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Antidepressant treatment resistance is associated with increased inflammatory markers in patients with major depressive disorder

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Abstract

Background: One third of patients with major depressive disorder (MDD) fail to respond to currently available antidepressant medications. Inflammation may contribute to treatment non-response through effects on neurotransmitter systems relevant to antidepressant efficacy. In post-hoc analyses, increased concentrations of inflammatory markers prior to treatment predict poor antidepressant response. However, limited data exists on whether depressed patients with multiple failed treatment trials in their current episode of depression exhibit increased inflammation.

Methods: Plasma concentrations of inflammatory markers were measured in unmedicated, medically stable patients with MDD ($n = 98$) and varying numbers of adequate antidepressant treatment trials in the current depressive episode as measured by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire. Covariates including age, sex, race, education, body mass index (BMI) and severity of depression were included in statistical models where indicated.

Results: A significant relationship was found between number of failed treatment trials and tumor necrosis factor (TNF), soluble TNF receptor 2 (sTNF-R2) and interleukin (IL)-6 (all $p < 0.05$ in multivariate analyses). Post hoc pairwise comparisons with correction for multiple testing revealed that patients with 3 or more failed trials in the current episode had significantly higher plasma TNF, sTNF-R2 and IL-6 compared to individuals with 0 or 1 trial (all $p < 0.05$). High sensitivity c-reactive protein was also associated with a greater number of treatment failures, but only in models with BMI excluded.

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Declarations of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.psyneuen.2018.05.026>.

Conclusions—Measuring inflammatory markers and targeting inflammation or its downstream mediators may be relevant for depressed patients with multiple failed antidepressant treatment trials in their current depressive episode.

Keywords

Cytokines; C-reactive protein; Interleukin-6; Tumor necrosis factor; Treatment resistant depression

1. Introduction

Major Depressive Disorder (MDD) affects approximately 10% of the US adult population and is the leading cause of disability worldwide (Friedrich, 2017; Global Burden of Disease Study, 2015). Despite recent advances in understanding the pathophysiology of MDD, approximately 30% of patients with MDD remain treatment refractory following multiple treatment trials with currently available antidepressant medications (Rush et al., 2006).

Many clinical factors have been related to treatment non-response including psychiatric comorbidities such as anxiety disorders, personality disorders, and bipolar disorder as well as obesity and a history of childhood maltreatment (Bock et al., 2010; Correa et al., 2010; Nanni et al., 2012; Raison et al., 2013a; Rush et al., 2008; Shelton and Miller, 2010). Similarly, medical conditions such as cardiovascular disease, diabetes, and cancer also have been associated with poor antidepressant treatment response (Iosifescu et al., 2004). Interestingly, each of these clinical factors has been linked to inflammation (Couzin-Frankel, 2010; Miller et al., 2009; Miller and Raison, 2016).

Recent data suggest that inflammation may be a pathway to pathology in some patients with MDD (Hodes et al., 2015; Miller and Raison, 2016). Research has shown that patients with MDD on average have higher levels of plasma inflammatory markers compared to non-depressed individuals, with tumor necrosis factor (TNF), interleukin (IL)-6 and c-reactive protein (CRP) being among the most reliably elevated in depressed populations (Dowlati et al., 2010; Howren et al., 2009). Administration of inflammatory cytokines also has been associated with the development of depressive symptoms (Brydon et al., 2008; Capuron et al., 2002a; Eisenberger et al., 2010), and blockade of inflammatory mediators has been shown to improve depressive symptoms in patients with autoimmune and inflammatory disorders and a subset of depressed patients with high baseline inflammation (Kappelmann et al., 2018; Raison et al., 2013b; Savitz et al., 2018).

Relevant to the potential contribution of inflammation to anti-depressant response, an association between increased baseline inflammation and subsequent treatment response to antidepressant treatment has been reported in post-hoc analyses of prospective studies. Indeed, a meta-analysis of 35 studies that examined inflammatory markers before and after antidepressant treatment found that patients who were antidepressant non-responders were more likely to have higher inflammatory markers at baseline and follow-up compared to treatment responders (Strawbridge et al., 2015). Despite these findings, there is a dearth of data on inflammatory markers as a function of prior treatment response in patients with MDD.

