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Original article

Depressive symptoms predict future simple disease activity index scores and simple disease activity index remission in a prospective cohort of patients with early inflammatory polyarthritis

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Abstract

Objective. To determine whether depressive symptoms assessed in treated patients with early inflammatory polyarthritis (EPA) influence disease activity during follow-up.

Methods. Consecutively recruited EPA patients were actively treated to remission. Simple disease activity index (SDAI) and Center for Epidemiologic Studies Depression Scale (CES-D) scores were calculated at inclusion and up to 42 months into disease. SDAI scores were log-transformed to compute univariate and multivariate linear regressions. Parametric interval-censored Kaplan–Meier and survival regressions using Weibull distribution were used to assess time to and predictors of SDAI remission.

Results. A total of 275 EPA patients were recruited at a median of 4 months into disease. In multivariate linear regression models, accounting for baseline demographic, clinical, serological and functional variables and 12-month inflammation markers, CES-D scores at 12 months into disease were correlated ($r^2 = 0.14$) with subsequent SDAI scores. Patients with 12-month high CES-D ($\geqslant 19$; suggestive of depression) had a lower proportion of SDAI remission (31.3% *vs* 84.3%; $P < 0.001$) and reached SDAI remission less rapidly [hazard ratio = 0.25 (95% CI 0.12, 0.53); $P < 0.001$].

Conclusion. Each follow-up SDAI correlated significantly with 12-month depressive symptoms, a median of 7 months after initiation of treatment. CES-D scores suggestive of depression at 12 months were strongly correlated with delay and failure to reach remission later on. Depressive symptoms in treated EPA patients represent important clinical issues with long-term association with disease activity. Interventions to alleviate persistent depressive symptoms in treated EPA warrant careful evaluation of their potential to improve disease remission rates.

Key words: rheumatoid arthritis, disease activity, outcomes research, psychology.

CLINICAL SCIENCE

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Rheumatology key messages

- Depression persisting after months of treat-to-target treatment of inflammatory arthritis markedly delays simple disease activity index remission.
- Depressive symptoms in treated-to-target arthritis patients were the best available biomarker to predict follow-up simple disease activity index.
- Treat-to-target strategies should include means to detect and address persistent depression in treated inflammatory arthritis.

Introduction

Early (or recent-onset) inflammatory arthritis is a syndrome grouping diseases with similar phenotypes. Recent classification criteria for early RA insist on the exclusion of systemic diseases and of non-immune causes, such as microcrystals, and emphasize the importance of larger numbers of affected joints (polyarthritis) to identify early RA within early inflammatory arthritis [1]. As a consequence, RA is the most frequent diagnosis emerging from early immune-mediated inflammatory polyarthritis (EPA) [1]. Aside from joint pain, deformity, stiffness and fatigue, patients with EPA and RA experience vexing psychological symptoms, such as sleep disturbance, depression and chronic pain [2]. Indeed, depression affects up to 42% of RA patients [2–4], two to three times the annual prevalence reported in the general American population (12% in men and 20% in women) [5].

The interplay between depression and RA disease activity is complex and poorly defined [6]. Definitions of RA and of depression both rely in part on subjective clinical assessments that may be affected by biological manifestations of the diseases [7]. For example, elevated pro-inflammatory cytokines negatively affect psychological adaptation to disease [8]. Disease remission in RA improves depression [9]. Conversely, depression increases pain, functional disability and poor perception of health status [10, 11], negatively impacting on the patient components of the simple disease activity index (SDAI) and DAS28 scores.

To our knowledge, the role of depression as a predictor of remission has been studied only short term in EPA patients treated with high-dose CS [12], but not long-term in EPA patients in general. Our study was initiated in 1998, long before the widespread use of composite activity indices (e.g. SDAI). From the beginning, we agreed as a group that, as the cardinal manifestation of inflammatory arthritis is synovitis, the best objective of treatment should be to reach a state in which no joint swelling would be detectable on careful physical examination. Treatment of our EPA patients was thus individualized to reach a swollen joint count (SJC) of 0 on 66 joints rapidly, using combinations of DMARDs and biologics, as required and clinically available, and the lowest doses of long-term CSs possible. From August 2006, questionnaires were used to assess depressive symptoms and disease activity prospectively. Our aim was to examine the impact on subsequent disease activity and disease remission of baseline depression and of depression persisting after initiation of treatment.

Methods

Patients

The longitudinal prospective Early Undifferentiated PolyArthritis (EUPA) cohort has been described previously [13–16]. We included consecutive adult patients evaluated at the Centre Hospitalier Universitaire de Sherbrooke (CHUS) and presenting at least three swollen joints for 1–12 months. Patients were excluded if they had bacterial or crystal-induced arthritis or if they met ACR criteria for a defined CTD or a defined systemic vasculitis [17]. Consenting patients were treated by rheumatologists with the objective of SJC = 0 on 66 joints, as described above [18, 19]. The Ethics Review Board of the CHUS approved the EUPA study (ClinicalTrials.gov ID: NCT00512239). This approval covers all analyses performed on the data.

