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Baseline C-Reactive Protein Levels are Predictive of Treatment Response to a Neuroimmune Modulator in Individuals with an Alcohol Use Disorder: A Preliminary Study

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Abstract

Background: Inflammation is implicated in alcohol use disorder (AUD). Ibudilast, a neuroimmune modulator, shows promise for the treatment of AUD. Elevated inflammation, indicated by high levels of C-reactive protein (CRP), represents a possible subtype of AUD, which may be associated with treatment response to ibudilast.

Objectives: The current study evaluated CRP as a predictor of treatment response to ibudilast; hypothesizing that ibudilast would be more effective at reducing drinking and alcohol cue-reactivity in individuals with higher CRP levels.

Methods: This is a secondary analysis of a clinical trial of ibudilast for AUD, which found that ibudilast reduced heavy drinking in individuals with AUD. Fifty-one individuals were randomized to receive ibudilast (n=24 [16M/8F]) or placebo (n=27 [18M/9F]) for two weeks. Participants provided blood samples at baseline to assess CRP levels, completed daily assessments of alcohol use, and an fMRI alcohol cue-reactivity task at study mid-point. Models tested the effects of medication, CRP levels, and their interaction on drinks per drinking day and alcohol cue-reactivity.

Results: There was a significant interaction between medication and CRP ($F(1,44)=3.80$, $p=0.03$), such that the ibudilast high CRP group had fewer drinks per drinking day compared

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to the ibudilast low CRP group. CRP moderated the effect of medication on brain activation in a cluster extending from the left inferior frontal gyrus to the right dorsal striatum ($Z=4.55$, $p<0.001$). This interaction was driven by attenuated cue-reactivity in the ibudilast high CRP group relative to the ibudilast low CRP and placebo high CRP groups.

Conclusions: This study serves as an initial investigation into predictors of clinical response to ibudilast treatment and suggests that a baseline proinflammatory profile may enhance clinical efficacy.

ClinicalTrials.gov identifier: NCT03489850 (https://clinicaltrials.gov/ct2/show/NCT03489850).

Keywords

alcohol use disorder; ibudilast; inflammation; C-reactive protein; fMRI

Introduction

Inflammation has been implicated in the development and maintenance of alcohol use disorder (AUD) (1–4). In preclinical models, chronic alcohol exposure has been shown to increase central and peripheral markers of inflammation (5, 6). Preclinical research also indicates that inflammation heightens motivation for alcohol consumption, enhances alcohol-related reward, and contributes to substance use-related cognitive impairment and depression-like behavior (7–9). Clinically, individuals with AUD show increased inflammation throughout the brain and body, and elevated peripheral levels of proinflammatory proteins have been proposed as biomarkers for AUD (10–13).

One such proposed proinflammatory biomarker is C-reactive protein (CRP), for which circulating levels are shown to be elevated in proportion to World Health Organization alcohol risk drinking category, such that increases in CRP levels are linearly related to alcohol risk category (14). CRP is an acute-phase protein induced in the liver by proinflammatory cytokines (15, 16), especially interleukin-6 (IL-6) – another proposed proinflammatory biomarker correlated with alcohol use (17) – in response to infection and inflammation. CRP is widely used in clinical practice as a marker of systemic inflammation (18, 19) and has been well-studied as a potential biomarker for major depressive disorder (20–23). A high-sensitivity assay for CRP is well-validated, accessible, and remains highly stable in long-term serum and plasma storage (24–27). CRP Levels greater than 3 mg/L have been defined as high-risk for cardiovascular events by the American Heart Association (28).

Targeting peripheral and neural immune pathways represents an important direction in the development of more effective treatments for AUD (29, 30). Ibudilast is a novel neuroimmune modulator that has shown promising preclinical and initial clinical outcomes for the treatment of AUD (31–33). Ibudilast is a selective phosphodiesterase (PDE) inhibitor (inhibiting PDEs-3, -4, -10, and -11) (34) and an allosteric macrophage migration inhibitory factor (MIF) inhibitor (35). Both MIF and PDEs are implicated in neuroinflammatory processes via regulation of inflammatory response in microglia (36, 37), and PDE4B expression is upregulated in chronic alcohol exposure (38). PDEs -4 and -10A are also implicated in the regulation of alcohol consumption (39, 40). In recent human laboratory and

clinical studies, ibudilast has been shown to reduce tonic craving, improve mood following stress and alcohol cue exposure, reduce heavy drinking, attenuate neural reward signaling in non-treatment-seeking individuals with AUD, and reduce peripheral and central markers of inflammation (32, 33, 41, 42). However, AUD is a highly heterogeneous disorder, subtypes of which present distinct characteristics and may require distinct treatment strategies (43, 44). Thus, it is unlikely that any one medication will be efficacious for all individuals with AUD, including ibudilast. As such, there have been extensive efforts to use precision medicine approaches to tailor pharmacotherapies to individuals with different presentations of AUD (45–48).

