT-R. The LOT-R is a 10-item continuous scale to measure optimism.[15] The questionnaire consists of six score items and four filler items, answered on a 0–4 Likert scale (0 strongly disagree, 4 strongly agree). Three items are keyed in a positive direction and three in a negative direction, and negatively worded items (i.e., items 3, 7, and 9) are reversely coded. The total score is calculated as the sum of the score items (i.e., items 1, 3, 4, 7, 9, and 10), with a range between 0 and 24 and higher scores indicate greater optimism. Low dispositional optimism has previously been defined as a total score <12 (often yielding ±20 % of the subjects with the lowest scores).[16] Missing values were replaced with the rounded mean of the remaining score items if at least four of the six score items were filled out.[17] Previously, college students in the USA scored a mean (standard deviation (SD)) LOT-R score of 14.3 (4.3); patients after bypass surgery scored 15.2 (4.1).[15]

Statistical analyses

Comparison between participants of IMPROVED who filled out the BDI-II and LOT-R and participants who did not were analyzed using the independent *t* test, the Wilcoxon rank sum tests, and the χ^2 test at the 5 % level. Linear regression analysis was used to assess the relationship between DAS scores and depressive symptoms severity scores, both at baseline and at 4 months follow-up. We adjusted for age, gender, and alcohol use (yes/no) because these characteristics are known to be related to depressive symptoms as well as (changes in) disease activity. Given the possible association between the questionnaire outcomes on the one hand and marital status (not married and living alone, not married and living together, married, divorced, widow(er)), having children (yes/no), level of education (highest level of education: primary school, secondary education, vocational education, or university), employment (yes/no), and tobacco use (yes/no); on the other hand, the analyses were repeated with these covariates included in the model. The analyses to assess the relationship at follow-up were also adjusted for baseline disease activity and baseline questionnaire scores. Subsequently, separate analyses were done for the components of the DAS: tender joint count and patients' sense of general well-being, measured with a VAS as subjective components, and swollen joint count and erythrocyte

sedimentation rate (ESR) as objective components. Univariate and multivariate analyses were done separately for tender joint count and swollen joint count because of collinearity. The regression analyses were also done for the LOT-R questionnaire.

Finally, questionnaire outcomes were compared at baseline and after 4 months using the paired *t* test at the 5 % level. Differences in change scores of the BDI-II and LOT-R between patients who achieved remission (defined as a DAS <1.6[18]) and those who did not were evaluated with an ANCOVA model with remission achievement (yes/no) as factor and the baseline values of BDI-II or LOT-R as a covariate. Statistical analyses were conducted with SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of participants

Six hundred ten patients were included in the IMPROVED-study of whom 222 patients gave informed consent to also fill out the questionnaires and filled out at least one of the questionnaires at baseline or after 4 months. Of these, 211 patients completed the LOT-R and 215 patients completed the BDI-II both at baseline and follow-up. Patient characteristics are presented in table 1. Among patients who filled out the BDI-II and LOT-R questionnaires, a higher percentage was ACPA positive (p=0.050) and had children (p=0.03) compared to those who did not fill out the questionnaires (table 1).

Eight of 610 patients (1.3 %) reported having a depression in their medical history. None of these patients reported having ongoing symptoms, three reported using antidepressants and two patients reported being under care of a psychologist/ psychiatrist. Seven other patients reported using antidepressants without mentioning having a depression in their medical history.

Depressive symptoms severity over time

Disease activity was at both time points independently positively associated with depressive symptoms severity (baseline beta, 0.26, p<0.001 and 4 months, beta 0.31, p<0.001). The results did not change after adjustment for marital status, having children, level of education, employment, and tobacco use. At baseline, the DAS component VAS for global well-being and after 4 months, both tender joint count and VAS for global well-being, but not swollen joint count or ESR, were independently associated with BDI-II score (table 2).