Disease variables and outcomes

A rheumatologist assessed 68 joints for tenderness and 66 for swelling at baseline and during predefined follow-up visits at 12, 18, 30 and 42 months after onset of disease, allowing for an interval of ±3 months around visits. Additional interim visits were added as needed for optimal clinical care. Time of onset was defined as the self-reported week of first perception of inflammatory signs/symptoms. A trained coordinator performed a structured interview at each study visit to ensure data completeness. Collected data included age, gender, BMI, symptom duration, modified HAQ (M-HAQ), RF and anti-CCP2 antibody status [13, 14], current tobacco use, type and dose of arthritis drugs used (DMARDS, CSs and biologics), as well as the individual components of the SDAI score [SJC, tender joint count (TJC), CRP, Patient General Health Visual Analogue Scale (PtVAS), Physician Disease Activity VAS (MDVAS)] and the Center for Epidemiologic Studies Questionnaire [Center for Epidemiologic Studies Depression Scale (CES-D); see below]. We defined the primary outcome as remission according to a SDAI score $\leqslant$3.3 [20]. In sensitivity analyses, DAS28 using CRP (DAS28-CRP; http://www.das-score.nl) and ACR/EULAR definitions of remission were also used [21].

Depression questionnaire

The CES-D questionnaire was completed by patients at each visit [16, 22, 23]. It is a 20-item scale created to assess and detect depression in the general population. Reliability and discriminate validity are good [22, 23]. The patients rate, from 0 to 3, the frequency, in the past week, at which they had depressive symptoms (0 = rarely or

none and 3 = most or all the time). The reported scores can range from 0 to 60. Depression is suggested at a score of 16 in the general population, but we used the recommended cut-off of 19 with increased specificity in a rheumatic disease population [23].

Statistical analysis

Descriptive analyses were performed to characterize the study population. Binary variables were presented with frequencies and percentages and were compared between visits with Generalized Estimating Equation with repeated measures, where *P*-values were obtained with the Wald χ^2 method. Continuous variables were presented as mean (S.D.) or median and interquartile range (IQR) depending on their distribution and were compared over time with the Friedman test. As the use of continuous variables does not easily translate into the clinical situation, categorical thresholds were defined as high CES-D (score $\geqslant$19), suggestive of a need to assess depression, and SDAI remission. SDAI remission and high CES-D (score $\geqslant$19) were compared with the Pearson χ^2 test. Log-transformed SDAI scores were used to compute univariate and multivariate linear regression. As the exact time at which individual patients reached SDAI remission was unknown, parametric interval-censored Kaplan–Meier curves and parametric survival regressions using Weibull distribution were computed. The right limit of interval was the time when remission was first observed and the left limit was the previous visit. Parametric and non-parametric (with right limit data) Kaplan–Meier curves were drawn to evaluate time to reach SDAI remission over the first 60 months of disease. Interval-censored Weibull survival regressions were used to determine which variables explained time to remission and to estimate hazard ratios (HRs) with 95% CI. Kaplan–Meier curves and Weibull regression using baseline variables started at inclusion; those using baseline and 12-month variables started at the 12-month visit, excluding patients already in remission at 12 months. For linear and Weibull survival regressions, one multivariate model was performed with all baseline variables and another with both baseline and 12-month variables with $P < 0.1$. All analyses used only available data without imputation (<5% missing values for each variable). Statistical analyses were performed with SAS software version 9.3 and GraphPad Software version 6. Two-sided $P < 0.05$ was considered significant.

Results

Patient characteristics at baseline

Until 30 October 2013, the ongoing EUPA cohort included a total of 669 patients, 349 of whom were recruited after the CES-D questionnaire was added to the protocol in August 2006. Twenty-four patients had been included too recently to have been followed up by 30 October 2013. We excluded 23 patients because they did not complete their CES-D questionnaires at baseline. Twenty-seven of the 302 remaining patients dropped out (including one death) before any scheduled follow-up visit and were also excluded. The baseline characteristics of the 275 evaluable patients are presented in Table 1. The 27 drop-outs had similar baseline characteristics, except for fewer positive anti-CCP2 (13% *vs* 35%) and 1.5 years less education, on average. The median (IQR) duration of follow-up was 37 months (17.5–—56.9).

Evolution of CES-D and SDAI scores

From inclusion, there was a rapid decrease in CES-D scores (Table 2). The number of patients with high CES-D, that is, CES-D score $\geqslant$19, declined from 45% at inclusion to 24% at the 12-month visit. This 12-month visit (calculated from the onset of symptoms) occurred a median of 7 months after the baseline visit. The prevalence of high CES-D was stable afterwards, remaining at 19% by 42 months. Forty of the 123 (32.4%) patients with high CES-D ($\geqslant$19) at baseline still had high CES-D at 12 months; these represented 71.4% of the 56 patients with high CES-D at 12 months. Women had numerically but not statistically higher mean CES-D scores at all visits (data not shown). The SDAI score also fell rapidly from inclusion to 42 months (Table 2). Over the same period, the percentage of patients with SDAI remission reached 40%. Biomarkers of inflammation markedly decreased between baseline and 12 months: median SJC from 9 to 2, TJC from 7 to 2 and CRP from 9.1 to 1.0 mg/l (Table 2).

