Relationship between Depression and Disease Activity in United States Veterans with Early Rheumatoid Arthritis Receiving Methotrexate

Running Head: **Depression Rheumatoid Arthritis Methotrexate**

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Abstract

Objective: Depression is common in rheumatoid arthritis (RA) patients, exacerbates disease activity, and may decrease response to first-line disease-modifying antirheumatic drugs. This study aimed to determine if depression affects disease activity among Veterans with early RA prescribed methotrexate (MTX).

Methods: Participants included Veterans enrolled in the Veterans Affairs Rheumatoid Arthritis registry with early RA (onset < 2 years) prescribed MTX. Depression was assessed at enrollment using International Classification of Diseases codes (296.2-296.39, 300.4, 311). Disease activity was measured using the 28 joint count disease activity score (DAS-28) and other core measures of RA disease activity. Propensity score weights were used to adjust depressed (n=48) and non-depressed (n=220) patients on baseline confounders within imputed datasets. Weighted estimating equations were used to assess standardized mean differences in disease activity between depressed and non-depressed patients at six months and one- and two-years follow-up.

Results: The analytic sample was composed of 268 Veterans with early RA prescribed MTX who were predominantly male (n=239; 89.2%) and older (62.7 years $\pm$ 10.6) than general population RA patients. Adjusted estimates indicated that depression was associated with significantly higher DAS-28 at six months (β=0.345; 95% CI: 0.007, 0.682) but not at one- or two-years follow-up. Also, depression was associated with significantly worse pain at six months (β=0.385; 95% CI: 0.040, 0.730) and one-year (β=0.396; 95% CI: 0.042, 0.750) follow-up.

Conclusion: In early RA, depression is associated with greater short-term disease activity during MTX treatment, as well as more persistent and severe pain.

Introduction

Rheumatoid arthritis (RA) is an autoimmune, inflammatory joint disorder, which affects 1.3 million American adults, and causes joint pain and permanent physical disability (1, 2). RA disease burden extends beyond the joint, and extra-articular manifestations include poor psychosocial health, especially depression (3, 4). Major depression affects approximately 17% of RA patients and more than one-fifth report a history of depressive symptoms (5, 6). Depression exacerbates the societal and economic costs of RA and is associated with an increased risk of work disability, higher medical care costs, and greater comorbidity and mortality (7-9). These detrimental effects are related to the under-recognition and -treatment of depression among RA patients, which contrasts with clinical guidelines recommending that physicians be cognizant of depression in those with chronic physical diseases (10).

The unique occupational demands of military service have resulted in an increasing awareness concerning the burden of co-occurring musculoskeletal and psychiatric disorders (e.g., RA and depression) among United States (U.S.) Veterans (11). Evidence also suggests the relationship between musculoskeletal and psychiatric disorders among Veterans is bidirectional (11). Prior research supports this contention and indicates that depression onset in RA is preceded by worsening severity in patient- and physician-reported RA disease activity measures (12, 13). Similarly, depressive symptoms are associated with slower declines in RA disease activity as measured by patient- and physician-reported metrics (13). Analogous results regarding the association of depression with RA disease activity have been found among U.S. Veterans (11). Given that depression worsens the severity and progression of RA disease activity, it may adversely impact clinical response to standard therapies (3).

The current treat-to-target paradigm involves identifying a target (e.g., remission) during therapy; routinely evaluating disease activity; and regularly adapting treatment if the target is not achieved (14). Medical comorbidities may influence RA disease activity and progression, and in turn, response to pharmacologic therapy; thus, it is critical to understand how depression affects RA treatment outcomes (3, 4). Several studies have shown that depression is associated with worse clinical response to biologic disease-modifying antirheumatic drugs (bDMARDs) (3, 15-17). However, bDMARDs are used after RA patients have not responded to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (18). Methotrexate (MTX) is the preferred csDMARD for RA treatment because of its superior efficacy and tolerability profile, accounting for 60% of first-line medication prescriptions in Veterans with RA (19). Nonetheless, approximately 40% of RA patients do not have a clinical response to MTX, and poor psychosocial health is associated with non-response (20).