After 4 months of treatment with methotrexate and prednisone, there was a significant decrease in mean BDI-II score in the entire group from 8.5 (SD 7.7) at baseline to 7.0 (SD 7.2) (95% CI -2.3; -0.6, p=0.001). Depressive symptoms after treatment were minimal, only 21 out of 215 (9.8 %) had mild depressive symptoms (BDI-II score 14–19), 11 out of 215 (5.1 %) had moderate (BDI-II score 20–28), and 5 out of 215 patients (2.3 %) had severe depressive symptoms (BDI-II >29). After 4 months, 138 patients (66 %) had achieved clinical remission, with a mean (SD) DAS of 0.9 (0.4). BDI-II scores after 4 months

Table 1. Baseline characteristics of 222 patients who filled out BDI-II and optimism questionnaires compared to all patients included in the IMPROVED study.

	Patients who filled out the BDI-II and LOT-R (n=222)*	Other IMPROVED patients (n=388)	p-value
Socio-demographics:			
Age (years)	51.4 ± 12.5	52.2 ± 14.7	0.45
Female sex	157 (71)	257 (66)	0.25
Married	143 (64)	237 (61)	0.40
Children	184 (83)	300 (77)	0.03
Higher education	73 (33)	177 (29)	0.12
Working	121 (55)	199 (51)	0.10
Disease characteristics:			
DAS	3.2 ± 0.9	3.2 ± 0.9	0.51
Duration of symptoms (weeks)	18 (9-36)	18 (9-32)	0.49
ACPA positive	134 (60)	199 (51)	0.050
ESR	24 (11-37)	25 (11-41)	0.21
Tender Joint count	6 (4-9)	6 (4-9)	0.96
Swollen joint count	6 (3-10)	5 (2-10)	0.38
VAS global health	44 ± 24	47 ± 23	0.10
HAQ	1.1 ± 0.7	1.2 ± 0.7	0.28
BDI-II	8.5 ± 7.7	-	-
LOT-R	16.7 ± 4.0	-	-
Health related factors:			
Smoking	63 (28)	114 (29)	0.79
Alcohol	130 (59)	232 (60)	0.67

Data are presented as means ± standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages (%) when appropriate. DAS: disease activity score, ACPA: anti-citrullinated protein antibody, ESR: erythrocyte sedimentation rate, VAS: visual analogue scale, HAQ: health assessment questionnaire, BDI-II: Beck Depression Inventory II, LOT-R: Life Orientation Test Revised.
*Data of patients who filled out at least one of the questionnaires, at one of the time points.

were significantly decreased in patients who achieved remission (mean (SD) 6.9 (6.4) to 4.8 (5.0), 95% CI -3.1; -1.2, p<0.001), but not in patients who did not achieve remission (mean (SD) 11.2 (8.9) to 11.0 (8.7), 95% CI -1.96;1.6, p=0.83). In patients who did achieve remission, the mean change in BDI-II was 4.0 (SE 0.8) points lower than in the patients who did not (p<0.001, figure 1).

Optimism over time

At baseline, disease activity was not associated with optimism scores as assessed with the LOT-R (beta 0.001, p=0.99). After 4 months, DAS score and LOT-R score (beta -0.14, p=0.02) were inversely associated, but this association disappeared after adjustment for age, gender, marital status, having children, level of education, employment, and alcohol and tobacco use (beta 0.02, p=0.79).

Table 2. The association between DAS-components and BDI-II, separately for tender joint count and swollen joint count.

	Crude beta (p-value)	Adjusted beta[1,2] (p-value)
Baseline		
Tender Joint Count	0.27 (<0.001)	0.12 (0.08)[1]
ESR	-0.004 (0.96)	0.02 (0.75)[1]
VAS	0.33 (<0.001)	0.31 (<0.001)[1]
4 months		
Tender Joint Count	0.41 (<0.001)	**0.14 (0.04)**[2]
ESR	0.04 (0.53)	0.04 (0.57)[2]
VAS	0.47 (<0.001)	**0.30 (<0.001)**[2]
Baseline		
Swollen Joint Count	0.11 (0.27)	0.04 (0.57)[1]
ESR	-0.004 (0.96)	0.01 (0.85)[1]
VAS	0.33 (<0.001)	0.34 (<0.001)[1]
4 months		
Swollen Joint Count	0.14 (0.04)	0.04 (0.79)[2]
ESR	0.04 (0.53)	0.04 (0.54)[2]
VAS	0.47 (<0.001)	**0.35 (<0.001)**[2]

1. Beta adjusted for: age, gender, alcohol consumption yes/no. 2. Beta adjusted for: age, gender, alcohol consumption yes/no, Disease Activity Score at baseline, outcome BDI-II at baseline.
ESR: erythrocyte sedimentation rate, VAS: visual analogue scale global health.