High CES-D defined as CES-D $\geqslant$19 and SDAI remission

Using cut-offs for SDAI and CES-D, high CES-D scores at baseline predicted failure to attain SDAI remission at 12 and 18 months, but only high 12-month CES-D also predicted failure to attain SDAI remission at all subsequent visits (Fig. 1). Similar results were obtained with the ACR/EULAR and DAS-28-CRP definitions of remission (supplementary Figs S1 and S2, respectively, available at *Rheumatology* Online).

CES-D and time to SDAI remission

High CES-D at both baseline and 12 months predicted time to SDAI remission as well as the proportion of patients who attained remission over time (Fig. 2). The median time to reach SDAI remission in the full cohort was 25.4 months. Between inclusion and 12 months, 14/123 (11.4%) patients with baseline CES-D $\geqslant$19 and 34/152 (22.4%) with baseline CES-D <19 reached SDAI remission ($P < 0.05$). Interval-censored time to remission was longer in patients with high CES-D at baseline compared with the other patients, 33.8 *vs* 22.9 months, Weibull HR (95% CI) = 0.68 (0.48, 0.95); $P = 0.025$. The proportion of patients who attained remission was also different: 74.9% with baseline high CES-D and 85.8% in the other patients.

Median time from 12 months to remission was 22.6 months with 12-month CES-D <19, but time to remission could not be defined (only 31.3% ever reaching remission) for patients with 12-month high CES-D. The Weibull HR (excluding patients in remission at 12 months) was 0.25 (95% CI 0.12, 0.53; $P < 0.001$) for patients with 12-month

high CES-D. The proportion of patients with 12-month CES-D <19 ever reaching remission over 5 years was 84.3%.

In Weibull multivariate regression using baseline variables only, CES-D, SJC, CRP, BMI and M-HAQ were significant to explain time to reach remission (Table 3). When baseline and 12-month variables (including M-HAQ) with a univariate $P < 0.1$ were used, 12-month CES-D and BMI were the only variables increasing time to reach SDAI remission (Table 3).

Table 1 Baseline characteristics of the 275 patients

Characteristic	Inclusion (*n* = 275)
Age, median (IQR), years	60.7 (51.8–69.8)
Women, *n* (%)	174 (63.3)
BMI, mean (S.D.), kg/m^2	26.8 (5.3)
Duration of symptoms, median (IQR), months	3.9 (2.3–6.5)
Education, mean (S.D.), years	11.7 (3.6)
Tobacco use, *n* (%)	
Current	44 (16.0)
Previous	123 (44.7)
ACR 1987 RA criteria fulfilled, *n* (%)	214 (78.7)
ACR/EULAR 2010 RA criteria, *n* (%)	236 (86.5)
RF ⩾ 40 IU/ml, *n* (%)	96 (35.8)
Anti-CCP2 positive, *n* (%)	97 (35.3)

IQR: interquartile range.

CES-D as independent predictor of SDAI scores over follow-up

In univariate analyses, baseline CES-D explained about 0.05 of the SDAI variability at each subsequent follow-up (Table 4). In multivariate analyses using baseline variables, only CES-D scores and BMI remained consistently significant regarding subsequent SDAI scores (Table 4, Model 1).

In univariate analyses, 12-month CES-D scores explained about 0.14 of SDAI variability at later visits (Table 4). Given that survival analyses indicated that patients with high CES-D at 12 months were less likely to reach remission, we computed a multivariate model incorporating all baseline and 12-month variables with a univariate $P < 0.1$ (Table 4, Model 2). The 12-month CES-D ($r^2 \approx 0.14$) was the only consistent predictor of SDAI at each follow-up visit. Adding 12-month M-HAQ to multivariate model 2 resulted in 12-month CES-D being predictive of SDAI at 18 and 30 months but not at 42 months, without increasing the strength of the model; 12-month M-HAQ was not independently predictive of SDAI at any visit (data not shown).