Based on previous literature, we hypothesized that a history of treatment non-response as determined by the number of failed treatment trials in the current episode of depression would be associated with increased peripheral blood markers of inflammation. Therefore, plasma immune markers were characterized in unmedicated patients with MDD with varying numbers of adequate treatment trials in the current episode.

2. Materials and methods

2.1. Participants

Subjects between the ages of 21 and 65 years were recruited by advertising campaigns on television, radio, newspaper and the internet (social media). All participants had a current diagnosis of major depressive episode (major depressive disorder or bipolar disorder – depressed phase) as determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual IV (SCID-IV) (First et al., 2002). Treatment resistance was not an inclusion criterion for this study. Participants with current suicidal ideation [as determined by item #3 on the 17 item Hamilton Depression Rating Scale (see below)] (Hamilton, 1960) or history of a psychiatric disease other than depression (schizophrenia or active psychotic symptoms, active restrictive eating disorder, substance use disorder within the previous 6 months [determined by SCID-IV and urine drug screen]) were excluded from study participation. Patients with co-morbid anxiety disorders were not excluded as long as depression was the primary diagnosis. Other exclusion criteria (determined by medical history, physical examination, laboratory testing and electrocardiography) included comorbid conditions affecting the immune system, including autoimmune or inflammatory disorders (e.g. rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis), recent acute infection requiring antibiotics within the preceding one month, chronic infection (HIV, hepatitis B or C), history of cancer, current pregnancy or lactation, or poorly controlled cardiovascular, renal, hepatic, hematologic, endocrine, or neurologic disease [including those with a history of clinically significant head trauma or a score < 28 on mini-mental status examination (Folstein et al., 1983)]. Subjects with diabetes and glycosuria (indicating lack of disease control) were excluded. At time of study, participants reported no current use of medications known to affect the immune system, including corticosteroids, non-steroidal anti-inflammatory drugs, statins and angiotensin receptor blockers. Enrolled participants also had not taken any psychotropic medications (including antidepressants, antipsychotics, mood stabilizers, stimulants, anxiolytics and sedative-hypnotics) for at least 4 weeks prior to study entry (eight weeks for fluoxetine) and were medication-free throughout study participation. No psychotropic medication was stopped for purposes of the study, and all other (non-psychotropic) medications were continued at the discretion of the patients' primary care physicians. The study was approved a priori by the Institutional Review Board of Emory University. All subjects provided written informed consent prior to participation. Subjects presented in this manuscript represent a subset of those recruited for studies NCT01426997 and NCT00463580 ([ClinicalTrials.gov](https://clinicaltrials.gov)).

2.2. Psychiatric assessments

To assess depressive symptom severity, subjects completed the 17-item Hamilton Depression Rating scale (HAM-D) administered by a trained clinician (BJW)(Hamilton, 1960). Prior treatment history was determined by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) for the current episode of depression with the assistance of a trained clinician (BJW) (Chandler et al., 2010). Patients were subsequently categorized based on the number of adequate antidepressant trials in the current episode irrespective of adjunctive therapy. An “adequate” trial of a conventional antidepressant (e.g. selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants and others) was defined by MGH-ATRQ criteria, which stipulates treatment for 6 weeks duration at the recommended starting dose or higher. Patients were divided into four treatment categories including those with no previous treatment (n = 57) (Treatment Category 0), those with 1 adequate treatment trial in the current episode (n = 12) (Treatment Category 1), those with 2 adequate treatment trials in the current episode (n = 13) (Treatment Category 2), and those with 3 or more adequate treatment trials in the current episode (n = 16) (Treatment Category 3). Subjects in Treatment Category 3 failed a mean number of 4.6 trials (range 3–8).

