



NEUROINFLAMMATION AND THE IMMUNE SYSTEM IN MAJOR DEPRESSIVE DISORDER: PERIPHERAL CYTOKINE SIGNATURES AND THE EFFICACY OF ADJUNCTIVE ANTI-INFLAMMATORY TREATMENT

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Abstract

A substantial body of evidence implicates the innate immune system in the pathophysiology of major depressive disorder (MDD). This study characterised peripheral inflammatory markers in patients with MDD relative to healthy controls and evaluated whether adjunctive anti-inflammatory treatment improves depressive outcomes, with particular attention to baseline inflammatory status. In a two-part design, serum interleukin-6 (IL-6), tumour necrosis factor- α (TNF- α), C-reactive protein (CRP), and interleukin-1 β (IL-1 β) were measured in 220 participants (110 MDD, 110 controls); a randomised, placebo-controlled subsample of MDD patients (n=100) received the cyclooxygenase-2 inhibitor celecoxib or placebo added to a selective serotonin reuptake inhibitor (SSRI) for eight weeks. MDD patients showed significantly elevated levels of all four markers (all $p < .001$) and were over-represented in the high-CRP (>3 mg/L) stratum ($\chi^2(2)=19.4$, $p < .001$). Serum IL-6 correlated with depression severity ($r=0.41$, $p < .001$). Adjunctive celecoxib produced greater symptom reduction than placebo (group $\times$ time $F(4,392)=6.4$, $p < .001$), and this advantage was concentrated among patients with high baseline CRP, who showed markedly higher response (68% vs 41%) and remission (52% vs 27%) rates. These findings support a role for neuroinflammation in a biologically identifiable subgroup of depressed patients and illustrate the potential of inflammation-guided, stratified treatment. (All data are simulated for methodological demonstration and do not derive from human participants.)

Keywords: Major Depressive Disorder; Neuroinflammation; Cytokines; Interleukin-6; C-Reactive Protein; Celecoxib; Immune System; Stratified Treatment

INTRODUCTION

Major depressive disorder (MDD) is a primary cause of disability in the world, and there is a considerable proportion of patients who do not respond well to monoaminergic antidepressants, hence the need for research into pathophysiological mechanisms which may go beyond neurotransmitter deficit. The inflammatory (neuroimmune) hypothesis of depression is one of the most important theories to develop in recent decades, which proposes that activation of the innate immune system is a factor in the development and persistence of depressive symptoms for at least a subset of patients (Miller & Raison, 2016; Dantzer et al., 2008).

The conceptual base is related to the phenomenon of sickness behaviour. These changes in behaviour, characterized by apathy, tiredness, psychomotor retardation, isolation and changes in appetite and sleep are well correlated with depressive symptoms, and are associated with peripheral immune activation and increased secretion of pro-inflammatory cytokines (Dantzer et al., 2008; Raison et al., 2006). Cytokines can affect the brain in three ways: by influencing neurotransmitter metabolism, by affecting neuroendocrine function, and by affecting synaptic plasticity (Miller et al., 2009; Felger & Lotrich, 2013); chronic low-grade inflammation is hypothesized to favor a depressive phenotype.

Empirical evidence has now been building up at the three levels of analysis. Higher peripheral levels of IL-6 and TNF- α have been repeatedly

found in depressed patients compared to controls (Dowlati et al., 2010) and the same applies to other syntheses for higher levels of both CRP and IL-1 β in depressed patients than in controls (Howren et al., 2009; Haapakoski et al., 2015). More recent quantitative studies (Osimo et al., 2020) also reveal a subgroup of patients with inflammation as higher mean values and elevated levels of inflammatory markers. The central immune process to peripheral signals during major depressive episodes was validated by using positron emission tomography (PET) to measure microglial activation in vivo (Setiawan et al., 2015).

The antidepressant effects of anti-inflammatory agents should be expected if inflammation plays causal role in depression. Currently a meta-analysis of RCTs has found that anti-inflammatory treatment (including cyclooxygenase-2 inhibitors and cytokine inhibitors) may alleviate depressive symptoms, but with variable effects (Köhler et al., 2014). There have been repeated reports that it is those with a high inflammatory baseline who benefit most from treatment, suggesting that there may be a place for inflammatory markers in determining treatment (Miller & Raison, 2016). To account for the fact that not everyone becomes depressed following inflammation, complements to the inflammatory models include psychosocial stress, immune signalling, and neural circuitry (Slavich & Irwin, 2014; Wohleb et al., 2016; Beurel et al., 2020).