Discussion

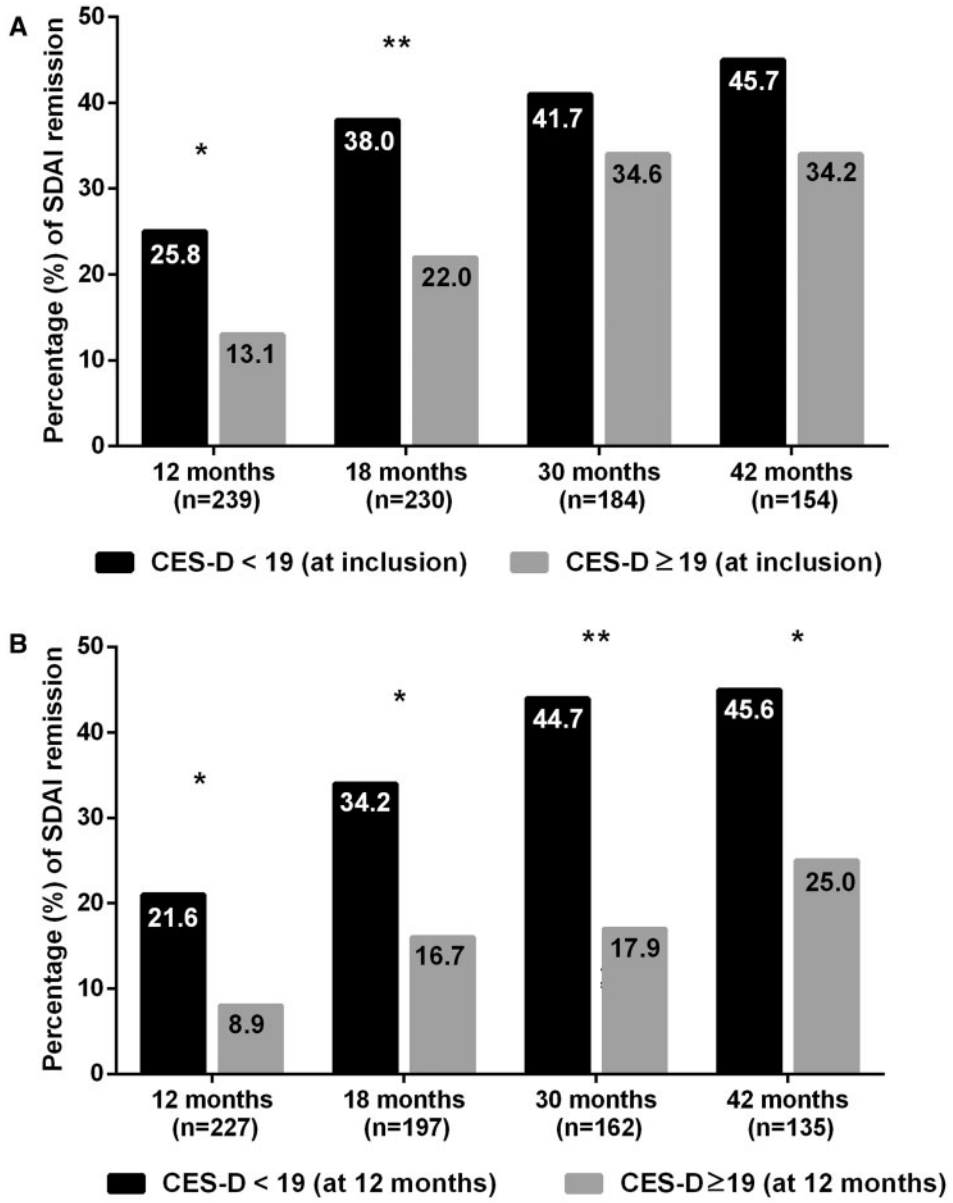
The prospective nature of our study allowed us to determine the relative contribution of a number of baseline and early variables to disease activity observed longitudinally. High (⩾19) CES-D scores, suggestive of depression, at baseline but especially at 12 months into disease

Table 2 Comparison of selected characteristics measured at baseline and at 12, 18, 30 and 42 months into disease

Characteristic	Inclusion (*n* = 275)	12 months (*n* = 249)	18 months (*n* = 239)	30 months (*n* = 190)	42 months (*n* = 157)
M-HAQ, median (IQR)	0.8 (0.3–1.4)	0.3 (0–0.6)	0.1 (0–0.6)	0.1 (0–0.5)	0.1 (0–0.5)
M-HAQ ⩾1.0, *n* (%)	111 (40.4)	34 (14.1)	25 (11.4)	20 (11.3)	18 (12.3)
CES-D, median (IQR)	17.0 (11.0–25.6)	12.0 (7.0–18.0)	12.0 (6.0–17.0)	9.0 (5.0–16.0)	11.0 (5.0–17.0)
CES-D ⩾19, *n* (%)	123 (44.7)	56 (24.4)	47 (21.3)	32 (18.3)	26 (18.7)
DMARD before visit, *n* (%)	40 (14.5)	239 (96.0)	235 (97.9)	189 (98.9)	155 (98.7)
Current CS at the visit, *n* (%)	56 (20.4)	47 (18.9)	26 (10.8)	16 (8.4)	9 (5.7)
Biologics in the last year, *n* (%)	1 (0.4)	14 (5.6)	28 (11.7)	41 (21.5)	31 (19.8)
SDAI score, median (IQR)	28.2 (17.1–40.3)	9.2 (4.2–18.4)	6.3 (2.8–11.8)	5 (2–8.8)	4.6 (1.5–8.6)
SDAI remission, *n* (%)	0 (0)	48 (20.1)	70 (30.4)	71 (38.6)	62 (40.3)
DAS28-CRP, median (IQR)	4.8 (3.9–5.8)	2.9 (2–3.9)	2.4 (1.8–3.4)	2.1 (1.6–2.9)	2.2 (1.6–2.8)
DAS28-CRP remission, *n* (%)	14 (5.1)	97 (40.6)	133 (57.8)	126 (68.5)	108 (70.1)
ACR/EULAR remission, *n* (%)	2 (0.7)	31 (13.0)	41 (17.8)	42 (22.8)	43 (27.9)
SDAI components					
SJC28, median (IQR)	9 (5–14)	2 (0–5)	0 (0–3)	0 (0–2)	0 (0–1)
TJC28, median (IQR)	7 (3–12)	2 (0–5)	0 (0–3)	0 (0–2)	0 (0–1)
PtVAS, median (IQR), mm	53.0 (32.0–76.0)	34.5 (11.0–56.0)	27.0 (10.0–52.0)	21.0 (5.0–48.0)	19.0 (5.0–48.0)
PtVAS ⩽10 mm, *n* (%)	26 (9.5)	57 (23.6)	60 (26.1)	60 (32.4)	56 (36.1)
MDVAS, median (IQR), mm	39.5 (26.0–67.0)	14.0 (4.0–35.0)	6.0 (1.0–21.0)	3.0 (0–17.0)	2.0 (0–13.5)
CRP, median (IQR), mg/l	9.1 (1.0–27.0)	1.0 (1.0–9.0)	3.2 (1.0–7.0)	1.0 (1.0–6.0)	1.0 (1.0–5.6)