In the depression literature, proinflammatory markers like CRP have been tested as personalized medicine targets to identify treatment responders. Individuals with treatment-resistant depression, who have elevated levels of proinflammatory cytokines, are hypothesized to display a distinctive clinical profile that may be more responsive to pharmacotherapies targeting the immune system (49–52). No study has yet investigated whether baseline levels of inflammation might be related to treatment response in individuals with AUD. Furthermore, depression studies have found heightened inflammation to be associated with decreased neural activation in brain regions related to reward processing = (21, 53, 54). Given that we have previously found that ibudilast was found to attenuate neural response to alcohol cues in similar corticostriatal regions (33, 41), it is also possible that baseline inflammation levels might also relate to changes in neural activation to alcohol cues following ibudilast treatment.

The current study is a secondary analysis of a two-week placebo-controlled randomized clinical trial of ibudilast in non-treatment seeking individuals with an AUD (30), which assessed drinking and behavioral outcomes as well as the effects of ibudilast on neural alcohol cue-reactivity. The primary aim of the present study was to probe CRP as a predictor of treatment response to ibudilast in AUD. We hypothesized that ibudilast would be more effective in individuals with high CRP levels at baseline compared to individuals with non-elevated CRP levels at baseline and that this effect would not be seen in individuals treated with placebo. Given that the main study found that ibudilast reduced heavy drinking and attenuated neural cue-reactivity compared to placebo (33), we specifically hypothesized that individuals with elevated baseline CRP levels who received ibudilast would show greater reductions in both clinical (i.e. drinks per drinking day [DPDD]) and biological (i.e. cue-elicited neural activation) outcomes.

Materials and Methods

Participants

Fifty-two individuals with AUD who were not seeking alcohol treatment were enrolled and randomized to receive oral ibudilast (n=24) or matched placebo (n= 28) for two weeks. Non-treatment-seekers were enrolled in this study as it was the first clinical trial of ibudilast to as a possible treatment for AUD. Eligible participants were between 21 and 50 years of age, met criteria for a current DSM-5 diagnosis of mild-to-severe AUD, and drank >14 drinks/week for males or >7 drinks/week for females. Exclusion criteria can be found in the

Supplement. Participants were randomized between July 2018 and March 2020 (see (33) for full study details).

Study Design

This was a micro-longitudinal clinical study (ClinicalTrials.gov identifier: NCT03489850). Participants provided blood samples and completed questionnaires at baseline, prior to randomization. At study mid-point (Day 8) participants underwent magnetic resonance imaging and completed an alcohol cue reactivity task. Participants also completed daily diary assessments to report on their past day drinking, mood, and craving (see (33)). This trial was approved by the Institutional Review Board of the University of California, Los Angeles. All study participants provided written informed consent after discussing the study medication with the study physician.

Participants were randomized to receive 50 mg b.i.d. of ibudilast or placebo, supplied by MediciNova, Inc. The UCLA Research pharmacy prepared both test medications in blister packs, which were dispensed on the randomization study visit. Participants, providers, and research staff remained blind to medication assignment throughout the study. Ibudilast was titrated as follows: 20 mg b.i.d. during days 1–2 and 50 mg b.i.d. during days 3–14. Medication compliance was monitored through pill counts and through daily diary self-report. Participants were compensated up to $350 for their participation in the study, including a $100 completion bonus if they submitted at least 80% of their daily diary assessments.

Baseline Screening Measures

Participants completed a series of assessments for eligibility and individual differences. These measures included the Structured Clinical Interview for DSM-5 (SCID-5) (55), which assessed for current AUD, the Clinical Institute Withdrawal Assessment for Alcohol Scale - Revised (CIWA-Ar) (56), and the 30-day Timeline Followback Interview (TLFB) (57) for alcohol, cigarette, and cannabis. Baseline drinking variables were calculated from the TLFB interview, including DPDD. Participants also completed assessments regarding their alcohol use, including the Alcohol Use Disorder Identification Test (AUDIT) (58), which measures severity of alcohol use problems.

Daily Diary Assessments

Participants completed morning electronic daily diary assessments, reporting on their past-day alcohol use, mood, and craving (primary results reported in (33)). Alcohol use was assessed by asking the number of standard drinks that were consumed yesterday. Non-standard alcohol use was assessed by asking the type of non-standard alcohol consumed (e.g., malt liquor) and the number of drinks consumed; this information was used to convert non-standard drinks into standard drinks.

Assessment of peripheral inflammation

Fifty-one participants provided blood samples at baseline (ibudilast: n=24; placebo: n=27). Blood samples were collected by venipuncture into EDTA tubes, placed on ice, centrifuged for acquisition of plasma, and stored at −80°C for batch testing. CRP levels were determined

utilizing the high-sensitivity Human CRP Quantikine ELISA (R&D Systems) according to the manufacturer's protocol with a lower limit of detection of 0.2 mg/L. Samples were assayed in duplicate. Intra- and inter-assay variation of the tests was <6.1%. For the small proportion (4%, n=2) of samples with CRP concentrations above the upper limited of the standard curve (>25 mg/L) a value of 25 mg/L was assigned. For the small proportion (10%, n=5) of samples with CRP levels below the limit of detection (0.2 mg/L), a value of 0.2 mg/L was assigned.