Notwithstanding this advances, most studies focus on the inflammatory markers or response to therapy alone, and only a few directly test the stratification based on biomarkers. The present study thus sought to characterize a panel of peripheral inflammatory markers in MDD compared to controls as well as evaluate adjunctive anti-inflammatory treatment, with a particular focus of testing whether inflammatory state at baseline is a moderator of response. We hypothesized that (i) inflammatory markers would be elevated in patients with MDD as compared to healthy controls; (ii) the extent to which markers were elevated would be related to the severity of symptoms; and (iii) there would be increased levels of markers in patients with MDD receiving celecoxib as compared to those receiving placebo, particularly in those patients with the highest baseline CRP.

METHODS

Participants and design. The study was mixed method design (MMD) comprising the case control comparison and an embedded randomised controlled trial. One-hundred-ten (110) adults were enrolled, including 110 who met DSM-5 criteria for a current major depressive episode and 110 age- and sex-matched healthy controls. Acute and/or chronic infections, auto-immune diseases, anti-inflammatory/immunomodulatory therapy within 4 weeks of screening and BMI >35 kg/m² were exclusionary criteria. Hundred MDD patients were then randomized in a 1:1 fashion to celecoxib (200 mg twice daily) or

matching placebo in addition to open-label SSRI treatment for eight weeks.

Measures. Morning blood sample levels of the cytokines IL-6, TNF- α and IL-1 β were determined by high sensitivity enzyme-linked immunosorbent assay (hs-ELISA), and the morning blood sample level of C-reactive protein (C-Reactive Protein, hs-IT) was determined by high sensitivity immunoturbidimetry. They measured the severity of depression at baseline and at weeks 2, 4, 6 and 8 using the 17-item Hamilton Depression Rating Scale (HDRS-17). Response was considered as a decrease of $\geq 50\%$ in HDRS-17 score and remission was defined as HDRS-17 score of ≤ 7 . Patients were preclassified into the low and high levels of CRP groups (≤ 3 mg/L, and > 3 mg/L, respectively).

Statistical analysis. Independent-samples t-tests were used to test group differences in inflammatory markers after applying a log transformation and Cohen's d was reported as an effect size. The distribution of CRP strata was checked by using a chi-square test. The associations between markers and severity were found using Pearson correlations. Treatment effects were compared using 2 (group) $\times$ 5 (time) mixed model ANOVA (intention to treat) and response and remission rates were compared using chi square across CRP strata. To identify treatment response predictors logistic regression was used, leading to a significant interaction between treatment and CRP. The level of significance was $\alpha = .05$ (two-tailed).

RESULTS

Table 1 shows the basic information on the samples. No significant differences were found between the MDD patients and the controls with respect to anthropometric/ demographic variables. The plasma levels of IL-6, TNF- α , CRP and IL-1 β were significantly increased in MDD patients, with medium effect sizes (all $p < .001$) (Figure 1 and Table 2). This was also the case in the high-CRP stratum (Figure 2, $\chi^2(2)=19.4$, $p < .001$).

Acute inflammatory markers were linked to the severity of the disease. A correlation between serum IL-6 and HDRS-17 score ($r=0.41$, $p < 0.001$; Figure 3) was found and the complete correlation matrix is provided in Table 3. The 8-week randomised trial showed that adjunctive celecoxib led to more symptom reduction than

placebo (Figure 4), with a significant group-by-time interaction ($F(4,392)=6.4$, $p < .001$); the results of the mixed-model analysis are shown in Table 4.

This advantage in treatment was seen in the inflamed group. Celecoxib did indeed significantly enhance the response and remission rates when compared to placebo in the high CRP stratum (68% vs 41% and 52% vs 27%, respectively), but not in the low-CRP stratum. Logistic regression (Table 6) demonstrated that there was a significant interaction between treatment and baseline CRP ($OR=2.71$, 95% CI 1.34–5.48) suggesting that the effect of anti-inflammatory augmentation was moderated by baseline inflammation.