Research assessing the efficacy of RA treatments in the presence of depression is necessary, particularly MTX, which has not been rigorously evaluated in the context of psychiatric comorbidity (3). Given the high rate of depression among U.S. Veterans with RA and their under-utilization of MTX, despite being the optimal first-line therapy, the current study aimed to determine whether this comorbidity affects disease activity in early RA patients treated with MTX (11, 18, 21). It was hypothesized that Veterans with co-occurring RA and depression experience worse disease activity than those without depression despite MTX treatment.

Methods

Study Data & Sample

The current study used data from the Veterans Affairs Rheumatoid Arthritis (VARA) Registry, a cohort study of U.S. Veterans with RA, and design details are available elsewhere

(22). Briefly, VARA is a multicenter study that enrolled U.S. Veterans satisfying revised 1987 American College of Rheumatology RA classification criteria (23). Participants were from one of thirteen VA Medical Centers, and medications and ACR core measures of RA disease activity were recorded at each clinical encounter (22). All patients provided written informed consent before enrollment into the VARA study, which was approved by an Institutional Review Board (IRB) at each participating VA medical center. The current research was approved by the VARA Scientific and Ethics Advisory Committee and University of Maryland Baltimore IRB (HP-00075981). RA patients (n=2,692) who enrolled in the VARA registry from October 2002 to October 2018 were included in the current study (Figure 1). For this study, the VARA cohort was restricted to 635 individuals with new disease onset (duration < 2 years) at the time of enrollment in order to include those Veterans with RA who were most likely to have had a recent diagnosis and initiated their first csDMARD. Medication utilization, including glucocorticoids, bDMARDs, and csDMARDs were recorded during clinical encounters, and the analytic sample of Veterans with early RA was further limited to the those participants receiving MTX (n=268) (11, 24). The analytic sample represented 1662 clinical encounters among 268 Veterans with early RA treated with MTX.

Depression

The lifetime prevalence of depression has been demonstrated to influence the evolution of RA disease activity among Veteran and general population RA patients (11, 25). Additionally, the small number of Veterans with early RA being treated with MTX precluded (i.e., insufficient statistical power) a study design that excluded prevalent depression cases and identified incident depressive episodes prospectively. Thus, the primary exposure was operationalized as prevalent depression, occurring before or after RA onset, which was assessed

upon enrollment into the VARA registry. More specifically, treating providers enter comorbid conditions into the VARA database during enrollment using an associated International Classification of Disease, Ninth Revision (ICD-9) code (11). In contrast with other VA studies using administrative diagnostic codes for case ascertainment, comorbid conditions were not measured based on outpatient or inpatient claims data reported within specified time periods (26). Prevalent depression at study baseline measured and entered in to the VARA registry database by enrolling providers was defined using ICD-9 codes 296.2-296.39, 300.4, and 311.

Disease Activity

Differences in treatment-associated clinical outcomes were assessed using composite disease activity and ACR core measures of RA disease activity (27, 28). The primary outcome was the 28-joint count disease activity score (DAS-28), a measure incorporating tender and swollen joint counts based on 28 counts (TJC and SJC, respectively), patient global assessment of disease activity (PTGA; Visual Analogue Scale [VAS] 0-10 cm), and erythrocyte sedimentation rate (mm/hour), which is calculated using a mathematical formula: DAS-28=0.56×√TJC+0.28×√SJC+0.70×ln(ESR)+0.014×PTGA (28). Consistent with pharmacoepidemiologic recommendations, secondary outcomes included the disaggregated DAS-28 components, as well as the provider global assessment of disease activity (PRGA; VAS 0-100 mm), patient-reported pain (VAS 0-10 cm), and functional disability assessed using the multidimensional health assessment questionnaire (MDHAQ) (29, 30). Outcome measures were standardized (i.e., [observation-pooled sample mean]/pooled sample standard deviation), such that distributions were mean centered and normalized (i.e., mean=0; SD=1) and effect estimates could be interpreted in terms of standard deviations. Differences of 0.15, 0.4, and 0.75 standard deviations correspond to small, medium, and large effect sizes among older samples,

respectively (31). To address skewness of data, the SJC, TJC, and ESR distributions were log transformed before standardization, and if applicable, shifted by the lowest non-zero value. Due to between-person variability in the timing of data collection dictated by routine clinical care, RA disease activity was assessed from baseline through two years of follow-up as a trajectory, and 6-month and 1- and 2-year between-group differences in outcome measures were estimated to evaluate how depression affects disease activity during MTX treatment.