Neuroimaging Protocol

Alcohol Cue Reactivity—Forty-five participants (ibudilast: n=20; placebo: n=25) completed a 720-s-long visual alcohol cue-reactivity task (59), in which they were presented with 24 pseudo-randomly interspersed blocks of alcoholic beverage images (ALC), non-alcoholic beverage images (BEV), blurred images to serve as visual controls, and a fixation cross. Each block was composed of 5 individual pictures of the same category, each presented for 4.8 seconds, for a total of 24 seconds. Each block was followed by a 6-second washout period during which participants reported on their current urge to drink (craving). Alcoholic beverage blocks were distributed between images of beer, wine, and liquor (2 of each). Preprocessing followed conventional procedures as implemented in FMRIB Software (FSL v6.0.1 http://www.fmrib.ox.ac.uk/fsl). Detailed information on preprocessing procedures can be found in Grodin, et al. (33).

Data Analysis—Statistical analyses were conducted in SAS 9.4. Participants were separated into high and low inflammation groups using a value of >3 mg/L as a cut-off, indicative of high inflammation as defined by the American Heart Association (28) (mean = 3.39±4.68 mg/L; range 0.2–25 mg/L). Participants were then divided into four groups based on their baseline inflammation levels and medication condition: ibudilast high CRP; ibudilast low CRP; placebo high CRP, and placebo low CRP. As expected, the CRP marker levels were not normally distributed (skewness 3.04) and were therefore log-transformed prior to statistical analysis. Log-transformation was successful at achieving normality (skewness = 0.23, kurtosis = -0.67). Group differences in demographic and clinical variables were tested using 2x2 ANOVAs for continuous variables and Chi-squared tests for nominal variables.

A general linear model was used to evaluate the effects of medication (ibudilast, placebo), baseline inflammation (high CRP, low CRP), and their interaction on drinking during the trial. The dependent variable was drinks per drinking day (DPDD), derived from the daily diary assessment reports, averaged over the course of the 2-week trial. DPDD was selected *a priori* as the clinical outcome of interest based on findings from the main trial (33). Age, sex, smoking status, body mass index (BMI), and baseline DPDD were examined as covariates; only significant covariates were retained in the final model. Tukey post-hoc tests were used to conduct pairwise comparisons to identify group differences and correct for multiple comparisons. To support these results, an additional model was run to evaluate the effects of medication, baseline CRP as a continuous variable (log CRP levels), and their interaction on DPDD. These supporting results can be found in the Supplement.

For the neuroimaging data, whole-brain statistical analysis was performed using FSL's FEAT software (60). The primary contrast of interest, ALC vs. BEV, was defined in the first-level models for each subject. FSL's FLAME 1 (61) was used to conduct group-level analyses. Specifically, a 2-way ANOVA was conducted to evaluate the main effect of medication (ibudilast, placebo), baseline CRP (high, low) and their interaction on alcohol cue-elicited brain activation. Follow-up analyses evaluated group differences. Z-statistic images were thresholded using a cluster threshold of Z>2.3 and a (corrected) cluster significance threshold of p=0.05 (62). Age, sex, and smoking status were included as covariates. Similar to the above clinical outcome analyses, an additional model was run to evaluate the effects of medication, baseline CRP as a continuous variable (log CRP levels), and their interaction on alcohol cue-elicited brain activation. These supporting results can be found in the Supplement.

Results

Participants

Fifty-one participants were randomized to ibudilast or placebo and provided usable baseline blood samples to assess CRP levels (ibudilast: n=24; placebo: n=27). Of those 51 participants, 45 participants (ibudilast: n=20; placebo: n=25) completed the fMRI scan. The High vs. Low CRP groups differed on baseline CRP levels (p<0.001; see Figure S1 for individual data points). Regarding demographics, there were no significant medication by CRP group interactions. There was a main effect of CRP on BMI, such that individuals in the High CRP groups had higher BMIs than individuals in the low CRP groups (p=0.047). The groups did not differ on sex, cigarette smoking status, or cannabis use (p's>0.34). Regarding alcohol use and severity, there were no significant medication by CRP group interactions. However, there were main effects of CRP group on baseline DPDD and baseline percent heavy drinking days (PHDD), such that the High CRP group had higher DPDD and PHDD relative to the low CRP group. There were no significant main effects or interactions on AUDIT scores or number of AUD symptoms (p's>0.31; see Table 1).