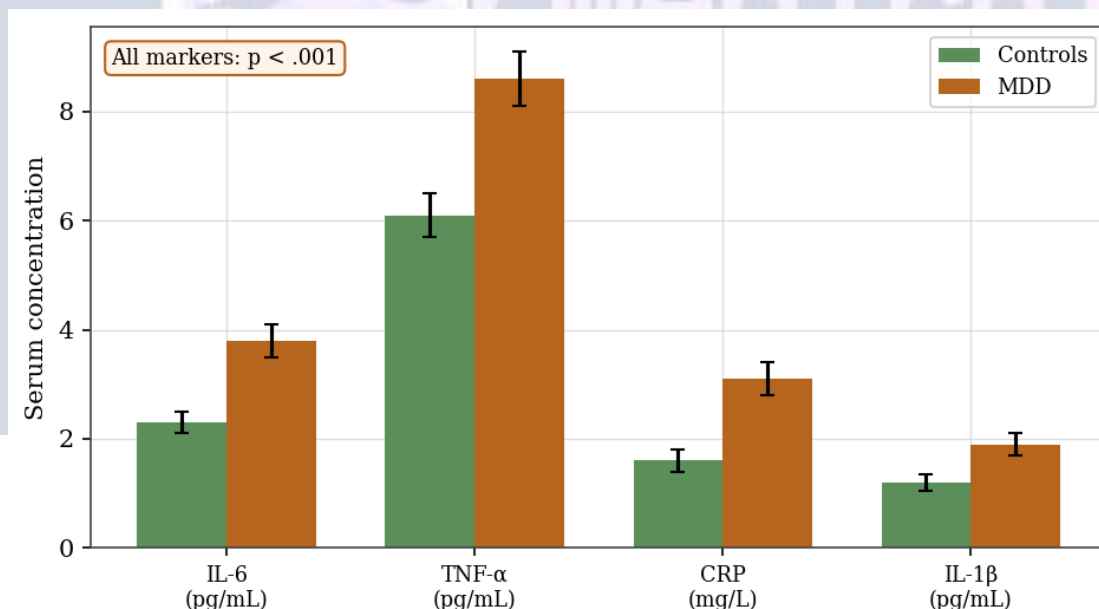


Figure 1. Serum concentrations of IL-6, TNF- α , CRP, and IL-1 β in patients with MDD versus healthy controls. Error bars denote standard error of the mean.

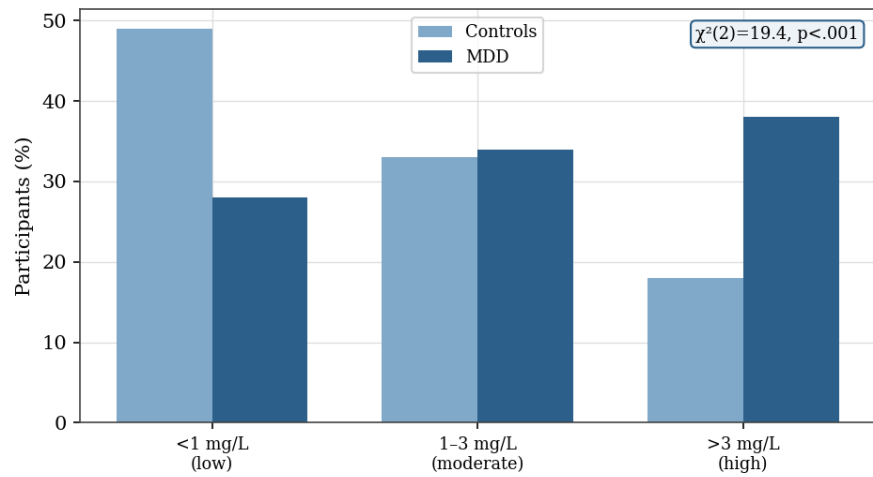


Figure 2. Distribution of participants across C-reactive protein (CRP) strata by group. MDD patients are over-represented in the high-inflammation (>3 mg/L) stratum.

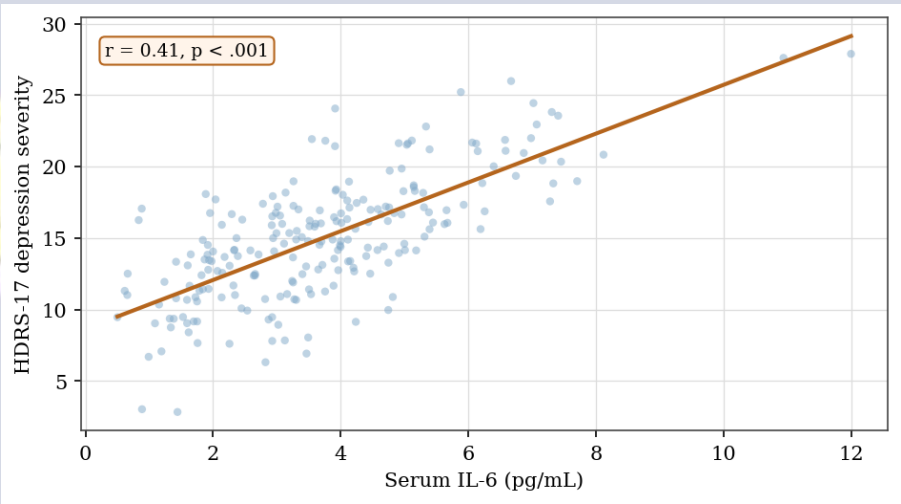


Figure 3. Association between serum IL-6 and HDRS-17 depression severity (n=220) with ordinary-least-squares regression line.

