Pro-inflammatory markers are associated with response to sequential pharmacotherapy in major depressive disorder: a CAN-BIND-1 report

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Abstract

Objective. There is limited literature on associations between inflammatory tone and response to sequential pharmacotherapies in major depressive disorder (MDD).

Methods. In a 16-week open-label clinical trial, 211 participants with MDD were treated with escitalopram 10–20 mg daily for 8 weeks. Responders continued escitalopram while non-responders received adjunctive aripiprazole 2–10 mg daily for 8 weeks. Plasma levels of pro-inflammatory markers—C-reactive protein, interleukin (IL)-1β, IL-6, IL-17, interferon-gamma (IFN)-Γ, tumor necrosis factor (TNF)-α, and Chemokine C–C motif ligand-2 (CCL-2)—measured at baseline, and after 2, 8 and 16 weeks were included in logistic regression analyzes to assess associations between inflammatory markers and treatment response.

Results. Pre-treatment IFN-Γ and CCL-2 levels were significantly associated with a lower of odds of response to escitalopram at 8 weeks. Increases in CCL-2 levels from weeks 8 to 16 in escitalopram non-responders were significantly associated with higher odds of non-response to adjunctive aripiprazole at week 16.

Conclusion. Higher pre-treatment levels of IFN-Γ and CCL-2 were associated with non-response to escitalopram. Increasing levels of these pro-inflammatory markers may be associated with non-response to adjunctive aripiprazole. These findings require validation in independent clinical populations.

Introduction

Major depressive disorder (MDD) is the leading cause of disability worldwide, with an estimated annual attributable financial loss of $210.5 billion in the United States.[1,2] Though antidepressant medications are effective for a considerable proportion of patients, large studies suggest that up to 50% of patients do not achieve remission with standard treatments.[3-5] A probable explanation for this variability in treatment outcomes is that patients with MDD are a heterogeneous group.[6-8] To achieve higher rates of remission, a "precision medicine" approach requires validated biomarkers to delineate subgroups of patients who are more likely to respond to specific treatments.

There is converging evidence to support an association between MDD and altered profiles of circulating inflammatory markers.[9-11] Based on evidence from longitudinal observational studies, high plasma pro-inflammatory cytokine levels precede, and thus potentially induce depressive symptoms.[12] In addition, there are reports that higher levels of circulating inflammatory mediators are associated with greater severity of illness, and are more prominent in people who are resistant to antidepressants.[13-15] Despite this, clinical trials of repurposed anti-inflammatory agents (eg, NSAIDs, cytokine inhibitors, minocycline) for MDD report inconsistent results, leading to calls for more targeted approaches to address the heterogeneity of the disorder.[16] Specifically, low-grade inflammation is more frequently associated with atypical subtypes of MDD than melancholic subtypes, informing the development of stratified clinical trials of repurposed anti-inflammatory agents for these specific symptom subtypes.[17-19]

Previous studies and meta-analyzes have shown associations between pre-treatment levels of, and changes in, levels of inflammatory cytokines and chemokines in patients with MDD who are treated with antidepressants.[20-24] However, there is a high degree of heterogeneity among the studies published to date. Controlling for different covariates across studies provides at least a partial explanation for this heterogeneity. This is particularly important as protein-based inflammatory markers are influenced by multiple factors including body mass index (BMI), physical health, medications, exercise, diet, and substance use; all of which are difficult to account for and poorly reported in studies. Despite these caveats, current evidence supports an association between altered inflammatory mediators and treatment response, in at least a subset of individuals with MDD.

One explanation—at least in part—for the antidepressant action of selective serotonin reuptake inhibitors (SSRIs) is their immunomodulating properties. A meta-analysis of 22 studies including 827 participants with MDD found that SSRI treatment decreased levels of pro-inflammatory markers IL-6, TNF-α, and IL-1β.[24] Conversely, others reported elevation in inflammatory markers post-treatment with both tricyclic antidepressants (TCAs) and serotonin noradrenaline reuptake inhibitors (SNRIs).[25,26] The diverse effects of antidepressants on levels of inflammatory makers may be due to differences in mechanisms of action: there is evidence that noradrenaline has pro-inflammatory effects on innate immune cells and thus potentiates cytokine production.[27]