Potential Confounders

Participant characteristics selected a priori as potential confounders were identified from prior studies of depression in RA patients (13, 16, 25). Demographic and behavioral variables included age (years), sex (male or female), race (white or non-white), smoking status (current, former, never), and body mass index (BMI; kilograms per meters squared [k/m^2]). Comorbidity was assessed using a modified version of the rheumatic disease comorbidity index (RDCI), a composite scale (range 0-8) comprising eleven different medical conditions (32). In the current study, the RDCI omitted depression and was calculated using the following formula: 2 × lung disease + [2 × (heart attack, other cardiovascular disease, or stroke) or 1 × hypertension] + fracture + diabetes + cancer + (ulcer or stomach problem). Concomitant treatments included hydroxychloroquine, sulfasalazine, leflunomide, and tumor necrosis factor (TNF) inhibitors; notably, no participants included in the current study were receiving non-TNF inhibitor bDMARDs at baseline. Disease activity exhibits intra-individual clustering, and baseline values are the strongest predictor of RA treatment response (33). Without accounting for differences in baseline disease activity between depressed and non-depressed, any association between depression and treatment response could be due to residual confounding (16). Baseline disease

activity measures (SJC, TJC, PTGA, PRGA, ESR, MDHAQ, pain) were included as covariates to remove them as a potential source of confounding (33).

Statistical Analysis

Baseline characteristics in the original study sample were assessed using means and standard deviations or medians and interquartile ranges for continuous variables and frequencies and percentages for categorical measures. T-tests or Wilcoxon rank sum tests and chi-square tests were used to evaluate differences in baseline characteristics between depressed and non-depressed participants for continuous and categorical variables, respectively. Missing values for smoking, BMI, SJC, TJC, ESR, PTGA, PRGA, pain , MDHAQ, and DAS-28 were imputed from fully observed variables (age, sex, race, comorbidity, and concomitant treatments) using a multilevel, multiple imputation by chained equations (34). Fraction of missing data for every estimation parameter across different outcome models was never greater than 10%, and estimates for the main effect of depression converged and changed little as new imputations were added after twenty data sets; thus, twenty data sets were imputed and analyzed.

Propensity score weights were used to control for between-group differences in baseline covariates to promote causal interpretations regarding the effect of depression on disease activity (35). Inverse probability weights implemented in the propensity score context account for differences in the probability of exposure between two comparison groups by weighting the exposed and unexposed to represent the overall study sample. Boosted regression models were used to estimate propensity score weights, an approach that outperforms other estimation methods in terms of bias reduction (36). The generalized boosted model is a machine learning algorithm involving an iterative process of fitting multiple regression trees to evaluate and define complex and non-linear relationships between exposure and covariates without overfitting data

(36). An exposure model was fit by regressing depression status on covariates using the boosting algorithm separately on 20 imputed data sets to estimate weights. Standard methods for evaluating propensity score weights were conducted to assess the validity of the underlying theoretical assumptions (37).

Propensity score weighted generalized estimating equations (i.e., weighted estimating equations [WEE]) modeled outcome trajectories and estimated differences in RA disease activity between depressed and non-depressed participants (38). Locally weighted scatterplot smoothing (LOESS) is a nonparametric regression method that fits smoothing curves between predictors and outcomes while relaxing traditional modeling constraints (39). LOESS curves were used to conduct exploratory assessments of time trends and showed non-linear longitudinal functional forms for every outcome measure. Therefore, WEE clustered by participants modeled outcome trajectories as a cubic function (i.e., time + time^2 + time^3) to address non-linearity and had a categorical indicator for depression, three continuous variables for time, and statistical interactions between depression and time parameters. Models were estimated across multiply imputed datasets, and results were pooled using Rubin's combining rules (34). Causal mean differences in clinical outcomes between depressed and non-depressed participants were interpolated at six months and one- and two-years follow-up. Tests were two sided, an alpha level of 0.05 was used, and all analyses were conducted with R statistical software (version 3.4.1).