2.3. Immune markers

To minimize the influence of diurnal variation and the stress of venipuncture, all blood samples were collected between 8:00–10:00 am following 30 min of rest. Blood samples were collected from indwelling catheters into chilled EDTA tubes and centrifuged at 1000g for 15 min at 4 °C. Plasma was immediately frozen at –80 °C until batched analysis. Interleukin (IL)-1beta, IL-1 receptor antagonist (IL-1ra), IL-6, IL-6 soluble receptor (IL-6 sr), IL-10, TNF, and soluble TNF receptor 2 (sTNF-R2) were measured in duplicate utilizing a multiplex bead-assay (R&D Systems, Minneapolis, MN, USA) and analyzed on a MAGPIX CCD imaging system (Luminex Corporation, Austin, TX, USA) as previously described (Felger et al., 2016). High sensitivity CRP was measured using the immunoturbidimetric method using a Beckman AU480 analyzer and Ultra WR CRP kit (Sekisui Diagnostics). Mean inter- and intra-assay coefficients of variation for all techniques were reliably < 10%. Two samples of IL-10 were below the limits of assay detection, otherwise, all other immune markers in all subjects were within the limits of assay detection.

2.4. Statistical analyses

Descriptive statistics were calculated for demographic and clinical characteristics and mean plasma concentrations of immune markers. Differences among treatment categories were assessed using Chi-Square (ChiSq) analysis for categorical data and one-way analysis of variance (ANOVA) for continuous variables. Non-parametric statistics were used for variables that deviated from normality. The study group was stratified into four Treatment Categories based on 0, 1, 2 and > 3 antidepressant trials in the current episode as documented by MGH-ATRQ. Normality of immune markers was assessed using Shapiro-Wilk test, naked-eye inspection of the histogram and by estimating skewness. Two of seven immune markers – TNF and IL6 sr – did not demonstrate deviation from normality (skewness scores = 0.5 and –0.6 respectively) and were retained as such. The remaining five

immune markers (CRP, IL-1beta, IL-1ra, IL-6, IL-10, sTNF-R2) were log-transformed. Multivariate analysis of variance (MANOVA) with post hoc testing was used to estimate cross-sectional associations between immune markers and Treatment Category. MANOVA was performed using Treatment Category as the fixed independent variable and immune markers as the dependent variables. Covariates including age, race, sex, education, HAM-D and BMI that had a significant association with Treatment Category or the immune markers were included in the final MANOVA model. Because BMI demonstrated high collinearity with plasma concentrations of CRP ($r = 0.49$, $p < 0.001$), IL-1beta ($r = 0.28$, $p = 0.006$), IL-6 ($r = 0.45$, $p < 0.001$), IL-1ra (0.56 , $p < 0.001$) and sTNF-R2 (0.36 , $p < 0.001$), MANOVA models were run first with BMI included and then with BMI excluded. After confirming the significance of the overall MANOVA model, post hoc multivariate regression was employed to determine which immune markers were significantly associated with one or more treatment categories. Pairwise mean contrast analyses were then employed to examine group-wise comparisons of individual immune markers that were significantly associated with Treatment Category in the MANOVA. Conservative corrections for multiple comparisons were applied to post hoc pairwise mean contrasts (Tukey). To confirm MANOVA results, inverse validation of the findings was examined using logistic regression models with Treatment Category as the dependent variable and immune markers significant in the MANOVA and all covariates indicated above as independent (predictor) variables. Logistic models were corrected for multiple comparisons by controlling for a False Discovery Rate (FDR) < 0.05 . Finally, receiver-operating curves (ROC) were generated to explore predictive associations between Treatment Category and immune markers significant in MANOVA and logistic regression. Statistical analyses were performed using STATA (STATA Statistical Software, College Station, TX) and JMP Pro (SAS Institute, Cary, NC).

3. Results

Of the 98 subjects, 57, 12, 13 and 16 subjects were classified as belonging to Treatment Categories 0, 1, 2 and 3 respectively. Demographic, clinical and immune data for the four treatment categories and the entire sample are summarized in Table 1.