Clinical Drinking Outcome

There was a significant interaction between medication and baseline CRP (F(1,44)=3.80, p=0.03, $\eta_p^2 = 0.11$), controlling for sex and baseline drinking (see Table 2). Tukey post-hoc tests showed that individuals in the ibudilast high CRP group had significantly fewer DPDD compared to individuals in the ibudilast low CRP group (p=0.007; see Table 2 and Figure 1). There were no significant differences on DPDD between any other groups (i.e., ibudilast High CRP vs. placebo High CRP, placebo Low CRP or between placebo High and Low CRP) when Tukey correction was applied (p's>0.17). Similar significant results were found when examining the interaction between medication and continuous log CRP levels on DPDD ((F(1,44)=5.36, p=0.03, $\eta_p^2 = 0.12$), see Supplement for details).

fMRI Alcohol Cue Reactivity

There was a significant interaction between medication and baseline CRP on alcohol cue-elicited brain activation (ALC vs. BEV), in a large cluster extending from the left inferior frontal gyrus through the anterior cingulate cortex to the right caudate and right putamen

(see Table 3 for full list of regions; and Figure 2A). Follow-up post-hoc analyses identified several group differences in alcohol cue reactivity. Specifically, individuals treated with ibudilast who had low CRP at baseline had greater alcohol cue-elicited activation in several brain regions including the right anterior cingulate, bilateral caudate and putamen, and left insula, relative to individuals treated with ibudilast who had high CRP at baseline (see Table 3 for full list of regions; and Figure 2B). Additionally, individuals treated with placebo who had high CRP at baseline had greater alcohol cue-elicited activation in several brain regions including the right caudate, bilateral frontal gyri, left frontal pole, and left parahippocampus and hippocampus, relative to individuals treated with ibudilast who had high CRP at baseline (see Table 3 for full list of regions; and Figure 2C). Finally, individuals treated with placebo who had high CRP at baseline had greater alcohol cue-elicited activation in the left medial orbitofrontal cortex, and left inferior and middle frontal gyri, relative to individuals treated with placebo who had low CRP at baseline (see Table 3 for full list of regions; and Figure 2D). Similar significant results were found when examining the interaction between medication and log CRP levels on alcohol cue-elicited brain activation (see Supplement for details).

Discussion

This preliminary study sought to evaluate if baseline levels of peripheral inflammation, assessed via CRP, were predictive of treatment response to ibudilast, a neuroimmune modulator, in individuals with an AUD. Specifically this study assessed if individuals with high CRP levels at baseline had better drinking outcomes and attenuated alcohol cue-elicited brain activation when treated with ibudilast. There was a significant interaction between medication and baseline CRP levels, such that individuals treated with ibudilast who had high CRP at baseline had significantly fewer DPDD relative to individuals treated with ibudilast who had low CRP at baseline. In contrast, no significant relationship between baseline CRP levels and drinking was detected among those receiving placebo. Similarly, there was a significant interaction between medication and baseline CRP levels on neural alcohol cue-reactivity in corticolimbic circuitry, such that ibudilast treated individuals who had High CRP levels had attenuated cue-activation relative to the Low CRP ibudilast group and to the High CRP placebo group. Together these preliminary results indicate that baseline CRP levels may be a useful signal to identify individuals who are likely to respond to a neuroimmune pharmacotherapy for AUD.

In this proof-of-concept study, baseline CRP levels significantly moderated the effect of ibudilast treatment on alcohol consumption, suggesting that individuals with elevated CRP levels showed a beneficial treatment response compared with placebo. The estimated means for drinks per drinking day for the ibudilast High CRP group was 2.8, while that of the ibudilast Low CRP group was 6.5, with placebo groups falling around 4.7 drinks per drinking day. Similarly, for the continuous CRP analyses, we found a significant simple slope showing that as baseline CRP levels increased, average DPDD during the trial decreased for the ibudilast group with both models displaying a medium-to-large effect size. Pertinently, the primary trial outcomes show a beneficial reduction in heavy drinking days by ibudilast for the full sample, supporting its promise for AUD treatment (33). When probing this CRP moderator, we found that these drinking reductions by ibudilast may

be driven, to a greater degree, by participants displaying elevated baseline inflammatory levels. Regarding its immunomodulatory mechanisms, ibudilast is thought to reduce the proinflammatory effects of alcohol by altering cAMP signaling pathways, suppressing proinflammatory cytokine expression, and promoting neurotrophic factors, either through actions in the periphery or direct actions in neural regions relevant to AUD (63, 64). While these processes are complex, it is plausible to hypothesize that elevated inflammation or abnormal immune signaling at baseline might be necessary to confer benefit from anti-inflammatory treatment for AUD. These preliminary findings warrant further exploration and replication in larger trials of immune treatments for AUD, particularly those enrolling treatment-seeking samples.