Results

Sample Characteristics

The original study sample included 48 and 220 depressed and non-depressed Veterans with early RA who were being prescribed MTX at baseline and had 283 and 1339 analytic

observations, respectively. The prevalence of major depressive disorder in this sample was approximately 18%, and comorbid depression was associated younger age and more comorbid conditions, but between-group differences in distributions for other covariates were not statistically significant (Table 1). Substantially more depressed than non-depressed RA patients were using hydroxychloroquine (47.9% versus 31.8%, respectively), and disease activity measures (DAS-28, TJC, SJC, PTGA, pain, MDHAQ) were consistently numerically higher in participants who had depression compared with those without depression, although these associations did not reach statistical significance.

Composite Disease Activity

DAS-28 trajectories (Figure 2) showed faster initial disease activity decline after study enrollment that plateaued by six-months follow-up in Veterans with early RA receiving MTX who did not have comorbid depression. By contrast, depressed participants experienced slower treatment-associated decreases in disease activity that did not intersect with non-depressed participants until after more than one-year of follow-up. Depression in Veterans with early RA treated with MTX was associated with significantly worse disease activity at 6-months follow-up, where depressed participants had DAS-28 scores approximately 0.345 standard deviations (95% CI: 0.007, 0.69; P=0.045) higher than non-depressed participants (Table 2). However, the differences in DAS-28 scores between those with and without depression decreased over time. The associations between baseline depression and DAS-28 at one- (β=0.145; 95% CI: -0.255, 0.545; P=0.477) and two-years (β=-0.067; 95% CI: -0.597, 0.463; P=0.804) follow-up were smaller in magnitude and not statistically significant.

Core Component Measures

Analogous to DAS-28 results, effect estimates for the SJC, TJC, PTGA, and ESR at 6-months follow-up ranged from 0.210-0.266 standard deviations, indicating higher disease activity among those with depression; however, the associations were not statistically significant (Table 2). The magnitude of the associations for DAS-28 component measures also decreased over time, and between-group differences were negligible by two-years follow-up. In contrast with the DAS-28 and its component measures, depression was associated with significantly higher patient-reported pain: 0.385 standard deviations (95% CI: 0.040, 0.730; P=0.029) at 6-months and 0.396 standard deviations (95% CI: 0.042, 0.750; P=0.028) at 1-year follow-up. However, associations for the PRGA and MDHAQ were smaller in comparison, not statistically significant, and generally decreased in magnitude over time.

Discussion

The current study examined disease activity trajectories among depressed and non-depressed Veterans with early RA receiving MTX therapy, and findings indicate that depression among these patients is associated with higher disease activity during the initial stages of treatment and more persistent pain after MTX initiation. More specifically, Veterans with co-occurring early RA and depression had significantly higher disease activity as measured by the DAS-28 six months after documented prescription of the most utilized first line csDMARD. However, differences in disease activity between depressed and non-depressed participants decreased as time progressed, and DAS-28 associations at one- and two-years follow-up were not statistically significant. By contrast, depression was associated with more persistent and severe self-reported pain as measured by VAS during the first year of follow-up among Veterans with early RA who were enrolled in VARA and prescribed MTX. Collectively, results suggest that depression could cause slower initial declines in disease activity after MTX treatment

initiation among patients with early RA, as well as worse pain that may be related to the primary condition or a consequence of other mechanisms associated with psychiatric comorbidity.

Findings are congruent with previous studies in civilian populations demonstrating that depression among RA patients receiving bDMARDs is associated with slower and/or reduced treatment response (3, 15, 17). Moreover, study results validate epidemiologic data from a national RA registry showing prevalent depression to predict slower clinical disease activity index (CDAI) declines and a reduced probability of CDAI clinical remission 6-months after initiating biologic therapy (16, 25). Evidence suggests the detrimental impact of depression on RA treatment response as measured by composite indices is primarily related to its negative correlation with the PTGA (16, 30). However, findings from the present study diverge from prior research as estimated associations for the DAS-28 components at 6 months follow-up were all similar in magnitude (0.210-0.266 standard deviations). Although statistically insignificant and small effect sizes, depression's collective influence on its component measures corresponded to a potentially meaningful, small-to-medium effect size-based difference in DAS-28 at 6-months follow-up (31). These broader and more uniform effects of depression on disease activity in Veterans compared with non-Veteran RA patients may be a consequence of their demographic and occupational characteristics. Foremost, the VARA sample is predominantly male and older, and sex-differences have been observed in the clinical manifestation and progression of both RA and depression (40, 41). In addition, Veterans are often subject to chronic exposure to highly stressful experiences during military service, which may activate biopsychosocial processes that underly and exacerbate chronic conditions, particularly musculoskeletal and psychiatric disorders (42, 43). Nonetheless, this is the first study to

