Clinical Utility of Inflammatory Biomarkers in Personalizing Treatment of Depressed Patients: Findings from CO-MED Trial

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Abstract

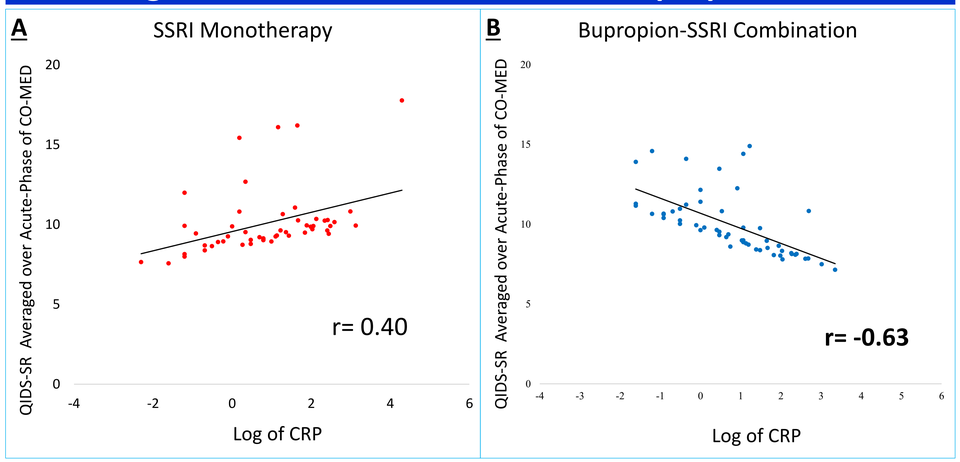
Introduction: Lack of objective markers for treatment selection is one of the biggest challenges in managing depressed patients. Even the practice guidelines recommend use of subjective factors such as cost or provider preference when making treatment decisions. Unsurprisingly, depressed patients go through multiple treatment trials before finding an effective medication. Uher et al. recently reported that pre-treatment level of C-reactive protein (CRP) <1 mg/L favored improved outcomes with escitalopram while higher levels predicted better outcomes with nortriptyline. The goal of this study was to replicate the role of CRP, and develop a paradigm for future research studies that demonstrate superiority of biomarker-informed clinical decision making over current standard of care.

Methods: Analytic sample for this study included participants of Combining Medications to Enhance Depression Outcomes (CO-MED) trial who provided plasma samples and were treated with either escitalopram-plus-placebo (SSRI monotherapy, n=51) or bupropion-plus-escitalopram (bupropion-SSRI combination, n=55). Multiplex immunoassays were used to measure levels of CRP and other inflammatory biomarkers (serum amyloid P component, arates in the two treatment arms differed based on a priori defined CRP threshold of 1 mnd alpha-2-macroglobulin). Logistic regression analysis was used to evaluate if remission /L. The remission rate if participants were assigned based on CRP threshold was estimatedg: [(remission rate with SSRI monotherapy)*(proportion of participants with CRP <1 mg/L)+(remission rate with bupropion-SSRI combination)*(proportion of participants with CRP ≥1 mg/L)]. Using remission rates in the first step of Sequenced Treatment Alternative to Relieve Depression (STAR*D) study as current standard of care, we estimated number needed to treat (NNT): 1/[(estimated remission rate with a CRP threshold based assignment)-(remission rate in STAR*D)].

Results: The treatment arms did not differ in overall treatment outcomes. Most participants (74/106, 69.8%) had CRP ≥1 mg/L. We found that in contrast to the bupropion-SSRI treatment arm, where ≥1 mg/L CRP level was associated with higher rates of remission (remission rate=51.35%) as compared to <1 mg/L CRP level (remission rate=33.33%), participants in SSRI monotherapy treatment arm with CRP level <1 mg/L had higher rates of remission (remission rate=57.14%) as compared to those with ≥1 mg/L CRP level (remission rate=29.73%). The estimated remission rate with CRP threshold based treatment assignment was 52.90%. When compared to the remission rate of 32.9% in first step of STAR*D, CRP threshold based treatment assignment had NNT=5. In other words, treatment of five depressed patients using CRP informed treatment assignment will result in 1 additional remission when compared to current standard of care.