Neuroimaging results showed that baseline CRP levels were associated with neural alcohol cue-reactivity in mesocorticolimibic regions associated with incentive salience and motivation attributed to alcohol-related stimuli. Individuals with High CRP at baseline who received ibudilast showed attenuation of neural activation to visual alcohol cues compared to the Low CRP ibudilast group and the High CRP placebo group. Greater neural cue-reactivity is positively correlated with craving and AUD severity (65–67) and is also predictive of future drinking behaviors following alcohol treatment (33, 68–70). Neural cue-reactivity can be modulated by medications targeting the rewarding properties of alcohol. For example, the FDA-approved pharmacotherapy, naltrexone, is evidenced to reduce frontostriatal activation to alcohol cues (45, 68, 71, 72). In addition, one study found that plasma CRP levels in patients with AUD were significantly correlated with alcohol craving(73). Findings from the primary trial show that ibudilast attenuated bilateral ventral striatal activation to alcohol cues compared with placebo and that one’s degree of activation predicted subsequent DPDD in the ibudilast group (33). Taken together, individuals with elevated inflammation at baseline may those who experience greater ibudilast-related reductions in neural cue-reactivity, which may then be predictive of lower subsequent alcohol consumption. Thus, ibudilast may normalize the ventral striatal dopaminergic response to alcohol cues in AUD, particularly among individuals displaying a proinflammatory profile. These findings support the role of immune signaling in processes of alcohol craving and incentive salience. Of note, these findings indicate that an increased inflammatory profile at baseline are associated with higher levels of brain activation to alcohol cues in relevant reward circuitry, which contrasts with findings from the depression literature where heightened inflammation is associated with attenuated brain activation to reward cues (20, 21, 53, 54). This indicates that ibudilast may not be an effective medication for individuals with comorbid depression; however, future studies will be needed to fully investigate this question. The effect of ibudilast on mood in individuals with AUD has been previously investigated (32, 33, 74), with nuanced results indicating that ibudilast may improve mood when alcohol is also consumed (32, 74), but may not be an effective medication for general mood improvements (33).

As reviewed above, CRP was selected as the biomarker of peripheral inflammation in the present study because it is an accessible and widely used clinical indicator of inflammation with a short half-life and sensitive, reliable response to inflammation (19). Elevated CRP levels are used to monitor, detect, and predict risk for various conditions such as cardiovascular disease, cancer, chronic inflammatory conditions, and bacterial infections (75). Further, a range of proinflammatory markers, including CRP, are shown to be elevated

in psychiatric conditions such as major depression, schizophrenia, bipolar disorder, and addiction, and have been proposed as biomarkers of disease (4, 76–78). Samples with heavy alcohol use show elevated levels of CRP and other proinflammatory cytokines (11, 14, 73, 79). A disease stage-specific biological marker, such as plasma CRP, that can help predict treatment response on the individual levels is highly desirable in medications development for AUD (48). Additionally, the fact that individuals with heightened CRP responded favorably to ibudilast treatment in the form of attenuated neural cue-reactivity and reduced drinks per drinking day during the trial, supports our hypotheses and its suspected immunomodulatory mechanism of action.

Findings from this secondary analysis should be interpreted in the context of the study's strengths and limitations. To start, we frame these results as preliminary given the modest sample size and unbalanced group sizes . Despite this limitation, we found consistent results predicting alcohol intake when dichotomizing baseline CRP levels into High vs. Low CRP groups and when treating baseline CRP as a continuous moderator. Moreover, models on neural alcohol cue-reactivity and drinks per drinking day similarly showed the High CRP ibudilast group as having the most favorable treatment outcomes. This two-week randomized trial was designed as a micro-longitudinal experimental medication study, and as such, the drinking outcomes are captured within this limited timeframe. Thus, these promising results should be replicated in full-scale clinical trials with longer treatment durations, more robust sample sizes, and higher severity AUD samples. Relatedly, this study was conducted in a non-treatment-seeking sample; future work should investigate the relationship between baseline inflammation and response to ibudilast in treatment seeking samples as differences between non-treatment-seekers and treatment-seekers have been previously identified (80, 81). The enrollment of non-treatment-seekers for this study offers a potential benefit, as participants may have had less motivation to reduce drinking and as such results may be more related to the pharmacological effects of the medication and the underlying inflammatory profile of participants. Moreover, the High CRP ibudilast group had more drinking at baseline, and as such may have had more room for reductions in drinking when taking the study medication. Future studies should match CRP groups at baseline on drinking. While a measure of CRP was selected in this study for its accessibility and clinical relevance, other peripheral markers of inflammation warrant exploration (e.g., IL-6, TNF- α). In addition, the fMRI data were restricted to a single timepoint, limiting a causal interpretation of the influence of baseline CRP levels and ibudilast treatment on neural activation to alcohol cues. Future studies might test whether baseline inflammation predicts treatment-related changes in cue-reactivity. Importantly, a major strength of this study is the clinical sample of AUD who completed a rigorous double-blind randomized clinical trial testing a promising pharmacotherapy with strong medication adherence rates and tolerability and demonstrating initial efficacy for heavy drinking reduction.

In conclusion, the present study presents secondary analyses from a two-week clinical trial of ibudilast for AUD examining the role of baseline CRP levels on clinical response and neural alcohol cue-reactivity. We find that individuals with elevated peripheral inflammation at baseline may be most responsive to neuroimmune treatment for AUD in regard to drinks per drinking day and neural cue-reactivity. Identifying subgroups of treatment responders to further personalized medication for AUD is a high priority area of research (43, 82).