Atypical antipsychotics (AAPs) are recommended as augmentation treatments for MDD when patients do not respond to first-line SSRIs or SNRIs.[28] Pre-clinical studies of AAPs (olanzapine and aripiprazole) demonstrate a decrease in the production of inflammatory cytokines in murine microglial cells and in healthy human blood cells.[29,30] Although there is limited evidence on the effect of AAPs on inflammatory markers in MDD patients, studies in participants with schizophrenia report mixed findings.[31,32] For instance, in a large meta-analysis of 85 000 participants with schizophrenia, CRP levels were moderately increased in persons with schizophrenia regardless of the use of antipsychotics.[33] This may be because AAPs exert diverse effects on the immune system, having both a direct anti-inflammatory activity and an indirect pro-inflammatory activity, mediated by their metabolic effects (ie, weight gain and increased adiposity). The lack of consensus on the immunomodulating effects of antidepressant and AAP medications highlights the need for larger clinical trials of longer durations. Investigating the effects of individual SSRI and AAP agents on inflammatory markers in subgroups of MDD patients with differing baseline inflammatory status, as well as in subgroups of treatment responders and non-responders, could help stratify medications and advance the quest for "precision psychiatry."

The Canadian Biomarker Integration Network in Depression (CAN-BIND) was developed to take a consistent integrated approach to biomarker discovery during multiple treatment trials.[34] The overall goal of CAN-BIND is to identify predictors, moderators, and mediators of treatment response and non-response in people with MDD that may guide clinical decision-making. CAN-BIND-1 is a multisite clinical trial with sequential pharmacotherapy over 16 weeks. The design includes assessment of clinical, molecular, genomic, electrophysiological, and neuroimaging parameters.[35,36] Using inflammatory marker data obtained during CAN-BIND-1, we conducted a secondary analysis to assess associations between individual pro-inflammatory chemokines and cytokines, and response to sequential treatment with escitalopram and adjunctive aripiprazole in MDD patients. We selected those inflammatory markers with established pro-inflammatory activity as replicated evidence has suggested that an activated inflammatory response is associated with unfavorable response to antidepressant medications [13, 15, 37]

Methods

Study overview

The study protocol and clinical outcomes for CAN-BIND-1, including details of eligibility criteria and study procedures, have been previously reported.[30-31] Participants were the outpatients of the age group between 18 and 60 years old, meeting Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR criteria for a major depressive episode (without psychosis) in MDD, with a baseline Montgomery-Åsberg Depression Rating Scale (MADRS)[38] score ≥ 24. Individuals with schizophrenia-spectrum disorders, bipolar disorders, and major neurological disorders, head trauma, or other unstable medical conditions were excluded.

The trial was registered on ClinicalTrials.gov (Identifier: NCT01655706) on August 2, 2012, and is a multisite initiative involving six Canadian academic health centers working collaboratively with other universities and research centers. During the first 8 weeks, participants received escitalopram 10–20 mg daily: responders (≥50% reduction in MADRS score) continued escitalopram for another 8 weeks, while non-responders received adjunctive aripiprazole 2–10 mg for the remaining 8 weeks. Escitalopram and aripiprazole were chosen since they are, respectively, evidence-based first-line mono and adjunctive pharmacotherapies for MDD. Both drugs are endorsed in international guidelines on treatment for MDD, including the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.[28, 39]

Ethics approval and consent to participate

Research Ethics Boards (REB) at each institution: University of British Columbia Clinical (UBC) Research Ethics Board (Vancouver); University of Calgary Conjoint Health Research Ethics Board (Calgary); University Health Network (UHN) Research Ethics Board (Toronto; primary site); Centre for Addiction and Mental Health Research (CAMH) Ethics Board (Toronto); Hamilton Integrated Research Ethics Board (Hamilton); Queen's University Health Sciences (QNS) and Affiliated Teaching Hospitals Research Ethics Board (Kingston), approved the trial. The UHN REB approval number is 11-0917. Participants provided written, informed consent for all study procedures.

Clinical measures

The primary symptomatic outcome measure to assess antidepressant response was the MADRS.[38] A full list of secondary clinical measures has been published previously.[35] A full assessment of physical health history including a history of immune-related conditions (eg, diabetes mellitus, asthma, ischemic heart disease, inflammatory bowel disease, rheumatoid arthritis, and autoimmune disease) was conducted with each participant.