replicate and build upon previous findings showing poor psychosocial health as a risk factor for primary non-response to MTX treatment in RA patients (20).

Among the ACR core component disease activity measures, depression was associated with persistently higher, small-to-medium effect size-based differences in patient-reported pain, which is analogous to results in prior studies among Veterans and other RA samples treated with bDMARDs (3, 11, 17). However, these findings may not represent higher RA disease activity, i.e., nociceptive pain, as differences in physician-reported tender joints were smaller and not statistically significant. Additionally, depressed participants' self-reported pain scores converged with non-depressed participants by two years follow-up. Chronic pain among depressed Veterans with early RA receiving MTX may be related to their depressive symptomology, which could exacerbate cognitive perceptions related to reporting pain or increase non-nociceptive pain by affecting physical activity and neurotransmitters related to pain sensitization (3). Unlike prior studies, the current research yielded no detectable signals between depression and TJC or MDHAQ, and therefore, more persistent and severe pain ratings related to depressed mood could be measurement response shift arising from negative affect associated with depressive symptoms (3, 17, 25). Alternatively, male RA patients experience slower disease progression, under-report pain, and over-estimate function compared with women, and participants may have had less extant joint damage and nociceptive pain than more representative samples, implying depression's effect on RA disease activity could be larger in female patients treated with MTX (40, 44, 45). Nonetheless, convergence in self-reported pain scores after two years suggests depressed patients received additional medical care beyond MTX treatment. For example, Veterans with early RA and depression could have escalated their RA treatment with bDMARDs in the presence of persistent pain (14). High-intensity depressive

symptoms leading to greater pain perception and sensitivity, despite MTX treatment, may also cause patients to seek alternative provider-management options (e.g., antidepressants, cognitive behavioral therapy) for chronic pain (46). Whether due to measurement response tendencies or substantive effects on pain sensitization, persistently higher pain ratings while receiving first-line RA treatment among depressed Veterans with early RA represents a gap in clinical care. Given depressed patients were also younger, findings emphasize the need for better interventions as Veterans with RA will live longer.

There are several study limitations. First, identification of new MTX users with an exact timing of medication initiation was not possible with the VARA registry dataset. Similarly, there was a lack of information on RA medication changes and depressive episodes during follow-up and no data available regarding depression severity, utilization of antidepressant treatments, and certain comorbid conditions (e.g., fatigue, sleep disturbance, etc.). To mitigate this issue, the current study included RA patients with recent disease onset who were prescribed MTX at enrollment. Given that depressed and non-depressed Veterans had a disease duration of approximately seven months, participants represented RA patients with active symptoms who had initiated their first DMARD. Second, administrative diagnostic codes were used to record and measure several study variables, which could potentially introduce misclassification, but any bias would have been non-differential and trended associations towards the null. In particular, depressive symptoms are often under-reported by RA patients and under-recognized by rheumatologists during routine clinical encounters (6, 47). Depression may have been under-reported and -coded in the current study sample, and non-differential misclassification bias could have reduced the magnitude of the observed associations and account for null findings regarding the PTGA and MDHAQ. This contention is supported by the lower than expected prevalence

(n=23; 8.6%) of post-traumatic stress disorder in the study sample, and although our estimated depression prevalence compared to the RA population (17.9% vs. 16.8%, respectively) supports the validity of this measurement approach, prior research indicates that Veterans with RA are more likely to develop depression than RA patients without military service (5, 11). Last, the demographic makeup and occupational exposure history of VARA participants may limit generalizability of the results to other patients (e.g., women).