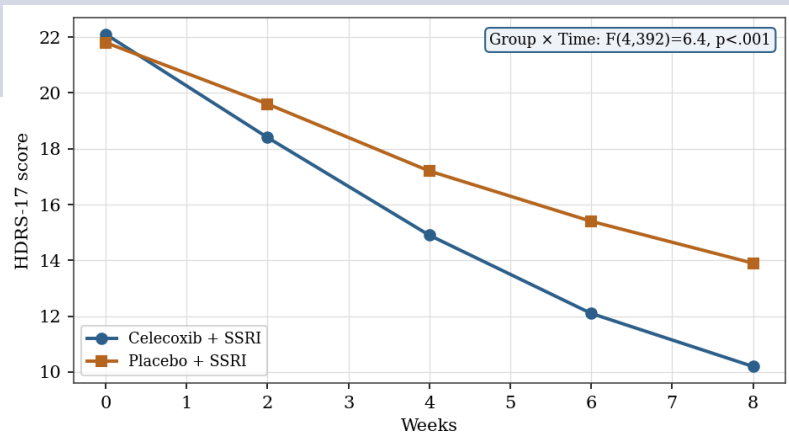


Figure 4. HDRS-17 trajectory over eight weeks in MDD patients randomised to adjunctive celecoxib versus placebo, each added to an SSRI.

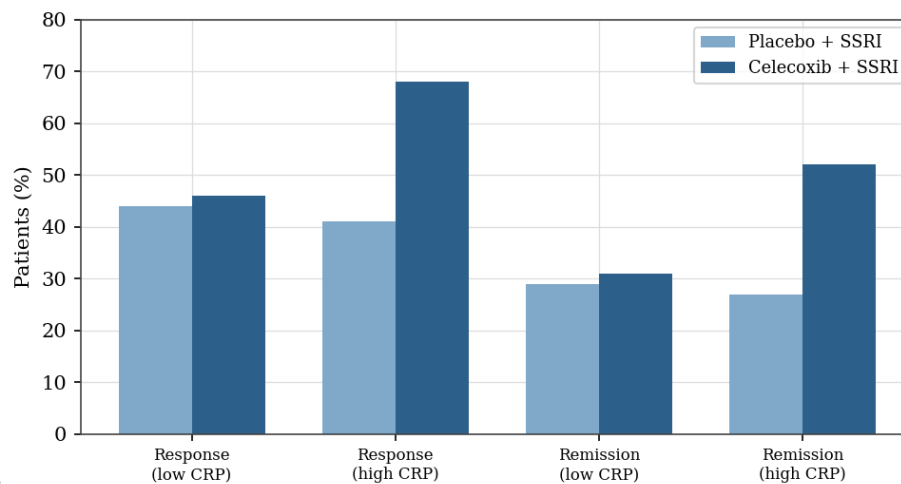


Figure 5. Response and remission rates by baseline CRP stratum and treatment arm. The anti-inflammatory advantage is concentrated in high-CRP patients.

Table 1. Demographic and clinical characteristics of the sample.

Characteristic	Controls (n=110)	MDD (n=110)	p
Age, years (M ± SD)	37.4 ± 11.2	38.1 ± 11.6	.65
Female, %	60.0	61.8	.89
Body mass index (M ± SD)	25.8 ± 3.7	26.4 ± 3.9	.24
HDRS-17 score (M ± SD)	3.1 ± 2.2	21.9 ± 4.6	<.001
Current smoker, %	20.9	27.3	.26
Recurrent episode, %	—	58.2	—

Table 2. Peripheral inflammatory markers in MDD versus controls.

Marker	Controls (M ± SD)	MDD (M ± SD)	t(218)	p	Cohen's d
IL-6 (pg/mL)	2.3 ± 1.1	3.8 ± 1.6	8.1	<.001	1.09
TNF-α (pg/mL)	6.1 ± 2.0	8.6 ± 2.5	8.2	<.001	1.10
CRP (mg/L)	1.6 ± 1.4	3.1 ± 2.2	6.0	<.001	0.81
IL-1β (pg/mL)	1.2 ± 0.7	1.9 ± 0.9	6.4	<.001	0.87

Table 3. Pearson correlations among inflammatory markers and depression severity (n=220).