Measurement of pro-inflammatory markers

Peripheral venous whole blood samples were collected in EDTA tubes at baseline, weeks 2, 8, and 16, and centrifuged at 1 500g at 4 °

C for 15 min. Following plasma extraction, aliquots were stored at −80 °C and subsequently transported to UT Southwestern on dry ice and stored at −80 °C until immediately prior to cytokine assays. Chemokine/cytokine levels were measured using the Microarray Core at UT Southwestern Medical Center using a Bioplex Pro human cytokine standard 27-plex kit (Bio-Rad Laboratories, Hercules, CA, USA) with a Bioplex 200 instrument that was equipped with Bioplex Manager software, version 6.0 (Bio-Rad Laboratories, Hercules, CA, USA). This assay has been used in previous studies.[21] High-sensitivity C-reactive protein (hsCRP) levels were measured in a separate plasma aliquot using Beckman DxC600 at McMaster University, Hamilton, ON. The present secondary analysis focussed on seven chemokines and cytokines with established pro-inflammatory activity: high sensitivity C-reactive protein (CRP), interleukin (IL)-1, IL-6, IL-17, interferon (IFN)-Γ, tumor necrosis factor (TNF)-α, and Chemokine C–C motif ligand-2 (CCL-2).[40,41] Immune marker levels were calculated in mg/L using the standards provided in the kit. Interplate controls were used to monitor for batch effects.

Statistical analysis

To explore differences in pre-treatment inflammatory marker levels between responders and non-responders, independent samples t-tests were performed as a preliminary analysis. A series of logistic regression models were then employed to assess associations between individual pro-inflammatory markers and response to escitalopram at week 8 and to adjunctive aripiprazole at week 16, with age (>40, ≤40), sex (male and female), history of immune-related illness (eg, autoimmune disease), and study site controlled as covariates. The present analysis did not assess associations between individual pro-inflammatory markers and specific depressive symptom subtypes (eg, atypical symptoms).

In the first set of analyzes, associations between individual inflammatory marker levels at baseline and response status at week 8 were examined using the logistic regression models described above. Next, focusing on non-responders to escitalopram at week 8, associations between inflammatory marker levels at week 8 and response status at week 16 were examined using similar logistic regression models.

We then investigated the relationship between response status at weeks 8 and 16, and changes in inflammatory marker levels. First, we examined associations between response status at week 8 and change in levels of each inflammatory marker from baseline to week 2, as well as change from baseline to week 8 using logistic regression analysis. After restricting our analytical sample to those who did not respond to escitalopram at week 8 and received adjunct aripiprazole, the association between the changes in levels of each inflammatory marker from week 8 to week 16, and response status at week 16 was examined. Adjusted Odds Ratios (ORs), with their 95% confidence intervals and associated p-values for all predictors are reported. All statistical analyzes were conducted in SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC).

Results

Recruitment took place between April 2012 and January 2017, during which 211 participants with MDD were recruited (Figure 1). Clinical and demographic details of participants evaluated for inflammatory markers are summarized in Table 1. Inflammatory marker levels at each time point are summarized in Tables 2 and 3.

Relationship between pre-treatment IFN-Γ and CCL-2 levels and response to escitalopram

Baseline levels of pro-inflammatory markers, IFN-Γ (DF 167, $t = 2.53$, $p = 0.012$) and CCL-2 (DF 167, $t = 2.39$, $p = 0.016$) were significantly higher in escitalopram non-responders. There were also significant effects of pre-treatment pro-inflammatory markers on response status at week 8 (Table 4). Specifically, higher levels of pre-treatment IFN-Γ were significantly associated with lower odds of response to escitalopram treatment (odds ratio [OR] = 0.900, 95% confidence interval [CI] = [0.815, 0.990], $p = 0.018$) and higher levels of pre-treatment CCL-2 were also associated with lower odds of response to escitalopram at week 8 (OR = 0.941, 95% CI = [0.895, 0.990], $p = 0.039$). There were no significant associations between pro-inflammatory marker levels at week 8 and response to adjunctive aripiprazole at week 16 (Table 4).

Change in pro-inflammatory markers are associated with response to adjunctive aripiprazole

Changes in pro-inflammatory markers during treatment appeared to associate with response to adjunctive aripiprazole (Table 5). Specifically, an increase in CCL-2 levels between week 8 and 16 in the adjunctive aripiprazole group was significantly associated with higher odds of non-response to adjunctive aripiprazole at week 16 (OR = 1.128, 95% CI = [1.020, 1.249], $p = 0.020$). None of the other pro-inflammatory markers appeared to associate with responses to either treatment in this sample (Table 5).