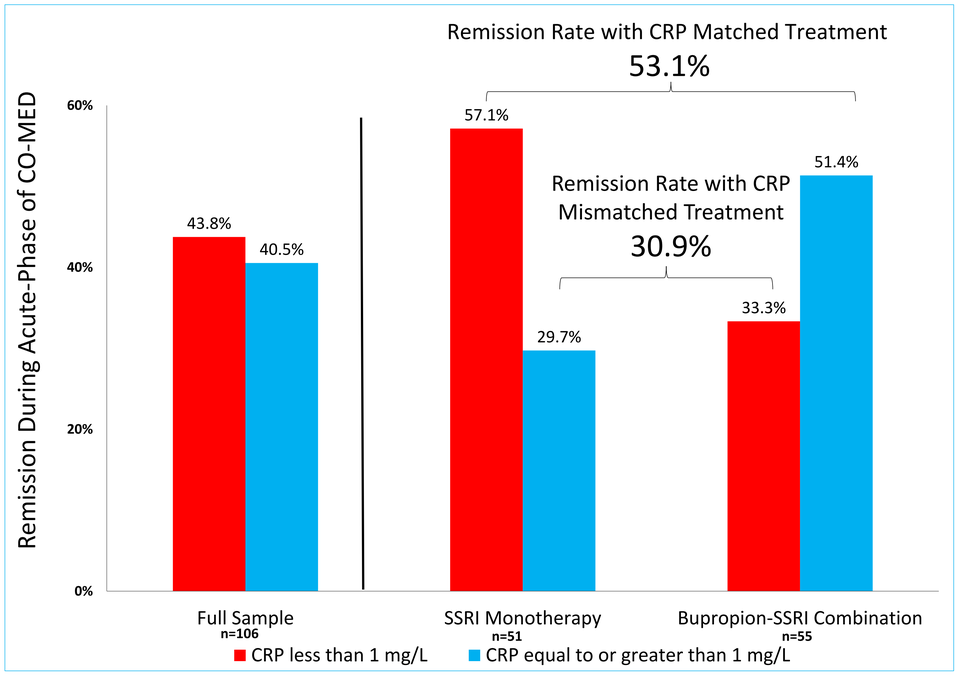
Conclusions: We found that depressed patients with pre-treatment CRP level less than 1 mg/L do better with SSRI monotherapy whereas those with higher levels respond better to SSRI-bupropion combination. Additionally, we found that using such a CRP threshold based treatment assignment, as compared to the current standard of care, will result in 1 additional remission for every 5 patients treated. As these findings are based on secondary analysis of previously collected data, they should be considered preliminary with future prospective studies needed that compare treatment assignment based on "high" or "low" inflammation as compared to current standard of care., depressed patients with low CRP benefit from escitalopram while those with higher CRP benefit from bupropion. Routine use of CRP, an inexpensive readily available lab test, in personalizing antidepressant medication selection will improve outcomes and transform clinical practice.

High CRP – Better Outcomes with Bupropion-SSRI



Panel A: Lower reduction in depression severity with higher baseline CRP on SSRI monotherapy
Panel B: Greater reduction in depression severity with higher CRP on Bupropion-SSRI

Higher Remission Rates with Treatment Assignment Based on Pre-treatment C-Reactive Protein (CRP) Level



Biomarker Measurement

- Assays run by UT Southwestern Microarray Core after obtaining plasma samples from NIMH RGR at the same time blinded to treatment arms and outcomes
- CRP and 3 other acute-phase reactants measured by Bioplex Pro™ 4-plex kit after 1:10000 dilution and levels reported in ng/mL (Bio-Rad, Hercules, CA, USA)
- On Bio-plex® 200 instrument which was equipped with Bio-Plex Manager software version 6.0 (Bio-Rad, Hercules, CA, USA).
- The intra and inter-assays variations were less than 10% of the detection limits (Bio-Rad, Hercules, CA, USA).

Demographics

		SSRI	BUP
Number		51	55
Sex	Male	16	16
	Female	35	39
Race	White	27	39
	Black	18	12
	Other	6	4
Educ	<12 years	4	11
	12 -15 years	35	29
	>15 years	12	15
Mean age in yrs		47.0	46.3
Anxious		33	43
Atypical		10	12
Melancholic		14	17
Suicidal ideation		27	31
Mean QIDS-SR		15.7	14.9

Mixed model results

	Depression Severity	
	F Value	p Value
C-Reactive Protein		
Atypical Depression	4.00	0.047
Gender	0.95	0.33
Race	3.26	0.041
BMI	0.28	0.60
Time	73.91	<0.001
Treatment arm	2.61	0.076
Log CRP level	0.10	0.39
Time-by-treatment arm interaction	0.77	0.70
Log CRP-by-treatment arm interaction	3.33	**0.038**

Number Needed to Treat

❖Remission rate if participants were assigned based on CRP:
[(remission rate with SSRI monotherapy)(proportion of participants with CRP <1 mg/L)+(remission rate with bupropion-SSRI combination)*(proportion of participants with CRP ≥1 mg/L)]*
❖Number needed to treat (NNT)
*1/[(estimated remission rate with a CRP threshold based assignment)-(remission rate in STAR*D)]*
❖ NNT = 1/(0.531 – 0.329) = 1/.202 = 4.95

Conclusions

❖ In CO-MED trial, a CRP matched treatment assignment resulted in remission rate= 53.1%

❖ When compared to remission rate in first step of STAR*D trial, 5 depressed patients will need to be treated to get 1 extra remission with CRP matched treatment assignment.

❖ Future clinical trials of antidepressatn vs. placebo should consider stratifying based on CRP level.

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