At baseline, the optimism score was 16.7 and after 4 months 16.5 (95% CI, -0.7; 0.3, p=0.42) in the entire group. The LOT-R scores for optimism and BDI-II scores for depressive symptoms severity were significantly associated both at baseline and after 4 months (beta -0.51, p<0.001) at baseline and (beta -0.44, p<0.001) after 4 months. Patients with higher optimism scores had less depressive symptoms.

Of the 211 patients who filled out the questionnaire twice, 138 (65.7 %) achieved remission after 4 months (mean (SD) DAS 0.9 (0.4)). LOT-R scores remained stable from baseline to 4 months, whether remission was achieved (mean (SD) 17.0 (4.1) to 17.1 (3.5), 95% CI -0.4; 0.7, p=0.08) or not (16 (3.9) to 15.2 (3.7), 95% CI -1.6; 0.1, p=0.68). Yet, the mean change in LOT-R was 1.4 (SE 0.4) points higher than in the patients who did not achieve remission (p=0.001, figure 1). In all patients, LOT-R scores were above the cut-off of 12.

DISCUSSION

In patients with recent onset rheumatoid and undifferentiated arthritis, disease activity showed a relationship with depressive symptoms severity. In patients who achieved clinical remission after 4 months of treatment with methotrexate and prednisone,

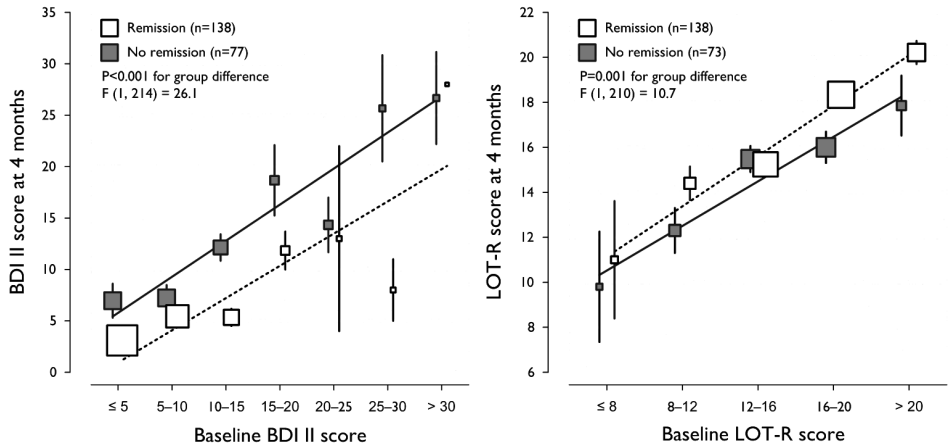

Figure 1. Difference between the patients with and without remission. The size of each square is proportional to the number of patients. Univariate regression lines are shown. P-values by analysis of covariance for the group difference, while adjusting for baseline values. Continuous values were used throughout the statistical analyses; categorization of baseline BDI-II and optimism scores was done for visualization purposes only. BDI-II: Beck Depression Inventory II, LOT-R: Life Orientation Test Revised.

both depression scores and optimism scores improved significantly more compared to patients who did not achieve remission.

Our intention was to monitor possible mood changes that might occur during treatment with the high tapered dose of prednisone used to try to induce remission of early arthritis in our patients. Depression, as well as mania, could be induced by corticosteroids.[10] Although we do not have a control group to compare the effect of corticosteroids, the finding that none of the patients in the IMPROVED-study expressed extreme values on either the depression or the optimism questionnaire, it is unlikely that prednisone greatly influenced depressive symptoms or optimism. More likely, the changes in mood scores that we saw are related to a previously described association between rheumatoid arthritis and depression.[4] The patients in the current study had early and relatively mild arthritis and did not carry the extra burden of joint destruction and the comorbidity of advanced rheumatoid arthritis, which may explain why only few patients had more than minimal depressive symptoms.