Discussion

Using a panel of established pro-inflammatory cytokines and chemokines in a large cohort of depressed patients, we identified two pro-inflammatory markers, IFN-Γ and CCL-2 that were associated with response to pharmacotherapy with escitalopram. Higher pre-treatment levels of these pro-inflammatory markers were associated with an unfavorable response after 8 weeks of escitalopram treatment. Increase in CCL-2 during treatment was also associated with an unfavorable response to 8 weeks of adjunctive aripiprazole in previous non-responders to escitalopram monotherapy.

Our results are in keeping with previous reports that elevated pro-inflammatory markers are associated with a poorer response to escitalopram. In a 12-week study of 71 participants with MDD treated with escitalopram, elevated CRP levels were associated with an unfavorable response.[42] Similarly, in a previous trial, MDD participants receiving escitalopram showed higher pre-treatment levels of pro-inflammatory cytokine TNF-α in non-responders. The authors did not assess other pro-inflammatory cytokines like IFN-Γ and CCL-2.[43] The differences in sample size and clinical populations may explain why the CRP and TNF-α findings were not replicated in CAN-BIND-1.

IFN-Γ is produced by several immune cells including natural killer (NK) cells, CD4+ T cells, and macrophages. It has also been implicated in the pathophysiology of MDD.[44] We are not aware of previous studies assessing associations between IFN-Γ and response to escitalopram monotherapy. However, in a meta-analysis of clinical trials involving other antidepressants, including several SSRIs, there were no significant differences in baseline IFN-Γ levels between responders (n = 223) and non-responders (n = 221).[15] In the same meta-analysis, there were no significant treatment effects on IFN-Γ levels in either responders or
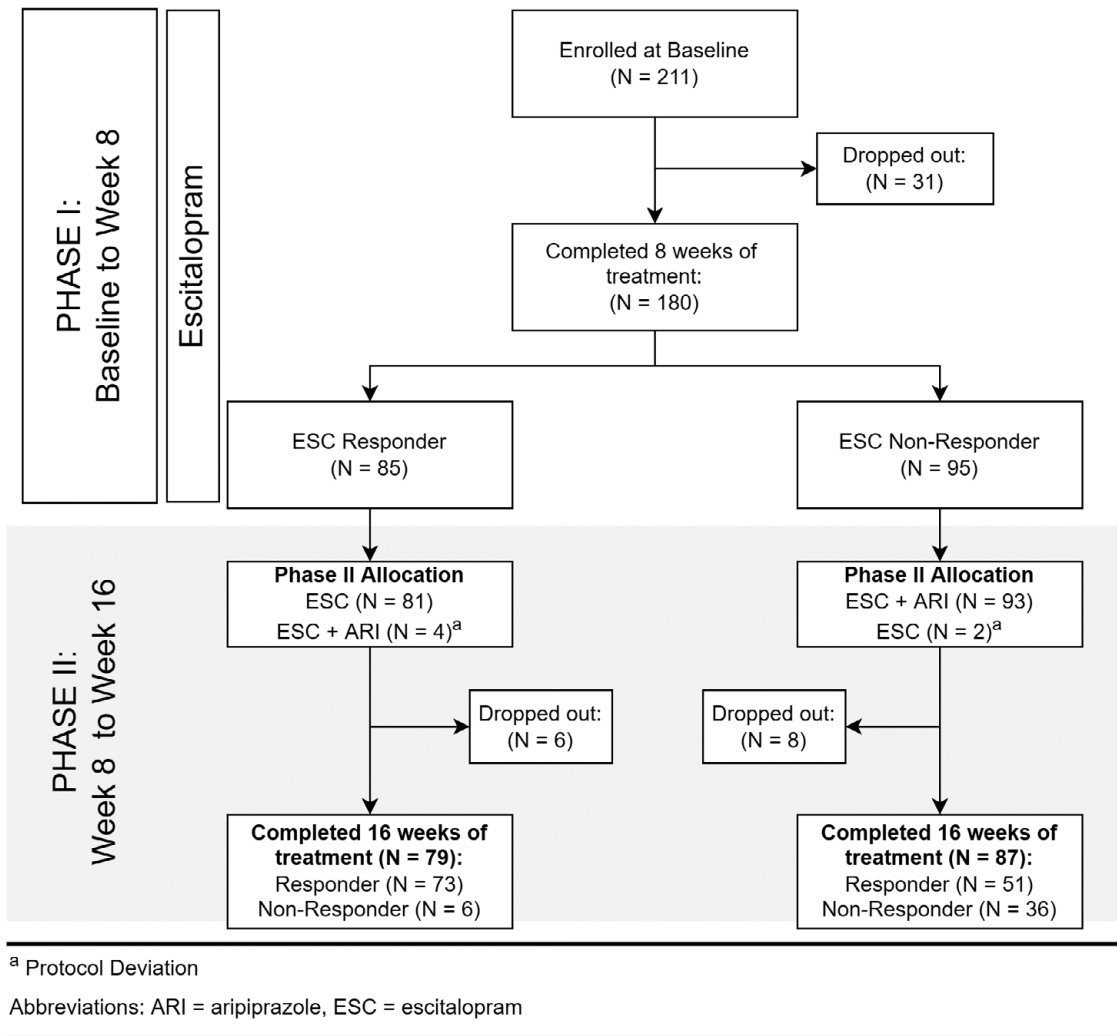
Figure 1. Flow of participants.

