# *Effects of Ibudilast on Central and Peripheral Markers of Inflammation in Alcohol Use Disorder*

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**Background**: Ibudilast, a neuroimmune modulator, shows promise as a pharmacotherapy for alcohol use disorder (AUD). *In vivo* administration of ibudilast reduces the expression of pro-inflammatory cytokines, but its effects on peripheral and central markers of inflammation in humans are unknown. Therefore, this analysis of a two-week randomized trial of ibudilast examined the effect of ibudilast on peripheral and putative central markers of inflammation. To provide clinical relevance, this study also explored the predictive relationship of markers of neuroinflammation and subsequent drinking in the trial.

**Methods**: Non-treatment-seeking individuals with an AUD (n=52) were randomized to receive oral ibudilast (n=24) or placebo (n=28) for two-weeks. Plasma levels of peripheral inflammatory markers were evaluated at baseline, after 1-week, and after 2-weeks of medication. At study mid-point, proton magnetic resonance spectroscopic imaging (MRS) was acquired to measure neurometabolite markers of inflammation: choline-compounds (Cho) and *myo*-inositol (MI) in frontal and cingulate cortices. The treatment groups were compared on peripheral and central markers of inflammation. To examine the clinical relevance of these markers, exploratory linear regression models were tested to evaluate the effect of medication, MRS metabolite levels, and their interaction on drinking in the week following the neuroimaging scan.

**Results**: Ibudilast-treated participants had lower Cho in superior frontal white matter ($F=6.88$, $p=0.0125$) and nominally lower MI in pregenual anterior cingulate cortex ($F=3.06$, $p=0.09$). There was a trend interaction between medication and time for CRP ($F=3.50$, $p=0.07$), such that at the 2-week timepoint ibudilast reduced CRP relative to placebo. At trend level, ibudilast-treated participants also had lower TNF-α/IL-10 ratios across timepoints relative to placebo ($F=3.68$, $p=0.06$). There was a main effect of medication on IL-8 across timepoints ($F=7.45$, $p=0.009$); however, this effect appears to be driven by an unexpected decrease in IL-8 in the placebo group. Choline and CRP levels were positively correlated ($r = 0.32$, $p = 0.04$), controlling for medication. Superior frontal white matter Cho predicted drinking in the week following the scan ($F= 5.05$, $p=0.03$), such that individuals treated with ibudilast who had low Cho levels had the fewest drinks per drinking day in the week following the scan.

**Conclusion**: Micro-longitudinal ibudilast treatment induces both peripheral and putative central anti-inflammatory responses in patients with AUD. The central responses may be associated with reduction in drinking, suggesting an anti-inflammatory component to the therapeutic action of ibudilast.

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