It has previously been hypothesized that the occurrence of depressive symptoms in RA is related to inflammatory processes and immune activation. This was based on the finding that in patients with depression, increased serum levels of cytokines IL-1, IL-6, and TNF-alpha were found.[5, 6] In our study, it appears that the depressive symptoms depended mostly on the presence and extent of joint tenderness on examination and reported global well-being as measured with a visual analogue scale rather than on joint swelling and increased erythrocyte sedimentation rate as signs of inflammation. Therefore, our results do not support the hypothesis on inflammation and depression but point into the direction of a relation between mood and pain.

This relation may be bidirectional, as already at baseline patients with more severe pain had more severe depressive symptoms, which is consistent with previous findings,[19] while patients who have more severe depressive symptoms may also be more susceptible for and report more pain.[20-22] Even if inflammation is well suppressed with prednisone and methotrexate, residual or non-inflammatory pain can prevent that the patient will be assessed as being in remission. This may explain why patients who did not achieve remission after 4 months had higher depression scores. And this in turn may be related to the fact that patients who did not achieve remission had significantly higher depression scores at baseline than patients who did achieve remission. Since all patients knew that the treatment goal in the IMPROVED trial was to achieve remission, after which medication would be tapered and finally discontinued, it may be that not achieving remission and therefore having to intensify medication also influenced feelings of depression.[3]

Changes in disease activity or arthritic symptoms in general were not related to level of optimism as measured with the LOT-R questionnaire which did not significantly change over time. This is possibly related to the fact that optimism levels at baseline were above the cut-off for low optimism in the majority of our patients. Also, in contrast to depressive symptoms, which are considered to be an affliction or reaction to events, optimism is a relative stable trait and one of the components of personality. Any differences in reported optimism over time appear to be limited and reverberate around what can be called an internal 'thermostat' of optimism.[23] Although the level of optimism after treatment in general did not significantly change in our patients, increase in LOT-R score was significantly higher in those who achieved remission compared to those who did not. Therefore, there may be a small state component to dispositional optimism. Our results also suggest that optimistic patients suffered less from depressive symptoms which in turn were influenced by arthritis related symptoms, especially pain and unwell being. Also, optimism influences pain and therefore possibly symptoms of arthritis. In general, baseline optimism has been related to slower disease progression and more efficient adjustment and coping strategies.[17, 24, 25]

A limitation of our study is that we chose self-report questionnaires to assess depressive symptoms severity and optimism because they are easy to answer and little time consuming. With the use of a structured psychiatric interview, the assessment of depressive symptoms in relation to RA disease activity might have been more extensive. The BDI-II provides a numerical score that makes it easy to assess improvement or reduction of the severity of depressive symptoms over time and a means to classify depressive symptoms severity. In view of the generally minimal reported depressive symptoms, we believe that the results are of scientific interests rather than of clinical significance.

We looked at optimism as a different focus on mood and chose the LOT-R to assess whether scores increase or decrease over time or in relation to changes in disease activity. However, although there are numerous reports on baseline optimism in relation to changes in aspects of (coping with) chronic illnesses, the literature on changes in repeated measurements of LOT-R scores in relation to changes in disease activity in patients with a chronic disease

are scarce. Previous studies on dispositional optimism in rheumatoid arthritis had cross-sectional designs, which therefore could not analyze effects on optimism in time.[26-28]

In conclusion, among these patients with early RA, treated with methotrexate and a tapered high dose of prednisone, generally already minimal depressive symptoms severity decreased with lower disease activity and was significantly lower in patients who achieve remission than in patients who do not. This appears to be mostly due to the relationship of depression severity with symptoms of arthritis (pain and unwell being) rather than signs of inflammation. Dispositional optimism scores in general stay stable over time, although there appeared to be significantly more improvement in optimism when remission was achieved. Our data suggest that depressive symptoms in RA patients may improve if, by targeted treatment, symptoms of RA are optimally suppressed.

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