All comparisons between variables at baseline and at each follow-up visit were highly significant ($P < 0.001$). CES-D: Center for Epidemiologic Studies Depression scale; IQR: interquartile range; MDVAS: Physician Disease Activity Visual Analogue Scale; M-HAQ: Modified Health Assessment Questionnaire; PtVAS: Patient General Health Visual Analogue Scale; SDAI: Simple Disease Activity Index; SJC28: swollen joint count on 28 joints; TJC28: tender joint count on 28 joints.

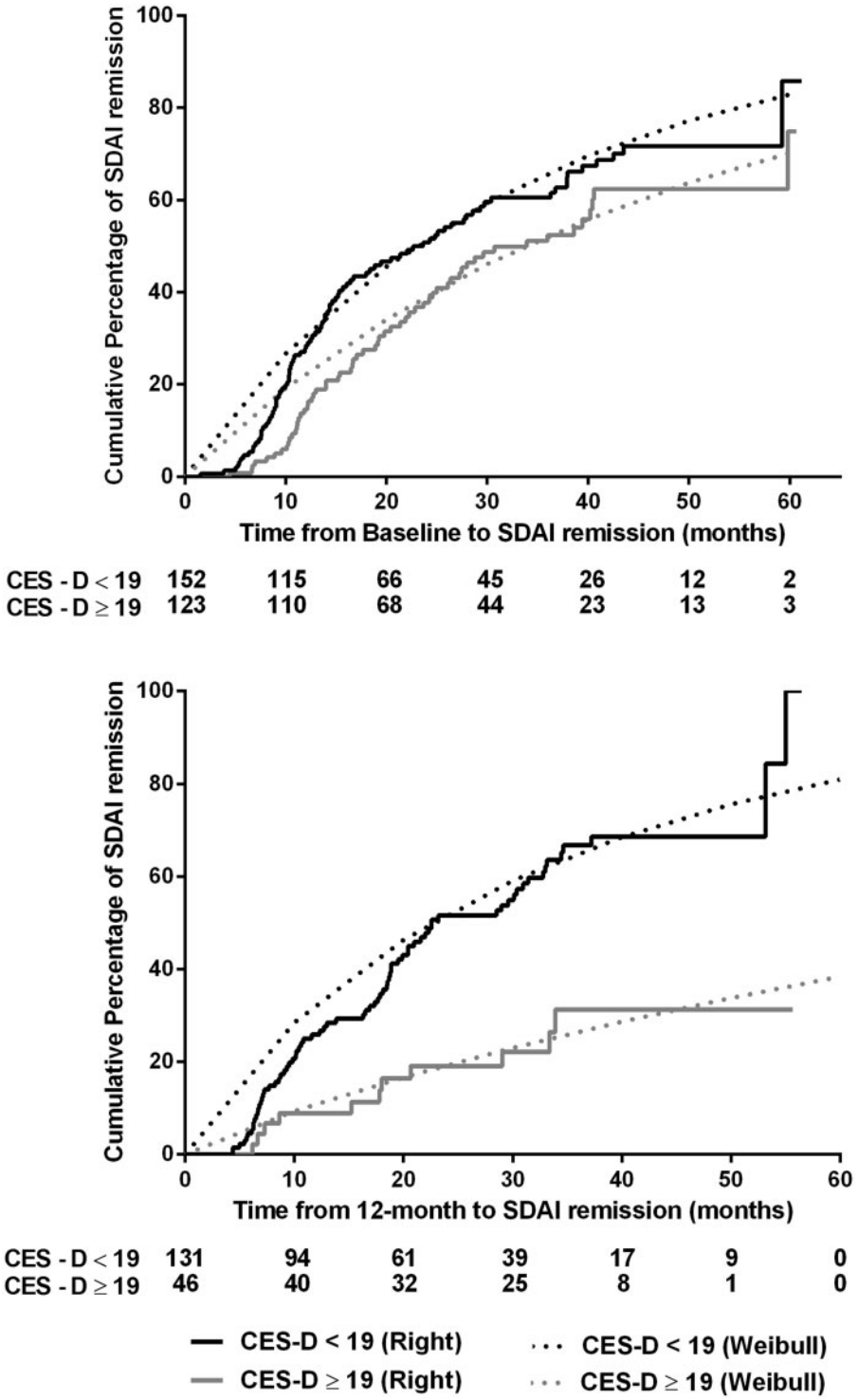
FIG. 1 Comparison of SDAI remission over time with depression