The present findings highlight a common challenge in medications development for AUD, in which medications do not work consistently well for all individuals enrolled in clinical trials. Because research on immune treatment for AUD is nascent, the field has minimal understanding of which individuals might benefit most from treatment (4). Yet, this piece is vital to the clinical application of immune therapies. This study serves as an initial investigation into predictors of clinical response to ibudilast treatment for AUD and suggests that a proinflammatory profile at baseline may enhance clinical efficacy. These findings advance precision medicine for AUD and suggest that a widely used and accessible measure of peripheral inflammation may inform patient selection for ibudilast treatment, should these preliminary results be supported in future trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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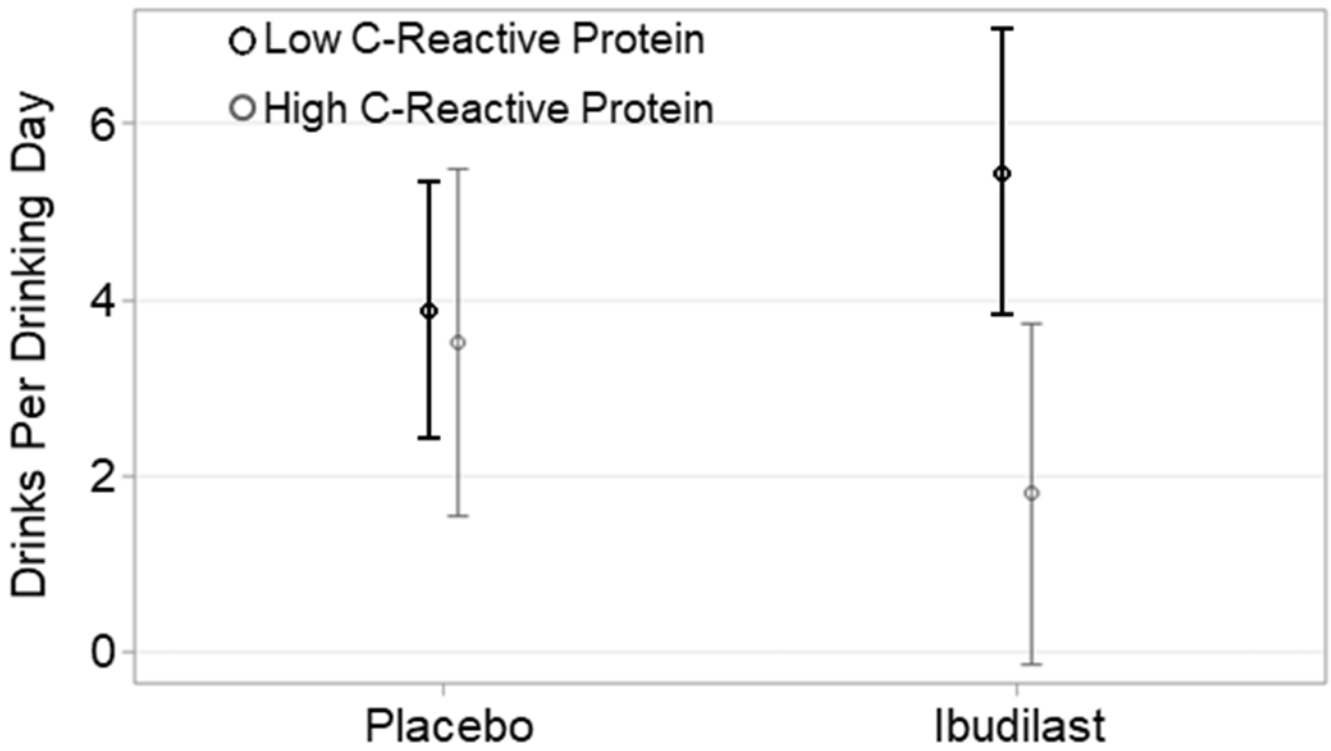

Figure 1. Medication by Baseline C-Reactive Protein Interaction on Drinks Per Drinking Day

There was a significant interaction between medication condition and baseline CRP groups on drinking in the trial. Individuals treated with ibudilast who had high baseline CRP levels had significantly fewer drinks per drinking day during the two-week trial relative to individuals treated with ibudilast who had low baseline CRP levels. Data are presented as estimated means with 95% confidence intervals.