To conclude, depression in Veteran patients with early RA receiving MTX is associated with worse disease activity and more severe and persistent pain, resulting in a less robust treatment response to this cornerstone pharmacological therapy. Thus, this comorbidity may be a risk factor for medication discontinuations, and interventions targeted at treating depression in affected RA patients could lead to more rapid disease activity control and better DMARD persistence. To facilitate such coordinated medical care, there needs to be routine patient-provider communication about depression, as well as prioritization of psychiatric comorbidity when utilizing treat-to-target medical management for RA patients (6, 16). Unfortunately, research indicates a lack of physician awareness to depression and suboptimal communication about depressive symptoms among rheumatologists (6). Provider- and/or system-level interventions could improve depression recognition and treatment among RA patients in large health care settings, and ultimately, augment medical care approaches that utilize multimodal interventions incorporating pharmacologic and non-pharmacologic treatments explicitly designed to address the co-occurrence of depression and pain in chronic rheumatic diseases.

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Figure Legends

Figure 1. Study sample flow diagram

Figure 2. DAS-28 trajectories in depressed and non-depressed Veterans with early rheumatoid arthritis during treatment with methotrexate

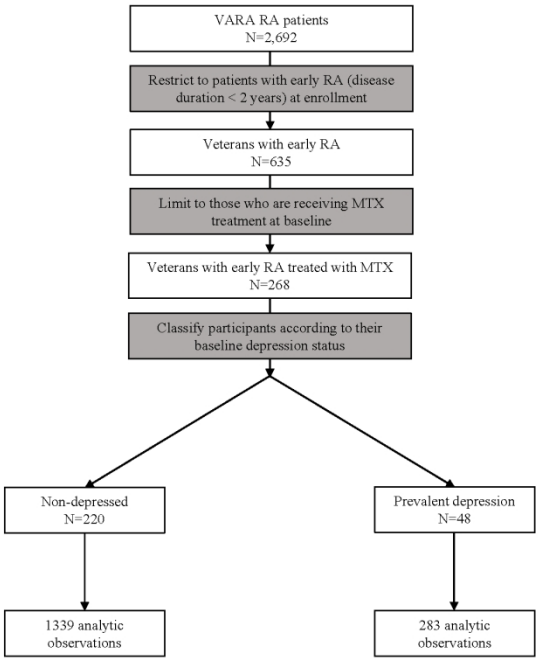

Figure 1.

254x190mm (200 x 200 DPI)

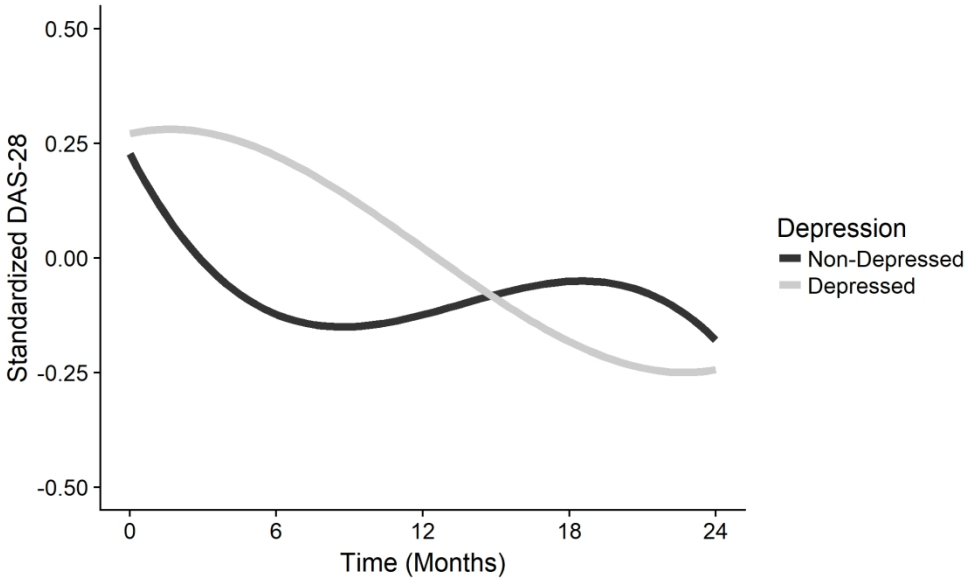

Figure 2.