At inclusion (**A**) and at 12 months (**B**). CES-D at 12 months was not available from 12 patients who were included very late in the inclusion period, that is, close to 12 months after disease onset. *$P < 0.05$, **$P < 0.01$. CES-D: Center for Epidemiologic Studies Depression scale; SDAI: Simple Disease Activity Index.

predicted a lower SDAI remission rate in EPA patients, despite active DMARD and/or biologic treatment aimed at rapid control of joint and systemic inflammation (SJC = 0/66). CES-D at baseline and at 12 months, respectively, explained about 5% and 15% of the SDAI variability at 30 and 42 months. The impact of CES-D scores at 12 months surpassed that of variables typically used as predictors of future disease activity, such as age, gender, BMI, TJC, SJC, autoantibodies, M-HAQ and CRP. Only BMI and 12-month SJC28 also contributed significantly to SDAI prediction at some time points. High CES-D scores persisting at 12 months into disease, a median of 7 months after the baseline visit, and, to a lesser extent, high CES-D at baseline also predicted a longer time to attain SDAI remission. Finally, having high CES-D scores at 12 months markedly decreased, from 84.3% to 31.3%, the proportion of patients who ever reached remission during the observation period. Only functional scores such as HAQ were previously shown to have such a significant predictive value [24, 25]. HAQ integrates multiple factors in addition to arthritis-induced joint inflammation and damage, such as musculoskeletal, cardiovascular and neurological co-morbidities, limitation due to age, and patient-related components that may or may not be

Fig. 2 Kaplan–Meier curves to evaluate time to reach SDAI remission according to CES-D scores



Given that the exact date at which individual patients reached SDAI remission was unknown, parametric interval-censored (smooth curves) and non-parametric (with right limit data; staircases) Kaplan–Meier curves are presented. For reasons of clarity, we do not present the non-parametric left limit staircase curve. (**A**) The median interval-censored time to reach SDAI remission was significantly longer in patients with high CES-D scores at inclusion: 33.8 *vs* 22.9 months, Weibull hazard ratio (95% CI) = 0.68 (0.48, 0.95), $P = 0.025$. (**B**) the median interval-censored time from the 12-month visit to reach SDAI remission was 22.6 months in patients without 12-month high CES-D scores, while remission was reached by only 31.3% of the patients with high 12-month CES-D scores, over the period of observation, Weibull hazard ratio (95% CI) = 0.25 (0.12, 0.53), $P < 0.001$. CES-D: Center for Epidemiologic Studies Depression scale; SDAI: Simple Disease Activity Index.

Table 3 Multivariate Weibull survival regression for time to SDAI remission

	Interval-censored Weibull regression	
	Univariate Hazard ratio (95% CI)	Multivariate Hazard ratio (95% CI)
Model 1, baseline variables only	($n = 275$)	($n = 271$)
CES-D, per unit	0.97 (0.96, 0.99)**	0.98 (0.96, 1.00)*
Age, years	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)
Gender	0.98 (0.69, 1.38)	1.05 (0.75, 1.47)
BMI, kg/m^2	0.93 (0.90, 0.96)***	0.95 (0.91, 0.98)**
Duration of symptoms, months	1.01 (0.96, 1.07)	1.01 (0.95, 1.07)
Current tobacco use	0.63 (0.38, 1.04)	0.73 (0.45, 1.17)
Anti-CCP2 positive	1.17 (0.83, 1.65)	1.23 (0.82, 1.87)
RF positive	1.04 (0.74, 1.47)	0.95 (0.62, 1.46)
CRP, mg/l	1.00 (1.00, 1.01)	1.01 (1.00, 1.01)*
SJC28	1.00 (0.98, 1.03)	1.04 (1.00, 1.07)*
TJC28	0.98 (0.95, 1.00)	0.97 (0.94, 1.00)
M-HAQ, per unit	0.59 (0.44, 0.78)***	0.65 (0.45, 0.92)*
Model 2 ($P < 0.1$)	($n = 188$)	($n = 187$)
CES-D at inclusion, per unit	0.98 (0.95, 1.00)*	1.01 (0.99, 1.04)
CES-D at 12 months, per unit	0.93 (0.9, 0.96)***	0.95 (0.91, 0.98)**
BMI, kg/m^2	0.92 (0.87, 0.97)**	0.94 (0.90, 0.99)*
SJC28 at 12 months	0.91 (0.86, 0.98)**	0.98 (0.92, 1.05)
TJC28 at 12 months	0.89 (0.82, 0.96)**	0.97 (0.88, 1.07)
M-HAQ at inclusion, per unit	0.68 (0.46, 1.02)	1.01 (0.64, 1.60)
M-HAQ at 12 months, per unit	0.24 (0.12, 0.46)***	0.49 (0.22, 1.09)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. In Model 2, patients already in remission at 12 months were excluded. CES-D: Center for Epidemiologic Studies Depression scale; M-HAQ: modified HAQ; r^2: coefficient of determination; SJC28: swollen joint count on 28 joints; TJC28: tender joint count on 28 joints.