Table 1. Clinical and demographic details of participants

Visit	Baseline	Week 2	Week 8	Week 16
n	210	191	174	166
Sex				
Female	132	118	108	101
Male	78	73	66	65
(Mean [SD])				
Age	35.3 [12.7]	35.2 [12.6]	35.4 [12.4]	36.0 [12.7]
BMI	26.5 [6.4]	26.7 [6.5]	26.8 [6.6]	27.0 [6.6]
MADRS	29.8 [5.6]	22.6 [8.3]	16.3 [10.1]	10.4 [8.6]
Number of prior depressive episodes	3.2 [3.8]	3.2 [3.8]	3.1 [3.3]	3.1 [3.3]
Antidepressant treatment (current episode)				
Treatment Naïve	121	109	98	93
Treated	89	82	76	73

BMI, body mass index; MADRS, Montgomery-Asberg Depression Rating Scale; SD, standard deviation.

non-responders to antidepressant treatment after pooling evidence from 10 clinical trials.[15] Again, differences in sample size, clinical population, or choice of antidepressant, may account for the divergence from our findings.

CCL-2, also known as monocyte chemoattractant protein 1 (MCP-1), is a key mediator of neuroinflammation, neurogenesis, neuroplasticity, and synaptic transmission. It is considered an essential mediator in the link between peripheral and central inflammation due to its role in cellular migration and immune coordination. There is support from animal and human studies that CCL-2 is involved in the pathophysiology of MDD,[45] although there are mixed findings on CCL-2 and associations with antidepressant response. In a small pilot study involving participants—with dysthymia and MDD who received escitalopram 10 mg, those with dysthymia but not MDD, had higher pre-treatment CCL-2 levels. There were no changes however in CCL-2 levels in either group during the 4 weeks of escitalopram.[46] Another study assessed changes in CCL-2 during treatment with higher escitalopram doses (20 to 40 mg) in MDD over 12 weeks. In this study, higher pre-treatment levels of CCL-2 were identified in MDD participants compared with healthy controls, but there were no changes in CCL-2 following escitalopram treatment.[47]

Table 2. Inflammatory marker levels (mg/L) at each time point by week 8 response

Cytokines	Response to escitalopram at Week 8					
	Responders (n = 82) Mean [SD]			Non-Responders (n = 87) Mean [SD]		
	Baseline	Week 2	Week 8	Baseline	Week 2	Week 8
CRP	4.01 [6.86]	2.23 [4.10]	2.92 [3.99]	3.45 [8.23]	2.51 [3.84]	3.43 [11.08]
IL-1	1.45 1.64]	1.67 [2.06]	1.77 [2.80]	1.86 [2.27]	1.74 [2.22]	1.87 [3.09]
IL-6	2.17 [3.97]	1.90 [3.62]	1.31 [1.55]	5.78 [26.17]	2.37 [5.21]	1.94 [2.46]
IL-17	11.7 [5.26]	11.5 [3.73]	11.5 [3.80]	13.1 [7.94]	12.0 [4.67]	12.4 [4.28]
TNF-α	74.8 [21.5]	72.9 [17.6]	74.3 [20.6]	75.6 [23.5]	70.9 [18.0]	73.2 [18.5]
CCL-2	13.6 [6.43]	13.0 [5.06]	13.9 [6.41]	17.0 [11.4]	14.0 [5.98]	14.6 [8.56]
IFN-Γ	1.95 [3.53]	2.01 [2.19]	1.77 [1.86]	4.26 [7.51]	3.46 [6.48]	3.06 [4.71]

CRP, C-reactive protein, CCL-2, Chemokine C–C motif ligand-2; IFN, interferon; IL, interleukin; SD, standard deviation; TNF, tumor necrosis factor.