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Table 1. Baseline characteristics depressed and non-depressed participants in the original analytic sample (n=268).

Variable (mean and SD, median and IQR, or n and %)		Depressed (n=48)		Non-depressed (n=220)		P
Age (years)		58.86	(10.04)	63.48	(10.56)	0.006
Male		41	(85.4)	198	(90.0)	0.503
White		39	(81.2)	171	(77.7)	0.731
Smoking status						0.477
	Former	24	(50.0)	121	(56.3)	
	Current	16	(33.3)	54	(25.1)	
	Never	8	(16.7)	40	(18.6)	
BMI (kg/m^2)		29.67	(5.10)	28.93	(5.33)	0.458
Comorbid conditions		1.90	(1.31)	1.45	(1.38)	<0.001
Hydroxychloroquine		23	(47.9)	70	(31.8)	0.051
Sulfasalazine		9	(18.8)	31	(14.1)	0.550
Leflunomide		2	(4.2)	7	(3.2)	1.000
TNF inhibitors		5	(10.4)	30	(13.6)	0.716
TJC (0-28)		5.50	(2.00-13.00)	4.00	(1.00-10.0)	0.176
SJC (0-28)		4.00	(2.00-10.00)	4.00	(1.00-8.75)	0.493
ESR (mm/hour)		20.00	(9.00-38.00)	24.00	(10.00-42.50)	0.347
PTGA (0-100 mm)		48.49	(26.11)	39.65	(27.55)	0.074
PRGA (0-100 mm)		34.37	(23.06)	34.66	(23.90)	0.951
Pain (0-10 cm)		5.16	(2.79)	4.30	(2.91)	0.102
MDHAQ (0-3)		0.96	(0.58)	0.81	(0.65)	0.231
DAS-28		4.32	(1.58)	4.08	(1.65)	0.430

BMI: Body mass index; DAS-28: 28 joint count disease activity score; ESR: Erythrocyte sedimentation rate; IQR: Interquartile range; MDHAQ: Multidimensional health assessment questionnaire; PRGA: Provider global assessment; PTGA: Patient global assessment; SD: Standard deviation; SJC: Swollen joint count; TJC: Tender joint count.

Table 2. Standardized mean differences in RA disease activity at 6 months and 1- and 2-years follow-up comparing those with prevalent depression to those without at baseline.

Measure	6 Months (β, 95% CI, P)			1 Year (β, 95% CI, P)			2 Years (β, 95% CI, P)		
DAS-28	0.345	(0.007, 0.682)	0.045	0.145	(-0.255, 0.545)	0.477	-0.067	(-0.597, 0.463)	0.804
SJC	0.243	(-0.034, 0.519)	0.086	0.092	(-0.241, 0.425)	0.589	0.058	(-0.565, 0.681)	0.856
TJC	0.249	(-0.064, 0.561)	0.119	0.115	(-0.249, 0.478)	0.536	-0.058	(-0.670, 0.553)	0.852
PTGA	0.266	(-0.057, 0.590)	0.106	0.275	(-0.028, 0.578)	0.075	-0.041	(-0.708, 0.626)	0.903
ESR	0.210	(-0.155, 0.574)	0.261	0.014	(-0.348, 0.375)	0.941	-0.019	(-0.581, 0.543)	0.947
PRGA	0.139	(-0.170, 0.447)	0.378	0.186	(-0.162, 0.533)	0.295	-0.229	(-0.951, 0.492)	0.534
Pain	0.385	(0.040, 0.730)	0.029	0.396	(0.042, 0.750)	0.028	0.105	(-0.504, 0.715)	0.735
MDHAQ	0.147	(-0.175, 0.470)	0.370	0.093	(-0.279, 0.466)	0.623	0.027	(-0.479, 0.533)	0.916

DAS-28: 28 joint count disease activity score; ESR: Erythrocyte sedimentation rate; MDHAQ: Multidimensional health assessment questionnaire; PRGA: Provider global assessment; PTGA: Patient global assessment; SJC: Swollen joint count; TJC: Tender joint count.