related to arthritis, such as pain, coping, depression, anxiety, anger, grief and sociocultural differences [26]. HAQ is thus best considered an outcome rather than a target of specific therapeutic interventions. On the contrary, our data strongly suggest that evaluation of persistent depressive symptoms using CES-D, a screening tool that is easy to complete and easy to score, identifies treated EPA patients at risk for an unfavourable course of disease. Assessment and treatment of depression in EPA patients, added to an optimized treat-to-target pharmacological treatment aimed at controlling inflammation, thus represents a significant issue to explore in order to improve disease outcomes.

CES-D is a well-characterized screening tool for depression in inflammatory arthritis, when set at a higher cut-off (CES-D $\geqslant$19) than in the general population (CES-D $\geqslant$16) [27]. Indeed, overlap between some symptoms of active inflammation and depression may spuriously increase CES-D scores [2, 3], particularly in untreated EPA patients and in patients with active inflammatory disease. As expected, CES-D scores at 12 months, a time when intensity of inflammation had significantly abated, were more negatively associated with SDAI remission at later times than were baseline CES-D scores. On the contrary, baseline and 12-month CRP, SJC and TJC, reflective of active joint inflammation, did not correlate with subsequent SDAI in multivariate models incorporating CES-D. It is plausible that many patients with high CES-D scores but low inflammation during follow-up may not have come to terms with the diagnosis and may still be distressed. This distress may contribute to persistently high PtVAS scores, the usual culprit for non-remission, although this clearly requires further investigation [28, 29].

The finding that higher CES-D scores are associated with increased SDAI scores and decreased remission rates suggests the importance of detecting depression early, in order to be able to treat it properly. Depression aggravates the functional consequences of RA by increasing work disability [30] and even mortality [31]. Unfortunately, RA patients are rarely assessed for depression, despite its high prevalence [32, 33]. In a recent study in patients taking high doses of CS, it was observed that patients not in remission at 4 months had higher depression scores [12]. However, our results are the first to demonstrate prospectively the contribution of depression in delaying and preventing remission over the long term. In addition, our data suggest that depression in untreated EPA patients may be a normal reaction and may not be strongly predictive of a poorer outcome by itself, if high CES-D at baseline had decreased to CES-D $<$19 by 12 months. Only those with high CES-D at 12 months, either persistent or developing after inclusion, were at increased risk of poorer clinical outcomes. It is thus the presence of depression in treated patients that bears a strong prognostic significance and needs our attention,

Table 4 Multivariate linear regression for SDAI at various times during follow-up