3.1. Background variables

A comparison of background variables did not reveal significant differences among the four treatment categories with regards to gender [ChiSq(df = 3) = 1.33, $p = 0.72$], education [ChiSq(df = 6) = 5.39, $p = 0.49$], age [Wilcoxon rank test ChiSq(df = 3) = 6.17, $p = 0.10$], HAM-D scores [$F(3,94) = 1.05$, $p = 0.37$] or BMI [$F(3,94) = 0.98$, $p = 0.40$]. However, there was a significant difference in the distribution of race across the groups [ChiSq(df = 3) = 11.12, $p = 0.01$]. African-Americans were more represented in treatment categories with a lower number of trials, i.e., Treatment Category 0 and Treatment Category 1 (proportion(95%CI) = 0.40 ± 0.36 – 0.57 and $0.75 \pm (0.20$ – $0.86)$ respectively), while Caucasians demonstrated the opposite pattern.

3.2. Multivariate analysis of variance

The MANOVA model included 3 covariates (education, race, BMI) that were significantly associated with the treatment categories and/or the immune markers. The model demonstrated overall significance [Roy's largest root = 0.26, $F(8,84) = 3.31$, $p = 0.002$], with individual treatment categories predicting TNF (parameter estimate $PE = 1.45$, $t = 2.15$, $p = 0.03$), sTNF-R2 ($PE = 0.24$, $t = 2.46$, $p = 0.2$) and IL6 ($PE = 0.33$, $t = 2.06$, $p = 0.04$). CRP was not significant when BMI was included as a covariate in the MANOVA, nor were any of the other immune markers.

MANOVA excluding BMI (but including race and education) also demonstrated overall model significance (Roy's largest root = 0.23, $F(8,85) = 3.65$, $p = 0.001$). Examination for significant effects within the model revealed that individual treatment categories predicted TNF ($PE = 1.60$, $t = 2.39$, $p = 0.02$), sTNF-R2 ($PE = 0.29$, $t = 2.91$, $p = 0.005$), IL-6 ($PE = 0.37$, $t = 2.25$, $p = 0.03$), and CRP ($PE = -0.93$, $t = -2.03$, $p = 0.046$). None of the other immune markers were significantly associated with Treatment Category in this analysis.

3.3. Pairwise comparisons

Based on significance in the MANOVAs with and without inclusion of BMI, post hoc pairwise analyses followed by Tukey correction for multiple comparisons were conducted for TNF, IL-6, sTNF-R2 and CRP (Fig. 1, Supplementary Table S1). Results revealed significant effects of Treatment Category contrasts (3 versus 0) and (3 versus 1) for TNF [$t = 2.87$, $p = 0.03$, $d(95\%CI) = 0.83 (0.25-1.39)$ and $t = 2.82$, $p = 0.03$, $d = 0.98(0.18-1.76)$, respectively]. For sTNF-R2, Treatment Group contrasts (3 versus 0) and (3 versus 1) were significantly different [$t = 3.43$, $p = 0.005$, $d = 1.96 \pm (1.32-2.60)$ and $t = 3.37$, $p = 0.006$, $d = 1.65 \pm (0.77-2.50)$, respectively]. For IL-6, Treatment Category contrasts (3 versus 1) and (2 versus 1) were significantly different [$t = 3.10$, $p = 0.01$, $d = 1.29 \pm (0.46-2.11)$ and $t = 2.94$, $p = 0.02$, $d = 1.09 \pm (-0.24-1.93)$, respectively]. None of the Treatment Category contrast associations with CRP survived conservative correction for multiple comparisons using the Tukey method. However, less restrictive (more powerful) t-test contrasts of CRP between Treatment Categories (3 versus 1) and (2 versus 1) were both significant [$t = 2.17$, $p = 0.03$ and $t = 2.51$, $p = 0.014$, respectively]. Of note, a power analysis revealed that the study was underpowered for the CRP contrasts (1-beta = 0.61) as opposed to the other three immune marker comparisons (see below).

3.4. Inverse validation

Stepwise logistic regression using a forward-selection algorithm with entry/exit p-value criteria of 0.1 and 0.05 was utilized to further confirm the association of Treatment Category (as the dependent variable) with TNF, sTNF-R2, and IL-6 (as independent variables) in 3 separate models to avoid variable inflation and overfitting. Covariates entered into the models included age, sex, race, education, HAM-D and BMI. Treatment Category was predicted by TNF (Likelihood Ratio (LR) $\chi^2 = 13.2$, $FDRp = 0.007$) and education ($p = 0.007$) in Model 1; sTNF-R2 (LR $\chi^2 = 13.0$, $FDRp = 0.009$) and education ($FDRp = 0.02$) in Model 2; and IL-6 (LR $\chi^2 = 13.3$, $FDRp = 0.01$), race and education ($FDRp = 0.01$ and 0.02) in Model 3.