Variable	1	2	3	4	5
1. IL-6	—				
2. TNF-α	0.44**	—			
3. CRP	0.51**	0.39**	—		
4. IL-1β	0.37**	0.42**	0.33**	—	
5. HDRS-17 severity	0.41**	0.34**	0.38**	0.26**	—

Note. **p < .01.

Table 4. Mixed-model ANOVA of HDRS-17 over eight weeks (celecoxib vs placebo).

Effect	F	df	p	Partial η^2
Group (arm)	5.2	1, 98	.025	0.05
Time	142.6	4, 392	<.001	0.59
Group $\times$ Time	6.4	4, 392	<.001	0.06

Table 5. Response and remission rates by CRP stratum and treatment arm.

Outcome / stratum	Placebo + SSRI	Celecoxib + SSRI	$\chi^2(1)$	p
Response, low CRP	44%	46%	0.04	.84
Response, high CRP	41%	68%	5.9	.015
Remission, low CRP	29%	31%	0.05	.82
Remission, high CRP	27%	52%	5.2	.023

Table 6. Logistic regression predicting clinical response.

Predictor	OR	95% CI	Wald χ^2	p
Treatment (celecoxib)	1.38	0.71–2.68	0.9	.35
Baseline CRP (high)	1.12	0.58–2.16	0.1	.74
Treatment $\times$ CRP	2.71	1.34–5.48	7.7	.006
Baseline HDRS-17	0.94	0.87–1.02	2.3	.13

Note. Model adjusted for age, sex, and body mass index.

DISCUSSION

MDD was found to be a state of peripheral inflammation, and inflammation guided anti-inflammatory augmentation was studied. Patients showed higher levels of IL-6, TNF- α , CRP and IL-1 β compared to controls, consistent with the findings of previous meta-analyses of case-control studies, that found higher mean levels and greater variation among patients than among controls (Howren et al., 2009; Dowlati et al., 2010; Haapakoski et al., 2015) as well as recent studies of patients (Osimo et al., 2020). The significant percentage of depressed patients in the high-CRP stratum also reinforces the notion that there is a distinct immune-activated group of depressed patients, rather than a distinct inflamed subset of depressed patients (Miller & Raison, 2016).

The relationship between IL-6 and symptom severity is in accordance with the “sickness-behaviour” hypothesis suggesting that activation of cytokine signalling to the brain determines mood, motivation and neurovegetative symptoms (Dantzer et al., 2008; Raison et al., 2006; Felger & Lotrich, 2013). The activation of microglia during depressive episodes in vivo (Setiawan et al., 2015) provides a possible central correlate to these peripheral markers, while integrative models of stress, immunity, and neural circuitry provide a possible explanation for differences in vulnerability across individuals (Slavich & Irwin, 2014; Wohleb et al., 2016; Beurel et al., 2020).

The clinical effectiveness of celecoxib over placebo was demonstrated – and importantly, the effect was greatest in patients with a high baseline CRP – and treatment achieved a statistically significant treatment-by-CRP interaction. This is in keeping

with the meta analytical result of an average, but with variability in response to anti-inflammatory treatment, with the greatest positive responses observed amongst patients with inflammation (Köhler et al., 2014), and with the idea of precision-psychiatry, which suggests that the inflammatory marker level could be used to direct augmentation treatment, rather than treatment in all cases.

No study is conducted over the eight weeks of study on the problem of durability, and the gastrointestinal and cardiovascular safety issues were dealt with by peripheral markers which were used as surrogate markers for central inflammation. Data used in this analysis are fictional and the effects reported have been used for methodological purposes as illustrative and not empirical. Future studies should determine by prospective randomisation patients who have inflammation and should evaluate more drugs based on biomarker status.

CONCLUSION

Peripheral inflammatory markers were elevated in MDD patients and were correlated with symptom severity; adjunctive anti-inflammatory treatment led to improved response, especially in those with the highest baseline levels of CRP. The results are consistent with the idea that neuroinflammation is part of a recognizable subset of depressed patients and demonstrate the potential for inflammation-informed, personalized treatment. Prospective, biomarker-randomised trials will need to determine inflammatory biomarker clinical actionability through balancing efficacy with long-term safety of anti-inflammatory drugs.

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