Model	12 months		18 months		30 months		42 months	
	Univariate r^2 * 100	100 * Regression coefficient (S.E.)	Univariate r^2 * 100	100 * Regression coefficient (S.E.)	Univariate r^2 * 100	100 * Regression coefficient (S.E.)	Univariate r^2 * 100	100 * Regression coefficient (S.E.)
Model 1 (baseline variables only)	($n = 239$)	($n = 236$)	($n = 230$)	($n = 226$)	($n = 184$)	($n = 183$)	($n = 154$)	($n = 153$)
r^2 * 100	–	16.88	–	11.49	–	14.70	–	20.14
CES-D	4.01**	0.26 (0.25)	3.26**	0.55 (0.27)*	5.87***	0.62 (0.29)*	4.69**	0.62 (0.31)*
Age, years	0.05	−0.03 (0.18)	0.00	0.05 (0.20)	0.74	0.33 (0.21)	3.17*	0.46 (0.25)
Gender	0.34	4.50 (5.18)	1.47	8.21 (5.37)	0.89	8.60 (5.73)	1.14	7.60 (6.53)
BMI, kg/m^2	2.39*	0.92 (0.45)*	2.78*	1.13 (0.48)*	4.94**	1.29 (0.50)*	5.53**	1.20 (0.57)*
Duration of symptoms, months	0.70	1.92 (1.09)	0.41	1.72 (0.97)	0.71	−1.02 (1.05)	0.40	1.77 (1.21)
Current tobacco use	0.73	−3.80 (3.57)	0.07	−0.89 (3.73)	0.29	−2.40 (4.01)	0.35	−2.57 (4.34)
Anti-CCP2 positive	0.21	9.49 (6.95)	0.05	5.64 (7.27)	0.30	10.78 (7.41)	0.13	−0.69 (8.40)
RF positive	0.05	−13.98 (6.97)*	0.25	−10.17 (7.29)	0.02	−4.04 (7.45)	0.22	−0.73 (8.86)
CRP, mg/l	1.08	0.07 (0.09)	0.50	−0.15 (0.09)	0.00	−0.11 (0.10)	0.03	−0.16 (0.12)
SJC28	0.08	−1.60 (0.54)**	0.03	−0.29 (0.57)	0.18	0.07 (0.60)	0.30	−0.43 (0.66)
TJC28	1.81*	1.51 (0.51)**	1.21	0.92 (0.55)	0.24	−0.30 (0.59)	3.76*	1.10 (0.65)
M-HAQ	7.26***	12.01 (5.04)*	2.18*	4.00 (5.31)	4.48**	7.98 (6.15)	6.98***	9.35 (6.82)
Model 2 (baseline and 12-month variables with univariate $P < 0.1$)	($n = 239$)	($n = 225$)	($n = 230$)	($n = 193$)	($n = 184$)	($n = 160$)	($n = 154$)	($n = 133$)
r^2 * 100	–	68.87	–	31.12	–	20.62	–	29.04
CES-D at inclusion	4.01**	−0.13 (0.17)	3.26**	−0.04 (0.29)	5.87***	0.18 (0.34)	4.69**	0.17 (0.36)
CES-D at 12 months	16.53***	0.54 (0.18)**	14.48***	0.94 (0.31)**	12.75***	0.84 (0.36)*	13.97***	0.80 (0.39)*
Age, years	0.05	−0.02 (0.11)	0.00	0.06 (0.19)	0.74	0.07 (0.22)	3.17*	0.43 (0.25)
Gender	0.34	3.68 (3.09)	1.47	8.05 (5.18)	0.89	4.44 (6.05)	1.14	8.06 (6.51)
BMI, kg/m^2	2.39*	0.35 (0.27)	2.78*	0.58 (0.45)	4.94**	1.14 (0.51)*	5.53**	0.84 (0.57)
CRP, at 12 months, mg/l	10.03***	0.49 (0.13)***	0.82	−0.02 (0.21)	0.56	−0.04 (0.24)	0.53	−0.08 (0.29)
SJC28 at 12 months	55.44***	3.62 (0.48)***	20.30***	1.97 (0.78)*	9.39***	1.96 (0.98)*	11.57***	0.43 (0.91)
TJC28 at inclusion	1.81*	−0.04 (0.24)	1.21	0.39 (0.41)	0.24	−0.47 (0.48)	3.76*	0.29 (0.51)
TJC28 at 12 months	52.27***	2.80 (0.54)***	20.12***	1.61 (0.91)	5.90**	−0.51 (1.09)	15.68***	2.16 (1.14)
M-HAQ at inclusion	7.26***	5.21 (2.85)	2.18*	−0.84 (4.85)	4.48**	4.06 (5.74)	6.98***	5.49 (6.32)
M-HAQ at 12 months	31.14***	–	14.22***	–	9.32***	–	21.88***	–

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. When 12-month M-HAQ was added to multivariate model 2, 12-month CES-D remained significant at 18 and 30 months but not at 42 months, and 12-month M-HAQ was not significant at any visit. At 42 months, no variable was significant, suggesting instability of the model, linked to moderate to high correlations of input variables. CES-D: Center for Epidemiologic Studies Depression scale; M-HAQ: modified HAQ; r^2: coefficient of determination; SJC28: swollen joint count on 28 joints; TJC28: tender joint count on 28 joints.

at least at a median of 7 months after initiation of intensive treat-to-target treatment.

Strengths of our study include the relatively large size of our cohort. Previous studies mostly addressed the effect of depression on pain, patient-related outcomes and fatigue, not on disease activity and remission. Our cohort consists of consecutive patients evaluated at a single centre with minimal loss to follow-up, bias and variability of evaluation and treatment. Our patients have been treated actively, following current treatment recommendations, and our observations are likely to be applicable in patients treated in a similar manner. The relatively long follow-up also allowed evaluation of long-term impact of early depression on remission.

Limitations include the use of a screening depression questionnaire. Although we used the recommended CES-D cut-off of 19 instead of the usual 16, a screening questionnaire cannot be used as a substitute for a diagnosis of clinical depression. In addition, we did not take into account any treatment for depression, used by patients at baseline or over the course of follow-up. The use of effective treatments in depressed patients could have blunted the true effect of depression on outcomes. Measuring CES-D earlier (e.g. 3 months after inclusion) could have yielded more or less positive correlations with subsequent SDAI. Finally, RA disease activity indices include the patient-derived PtVAS, a variable potentially more modified by depression than objective measures such as CRP or swollen joints. However, CES-D scores clearly give more clues to guide potential therapeutic interventions than does PtVAS. The consequences, if any, of early depression on objective measures of outcomes, such as radiographic scores of joint damage, use of biologic treatment and premature mortality, merit further study.

In conclusion, we propose that evaluation for depression should be viewed as important in the pursuit of remission in patients with EPA. Clinicians should be aware that depression during the first year of disease is associated with prolonged time to remission and decreased rates of remission, even in the favourable context of early diagnosis and treat-to-target approaches using the best pharmacological treatments of arthritis currently available. A causal relationship of early depression with higher SDAI scores during follow-up cannot be confirmed at this time. However, assessment of depressive symptoms during early follow-up visits identifies a variable that may potentially be modified in order to improve patient outcomes. Randomized controlled trials combining pharmacological and non-pharmacological interventions for depressed EPA patients are needed to evaluate whether controlling depression would indeed improve patient outcomes above the current situation.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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