Exploratory ROC curves (derived from the logistic models) were used to examine the overall ability of TNF, sTNF-R2 and IL-6 to discriminate treatment categories (Fig. 2). Area-under-the-curve (AUC) analysis indicated that TNF (AUC = $0.69 \pm (0.54-0.84)$, $z = 9.14$, $p < 0.001$); sTNF-R2 (AUC = $0.72 \pm (0.58-0.87)$, $z = 9.78$, $p < 0.001$) and IL-6 (AUC = $0.67 \pm (0.52-0.81)$, $z = 9.18$, $p < 0.001$) significantly predicted group membership in Treatment Category 3.

3.5. Power calculations

One-way ANOVA to test mean differences between Treatment Categories yielded effect sizes (partial eta-squared) of 0.14, 0.13 and 0.12 for TNF, sTNF-R2 and IL6, respectively. With an alpha = 0.05; group sizes = 57, 12, 13 and 16 respectively and the total number of covariates = 6 - a power (1-beta) = 0.86–0.92 was obtained for the association between the 3 markers and Treatment Category.

4. Discussion

The results of this study indicate that antidepressant treatment resistance, as assessed by the number of failed antidepressant treatment trials in the current depressive episode, is associated increased plasma markers of inflammation. Participants who had experienced multiple failed treatment trials in the current episode – an indicator of treatment non-response - exhibited higher plasma concentrations of TNF, sTNFR2, IL-6 and CRP compared to depressed individuals with no prior treatment or treatment with only one adequate treatment trial in the current episode. Controlling for BMI and following correction for multiple comparisons, TNF, sTNF-R2 and IL-6 were the most significantly associated with the number of failed treatment trials. These preliminary results suggest that there may be an overrepresentation of depressed patients with high inflammation in those individuals who have failed multiple treatment trials in their current episode. Thus, in patients who have a history of multiple failed antidepressant trials prior to therapy, it might be warranted to measure inflammatory markers and consider treatments that target inflammation and/or its downstream effects on the brain.

The findings of increased inflammatory markers in depressed patients with a history of treatment nonresponse especially TNF and IL-6 are consistent with post-hoc analyses of prospective antidepressant treatment trials that indicate that treatment non-responders show elevated inflammatory markers at the end of treatment compared to responders (Strawbridge et al., 2015). TNF has been one of the most measured markers of inflammation in this literature, with multiple studies showing elevations in TNF in non-responders following treatment compared to treatment responders (Eller et al., 2008; Gupta et al., 2016; Lanquillon et al., 2000; Strawbridge et al., 2015). Unfortunately, few studies have associated markers of inflammation with a history of treatment non-response. In one study, 45% of patients recruited for multiple treatment failures in the current episode exhibited a CRP > 3 mg/L, which is considered high inflammation according to guidelines from the American Heart Association regarding cardiac risk (Raison et al., 2013b). Our findings that CRP was higher in patients with multiple treatment trials is consistent with this finding.