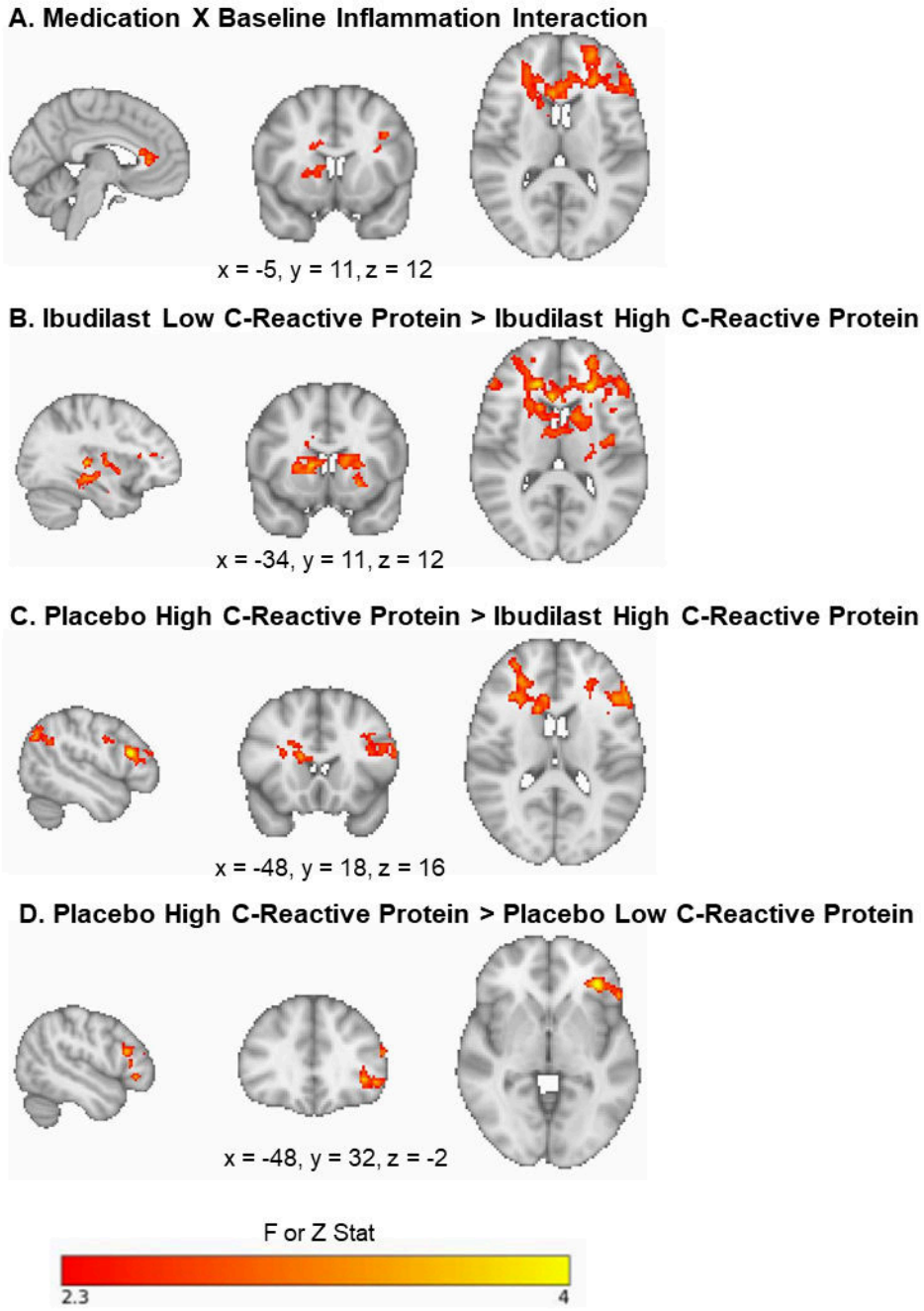

Figure 2. Medication by Baseline C-Reactive Protein Interaction on Neural Alcohol Cue Reactivity

There was a significant interaction between medication condition and baseline CRP groups on neural alcohol cue reactivity. **Panel A** displays regions where there was a significant interaction between dichotomized CRP levels at baseline and medication, including the bilateral anterior cingulate, right frontal pole, right caudate, and right putamen. **Panel B** displays higher activation to alcohol cues in the bilateral anterior cingulate, right frontal pole, right caudate, and right putamen, right medial orbitofrontal cortex, and left insula in

individuals treated with ibudilast with low baseline levels of CRP relative to individuals treated with ibudilast with high baseline levels of CRP. **Panel C** displays higher activation to alcohol cues in the left inferior frontal gyrus, left frontal pole, and right middle frontal gyrus in individuals treated with placebo with high baseline levels of CRP relative to individuals treated with ibudilast with high baseline levels of CRP. **Panel D** displays higher activation to alcohol cues in the left medial orbitofrontal cortex and left inferior and middle frontal gyri in individuals treated with placebo with high baseline levels of CRP relative to individuals treated with placebo with low baseline levels of CRP.

Table 1.