Table 3. Inflammatory marker levels (mg/L) at each time point by week 16 response

Cytokines	Response to escitalopram + aripiprazole at Week 16							
	Responders (n = 46) Mean [SD]				Non-responders (n = 34) Mean [SD]			
	Baseline	Week 2	Week 8	Week 16	Baseline	Week 2	Week 8	Week 16
CRP	3.37 [9.03]	1.87 [2.53]	1.90 [2.25]	3.32 [6.55]	4.01 [7.83]	3.34 [5.10]	5.69 [17.00]	3.06 [3.69]
IL-1	2.31 [2.83]	1.89 [2.43]	2.06 [3.75]	1.92 [2.59]	1.33 [1.29]	1.61 [2.15]	1.67 [2.11]	1.65 [1.74]
IL-6	2.71 [7.68]	2.18 [5.11]	2.00 [2.77]	2.93 [4.69]	8.92 [39.46]	1.96 [2.17]	1.94 [2.11]	4.72 [13.42]
IL-17	13.9 [10.1]	11.8 [4.1]	12.5 [4.1]	11.7 [4.0]	12.2 [4.4]	12.5 [5.5]	12.3 [4.7]	12.4 [5.0]
TNF-α	76.7 [26.7]	71.5 [18.5]	73.2 [17.1]	72.6 [17.5]	72.9 [19.0]	70.8 [16.8]	72.4 [19.4]	72.0 [18.4]
CCL-2	17.9 [10.7]	14.4 [5.5]	15.3 [10.0]	13.0 [5.0]	15.0 [5.5]	14.4 [6.7]	13.7 [6.3]	15.3 [6.8]
IFN-Γ	4.53 [8.80]	3.23 [7.34]	2.89 [4.12]	2.97 [4.09]	3.58 [5.44]	3.87 [5.80]	3.42 [5.57]	3.47 [6.56]

CRP, C-reactive protein; CCL-2, chemokine C–C motif ligand-2; IFN, interferon; IL, interleukin; SD, standard deviation; TNF, tumor necrosis factor.

Table 4. Associations between baseline inflammatory markers on treatment response at weeks 8 and 16

	Response to escitalopram at week 8		
	OR	95% CI	p-value
Baseline CRP	1.010	0.967–1.055	0.655
Baseline IL-1	0.869	0.721–1.047	0.140
Baseline IL-6	0.983	0.944–1.024	0.403
Baseline IL-17	0.974	0.920–1.030	0.351
Baseline TNF-α	1.001	0.987–1.015	0.853
Baseline CCL-2	0.941	0.895–0.990	0.018*
Baseline IFN-Γ	0.900	0.815–0.995	0.039*
	Non-response to escitalopram + aripiprazole at week 16		
	OR	95% CI	p-value
Week 8 CRP	1.182	0.949–1.471	0.136
Week 8 IL-1	0.904	0.755–1.081	0.268
Week 8 IL-6	0.926	0.751–1.141	0.569
Week 8 IL-17	0.971	0.861–1.096	0.637
Week 8 TNF-α	0.998	0.970–1.026	0.880
Week 8 CCL-2	0.959	0.895–1.027	0.230
Week 8 IFN-Γ	1.018	0.926–1.119	0.712

CI, confidence interval; CRP, C-reactive protein; CCL-2, chemokine C–C motif ligand-2; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; OR, odd ratio.
*p < 0.05.

There are limited data on the effect of aripiprazole on cytokine measures in MDD. Notwithstanding this, associations between inflammatory markers and adjunctive aripiprazole in our sample complement pre-clinical and clinical literature on the anti-inflammatory effects of aripiprazole in schizophrenia, where response to aripiprazole was associated with a reduction in inflammatory cytokines including IL-1β.[29,48] In our sample, non-responders to aripiprazole augmentation showed increases in CCL-2 over 8 weeks of treatment. The absence of an aripiprazole treatment effect on pro-inflammatory marker levels in CANBIND-1 responders may in part be explained by the small sample sizes, short duration of follow-up, or differences in clinical populations (ie, schizophrenia vs MDD) in previous studies.