There are several mechanisms by which inflammation may contribute to antidepressant treatment non-response (Miller and Raison, 2016). Most conventional antidepressants [e.g. the selective-serotonin reuptake inhibitors (SSRIs)] exert their clinical effect by blocking the reuptake of serotonin by the serotonin transporter. Inflammatory cytokines including TNF have been shown to circumvent this mechanism of action by increasing the expression and function of monoamine transporters especially those for serotonin. More specifically, TNF as well as IL-1 β have been shown to increase the expression and activity of monoamine transporters via activation of p38 mitogen-activated protein kinase, resulting in augmentation of serotonin reuptake at the pre-synaptic terminal, thereby reducing the availability of serotonin in the synapse (Zhu et al., 2006; Zhu et al., 2010). Inflammatory cytokines also have been shown to modulate the activity of the enzymes involved in monoamine synthesis, including indoleamine 2,3 dioxygenase, thus further leading to a reduction in neurotransmitter synthesis and availability (Capuron et al., 2003; Capuron et al., 2002b). In support of these basic and preclinical findings of inflammation's effects on serotonin, two large community studies have shown that patients with increased baseline inflammation as measured by CRP exhibit poor responses to SSRIs compared to drugs that target other monoamines including dopamine and norepinephrine (Jha et al., 2017; Uher et al., 2014). Along with modulation of monoamine neurotransmission, inflammatory cytokines also have been shown to inhibit brain-derived neurotrophic factor (BDNF) and block neurogenesis which is believed to play a role in the effects of antidepressants on some depressive-like behaviors (Borsini et al., 2015; Duman and Monteggia, 2006; Koo and Duman, 2008). Finally, inflammation has been associated with altered glutamate metabolism in MDD as manifested by increased region-specific glutamate correlated with increased plasma CRP (Haroon et al., 2016). In vitro and in vivo studies have shown that inflammatory cytokines can lead astrocytes to increase the release of glutamate while decreasing expression of glutamate transporters responsible for glutamate reuptake (Haroon et al., 2017). Through binding to extrasynaptic glutamate (N-methyl-D aspartate) receptors, increased glutamate can further contribute to decreased BDNF, while also leading to excitotoxicity (Haroon et al., 2017). Currently, there are no conventional antidepressants that specifically target glutamate, although ketamine, a drug that has dramatic effects in treatment resistant depressed patients, especially those with increased inflammatory markers (e.g. IL-6), is a glutamate receptor antagonist (Newport et al., 2015; Yang et al., 2015). Taken together, these multiple effects of inflammation on neurotransmission and neurogenesis may in part serve to undermine the efficacy of conventional antidepressants and explain the resistance to these drugs in patients with increased inflammation (Raison et al., 2013a).

There are several strengths and weakness of this study that warrant consideration. Plasma samples were collected at the same time of day after 30 min of rest from an indwelling catheter under highly standardized conditions from well-characterized, medically stable participants with clinician-verified MDD who were not taking any psychotropic medications at the time of study. Both stress and circadian variation can affect the concentrations of inflammatory markers, and being free of psychotropic medications is essential given that antidepressant medications have been shown to have direct (in vitro) and indirect effects on the production of inflammatory mediators (Kenis and Maes, 2002; Kohler et al., 2018). In

addition, all patients exhibited a similar severity of depression, limiting the effects of depression severity on the findings.

Major weaknesses of the study include the small sample size and the differential distribution of white and black participants in the treatment categories. The small sample size emphasizes the need for future studies with larger numbers of subjects to confirm the results. It should be noted however, that multiple statistical strategies were used to confirm our findings, and power analyses indicated that our results for TNF, sTNF-R2 and IL-6 were sufficiently powered (all > 0.80). Regarding the differential distribution of race, white patients were more likely to have received greater adequate medication trials than black patients. Although race was controlled for in all our statistical analyses, these data point to disparities in treatment practices as a function of race. Such disparities have been previously reported and warrant consideration in future studies (Chen and Rizzo, 2008). Of note, however, compared to whites, blacks have been found to have higher (not lower) markers of inflammation including CRP and IL-6 (Paalani et al., 2011). These data further support the notion that the association of fewer number of adequate treatment trials and lower inflammation is not likely a function of black race. Finally, only unmedicated patients were recruited for this trial, and such patients may not be representative of the general population of patients with depression.

5. Conclusions

This study examined plasma inflammatory markers in patients as a function of their prior antidepressant treatment history. We found that the number of adequate antidepressant treatment trials in the current episode was strongly associated with plasma concentrations of TNF, sTNF-R2 and IL-6 with a somewhat weaker association with CRP depending on the presence of BMI in our statistical models. These findings support the consideration of measuring inflammatory markers in patients with multiple failed treatment trials. Moreover, for those patients with evidence of increased inflammation, targeting inflammation or its downstream mediators may be most relevant to addressing and resolving treatment non-response (Miller et al., 2017).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Mean (± SEM) Plasma Inflammatory Markers by Treatment Category*.