Demographic and Clinical Characteristics

Characteristic	Ibudilast Low CRP (n=14)	Ibudilast High CRP (n=10)	Placebo Low CRP (n=18)	Placebo High CRP (n=9)	Main Effect of Medication	Main Effect of CRP	Medication X CRP Interaction
CRP (mg/L)	1.2 ± 0.9	6.3 ± 3.9	0.8 ± 0.8	8.8 ± 7.1	-	-	-
Log CRP *	−0.1 ± 0.4	0.7 ± 0.2	−0.3 ± 0.4	0.8 ± 0.3	F = 0.1, p = 0.7	F = 91.4, p < 0.001	F = 1.8, p = 0.2
Age	30.8 ± 8.0	39.6 ± 8.7	31.0± 8.6	31.3 ± 6.4	F = 3.0, p = 0.1	F = 3.8, p = 0.1	F = 3.2, p = 0.1
Sex (M/F)	8/6	8/2	12/6	6/3	X^2 = 0.03, p = 0.9	X^2 = 0.9, p = 0.3	
BMI *	25.1 ± 3.2	29.4 ± 5.5	25.2 ± 3.6	28.2 ± 3.8	F = 0.3, p = 0.6	F = 9.8, p = 0.003	F = 0.3, p = 0.6
Smoker (N/Y)	8/6	5/5	10/9	4/5	X^2 = 0.09, p = 0.76	X^2 = 0.25, p = 0.62	
Cannabis Use (N/Y)	10/4	7/3	13/6	7/2	X^2 = 0.002, p = 0.96	X^2 = 0.09, p = 0.76	
Baseline DPDD *	5.4 ± 2.9	6.1 ± 2.1	4.2 ± 1.6	7.7 ± 5.3	F = 0.1, p = 0.8	F = 6.8, p = 0.02	F = 2.8, p = 0.10
Baseline PHDD *	30.0 ± 26.9%	44.0 ± 28.3%	23.0 ± 22.1%	42.0 ± 32.4%	F = 0.4, p = 0.54	F = 4.4, p = 0.04	F = 0.2, p = 0.71
AUDIT	16.1 ± 6.0	16.8 ± 6.1	16.4 ± 4.8	17.3 ± 9.3	F = 0.1, p = 0.8	F = 0.2, p = 0.7	F = 0.003, p = 1.0
AUD Symptoms	5.2 ± 2.2	5.4 ± 2.6	4.5 ± 1.8	5.1 ± 2.3	F = 1.0, p = 0.3	F = 0.3, p = 0.6	F = 0.4, p = 0.5
Medication Adherence (Pill Count)	97.5 ± 3.1%	96.4 ± 7.7 %	96.6 ± 4.3 %	98.8 ± 2.5%	F = 0.3, p = 0.6	F = 0.2, p = 0.7	F = 1.4, p = 0.2

Data are presented as means ± standard deviation unless otherwise indicated.

Abbreviations: CRP = C-Reactive Protein; DPDD = Drinks per Drinking Day; PHDD = Percent Heavy Drinking Days; AUDIT = Alcohol Use Disorder Identification Test; AUD = Alcohol Use Disorder

* = significant main effect of CRP group.

Table 2.

Clinical Drinking Results

General Linear Model			
	F	***p***	***Partial Eta-Squared***
Medication (reference placebo)	0.01	0.92	0.002
Baseline Inflammation	6.98	0.01	0.15
Med X Baseline Inflammation	4.80	0.03	0.11
Baseline Drinks Per Drinking Day	32.76	<0.001	0.46
Sex	7.53	0.009	0.16
Estimated Group Means			
	Mean Trial DPDD	**SE**	
Ibudilast High CRP	2.79	0.80	
Ibudilast Low CRP	6.45	0.70	
Placebo High CRP	4.51	0.87	
Placebo Low CRP	4.87	0.56	

Abbreviations: CRP = c-reactive protein

Table 3.

Whole-Brain Group Results for Alcohol vs. Beverage Contrast

Comparison	Voxels	Region	X	Y	Z	Peak Z	p-value
Medication X CRP Level Interaction							
	4607	Left Inferior Frontal Gyrus, left frontal pole, bilateral anterior cingulate, right frontal pole, right caudate, right putamen	−48	22	20	4.55	<0.001
Ibudilast High CRP > Ibudilast Low CRP							
	N/A						
Ibudilast Low CRP > Ibudilast High CRP							
	4347	Right anterior cingulate, right caudate, right putamen, left caudate, left putamen, left insula bilateral cingulate, left inferior frontal gyrus	20	36	14	4.04	<0.001
	624	Left fusiform cortex, left parahippocampus, left hippocampus	−38	−36	−14	3.66	0.001
	381	Right frontal pole, right medial orbitofrontal cortex, right inferior frontal gyrus	30	50	−10	3.33	0.03
Ibudilast High CRP > Placebo High CRP							
	N/A						
Placebo High CRP > Ibudilast High CRP							
	929	Left inferior frontal gyrus, left precentral gyrus	−48	22	20	4.35	<0.001
	927	Right middle frontal gyrus, right caudate	18	14	28	3.54	<0.001
	412	Left lateral occipital cortex, left angular gyrus	−48	−68	36	3.39	0.02
	359	Right lingual gyrus, right parahippocampal gyrus, right hippocampus	32	−48	4	3.63	0.04
	344	Left frontal pole,	−26	50	10	3.72	0.049
Ibudilast Low CRP > Placebo Low CRP							
	N/A						
Placebo Low CRP > Ibudilast Low CRP							
	N/A						
Placebo High CRP > Placebo Low CRP							
	833	Left medial orbitofrontal cortex, left inferior frontal gyrus, left middle frontal gyrus	−38	36	−2	3.94	<0.001
Placebo Low CRP > Placebo High CRP							
	N/A						

CRP = c-reactive protein; Coordinates are in Montreal Neurological Institute (MNI) space.