Although we controlled for potential confounders including age, sex, and history of comorbid immune-related illness, a limitation of our study is the lack of control for other potential confounders such as cigarette smoking, and socioeconomic status. As this secondary analysis was exploratory in nature, we did not correct the results for multiple comparisons. An additional limitation is the applicability of our findings to other antidepressants or atypical antipsychotic augmentation treatments with different mechanisms of action. The results of the present study suggest that responders and non-responders to both escitalopram and aripiprazole show similar post-treatment inflammatory profiles, which may suggest regression to the mean. Despite these limitations, the relatively large sample size, broad inclusion criteria, and serial assessments of a comprehensive panel of established pro-inflammatory markers are strengths of the present study.

Table 5. Associations between changes in inflammatory markers on treatment Response at weeks 8 and 16

	Response to escitalopram at week 8		
	OR	95% CI	*p*-value
CRP (baseline–week 2)	0.978	0.930–1.029	0.388
IL-1 (baseline–week 2)	1.267	0.957–1.677	0.098
IL-6 (baseline–week 2)	1.019	0.967–1.073	0.483
IL-17 (baseline–week 2)	1.016	0.968–1.067	0.515
TNF-α (baseline–week 2)	1.006	0.990–1.022	0.486
CCL-2 (baseline–week 2)	1.044	0.992–1.098	0.096
IFN-Γ (baseline–week 2)	1.050	0.965–1.141	0.257
CRP (baseline–week 8)	0.992	0.959–1.026	0.625
IL-1 (baseline–week 8)	1.083	0.903–1.299	0.389
IL-6 (baseline–week 8)	1.012	0.983–1.043	0.413
IL-17 (baseline–week 8)	1.011	0.967–1.056	0.636
TNF-α (baseline–week 8)	1.008	0.964–1.054	0.717
CCL-2 (baseline–week 8)	1.030	0994–1.068	0.109
IFN-Γ (baseline–week 8)	1.028	0.969–1.092	0.360
	Non-response to escitalopram + aripiprazole at week 16		
	OR	95% CI	*p*-value
CRP (week 8–week 16)	0.828	0.649–1.056	0.129
IL-1 (week 8–week 16)	1.052	0.886–1.249	0.562
IL-6 (week 8- week 16)	1.016	0.955–1.081	0.621
IL-17 (week 8- week 16)	1.044	0.941–1.157	0.418
TNF-α (week 8–week 16)	0.997	0.973–1.022	0.828
CCL-2 (week 8–week 16)	1.128	1.020–1.249	0.020*
IFN-Γ (week 8- week 16)	0.990	0.889–1.102	0.850

CI, confidence interval; CRP, C-reactive protein; CCL-2, chemokine C–C motif ligand-2; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; OR, odd ratio.
*$p < 0.05$.

Conclusion

This secondary analysis of the CANBIND-1 trial suggests that IFN-Γ and CCL-2 may have utility as biomarkers of treatment response to escitalopram monotherapy and adjunctive aripiprazole in escitalopram non-responders. We encourage validation of these findings in independent studies. Predicting antidepressant treatment response is a clinical challenge for MDD. The inflammatory hypothesis of depression suggests that inflammatory processes play a key role in the pathophysiology of MDD in at least a subgroup of the population and evidence indicates that alterations in peripheral cytokine levels are associated with antidepressant treatment outcome.[11,15] However, results from clinical trials of anti-inflammatory agents in MDD continue to be conflicting and the antidepressant efficacy of anti-inflammatories has yet to be established.[16,49] Further longitudinal studies are required to elucidate sources of heterogeneity in the present literature and to examine the feasibility of using peripheral inflammatory markers as predictive biomarkers for the treatment of MDD. There is emerging evidence that distinct depressive symptom profiles may be associated with an activated inflammatory response.[50] Moving beyond the search for a single biomarker of disease activity and toward the development of composite biomarkers associated with clinical phenotypes of treatment response may more likely lead to the identification of MDD subtypes that inform personalized treatments including immunomodulatory drugs.

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