Fig. 2. Receiver Operating Curves (ROC) for Tumor Necrosis Factor (TNF), soluble TNF receptor 2 (sTNF-R2) and interleukin (IL)-6 as a function of Treatment Category*.

Table 1

Demographic, Clinical and Immune Characteristics of the Study Sample.

Variable	All subjects	Treatment Category*			
mean (SD) / No %	[n =98]	0 [n= 57]	1 [n= 12]	2 [n= 13]	3 [n =16]
Demographic and Clinical Factors					
Age	39.6 (11.1)	37.8 (10.7)	38.8 (11.6)	40.4 (11.4)	46.2 (10.6)
Gender:					
Female	65 (66.3)	36 (63.2)	9 (75.0)	8 (61.5)	12 (75.0)
Male	33 (33.7)	21 (36.8)	3 (25.0)	5 (38.5)	4 (25.0)
Race:					
White	46 (45.9)	23 (40.4)	3 (25.0)	7 (53.8)	13 (81.3)
Black	52 (54.1)	34 (59.6)	9 (75.0)	6 (46.2)	3 (18.8)
HAM-D	23.3 (3.5)	23.5 (3.6)	22.6 (2.9)	22.0 (3.8)	23.9 (3.2)
BMI	31.4 (8.4)	31.2 (8.4)	28.4 (5.7)	32.6 (10.5)	33.7 (8.2)
Education:					
Postgraduate	14 (14.3)	7 (50)	1 (7.1)	1 (7.1)	5 (35.7)
College grad	33 (33.7)	15 (45.4)	6 (18.2)	5 (15.2)	7 (21.2.1)
Some college	41 (41.8)	29 (70.7)	4 (9.8)	5 (12.2)	3 (7.3)
High school	10 (10.2)	6 (60.0)	1 (10.0)	2 (20.0)	1 (10.0)
Immune Markers					
TNF (pg/ml)	5.6 (2.2)	5.2 (1.9)	4.6 (1.9)	6.4 (2.5)	6.9 (2.6)
sTNF-R2 (ng/ml)	2.6 (1.0)	2.4 (0.7)	2.2 (1.0)	2.7 (0.7)	3.4 (1.5)
IL-6 (pg/ml)	1.8 (1.4)	1.6 (1.0)	1.1 (0.3)	2.6 (2.5)	2.4 (1.8)
CRP (mg/L)	2.7 (3.1)	2.2 (1.8)	2.1 (3.8)	4.3 (5.2)	3.5 (3.7)
IL-1beta (pg/ml)	0.4 (0.2)	0.4 (0.4)	0.4 (0.4)	0.4 (0.2)	0.4 (0.2)
IL-1ra (ng/ml)	3.5 (12.56)	3.8 (14.8)	1.1 (0.9)	2.1 (3.7)	5.6 (13.4)
IL-6 sr (ng/ml)	15.9 (3.3)	15.3 (3.5)	14.9 (2.2)	17.2 (3.2)	17.5 (3.0)
IL-10 (pg/ml)	0.6 (0.6)	0.6 (0.6)	0.5 (0.2)	0.7 (0.6)	0.5 (0.4)

* - 0 = no adequate antidepressant treatment trial[†] in the current episode; 1 = 1 adequate antidepressant treatment trial[†] in the current episode; 2 = 2 adequate antidepressant treatment trials in the current episode; 3 = 3 or more adequate antidepressant treatment trials in the current episode. [†] Adequate antidepressant treatment trial defined as antidepressant treatment for 6 weeks at minimal or higher dose as determined by the Massachusetts General Hospital Antidepressant Treatment Response Scale. SD: Standard Deviation; HAM-D: Hamilton Depression Scale; BMI: Body Mass Index; TNF: tumor necrosis

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factor; sTNF-R2: soluble TNF receptor 2; IL-6: interleukin 6; CRP: high sensitivity c-reactive protein; IL-1 β : interleukin 1 beta; IL-1-ra: interleukin 1 receptor antagonist; IL-6 sr: interleukin 6 soluble receptor; IL-10: interleukin 10.