Moving towards a new psychiatry: targeting patient subtypes and symptom domains

an industry perspective of the current challenges

Giacomo Salvadore, MD
Neuroscience Experimental Medicine, Janssen R&D
Disclosures

• Employee and shareholder of Johnson & Johnson, LLC
Peripheral immune dysregulation as a potential antidepressant target

- Patients with depression show increased levels of peripheral inflammatory markers, including TNF-alpha, IL-6 and CRP

- Preclinical evidence that drugs which suppress peripheral inflammation (anti IL-6 antibodies) are able to trigger antidepressant-like response in susceptible animals

- Clinical evidence that antibodies which suppress peripheral inflammation improve depression symptoms in subjects with elevated peripheral inflammatory markers as well as subjects with primary inflammatory conditions

- PoC study to test the hypothesis that treatment with the anti-IL-6 antibody sirukumab improves depression symptoms in patients with MDD with increased CRP levels

- Investigation of the effects of sirukumab on anhedonia using the SHAPS scale
Association between peripheral inflammation and activity in the reward circuitry

- Elevation of peripheral cytokines through LPS challenge blunts ventral striatal activity
- Decreased activity in the reward circuitry might mediate depressive symptoms post-LPS challenge
- Increased CRP correlates with decreased FC between the ventral striatum and the vmPFC
- This association mediates the relationship between CRP and anhedonia

Eisenberger et al., 2010. Biol Psychiatry 68: 748-54;
Felger et al., in press. Mol Psychiatry
Study design

**SCREENING**
- Meet DSM-V criteria for MDD
- Have failed no more than 3 AD's in current episode
- HDRS\(_{17}\) ≥18 at screening and baseline
- Currently receiving an allowed monoaminergic AD

**Injection timepoints (Week)**

- Week -4: Screening
- Week 0
- Week 4
- Week 8

**CNTO136 + AD**
- N = 96

**Placebo + AD**
- N = 96

Only subjects with screening and baseline CRP ≥ 3.00 mg/L will contribute to the primary analysis.
Depressed subjects showed elevation of CRP at screening: average CRP 4.2 mg/L (N=931)
HDRS-17 primary efficacy results in mITT1 population

No effect of sirukumab at Week 12 on HDRS-17 scores (independent raters) in mITT1 population
Response Rate is comparable between sirukumab and placebo at Week 12

Response defined as $\geq 50\%$ improvement in HDRS-17 total score from baseline

Week 12 response rate didn't favor sirukumab over placebo
HDRS-17: Sirukumab Fails to Differentiate from Placebo at 12 weeks Regardless of Screening CRP levels

Least Squares Mean Changes ± SE

![Graphs showing changes over time in least squares mean for two different sets of data.](image-url)
Sirukumab treatment is associated with decreased peripheral inflammatory biomarkers

Changes from baseline to week 12 in IL-6 (Left) and hsCRP (Right) stratified by baseline hsCRP levels
SHAPS: Sirukumab improves anhedonia symptoms in MDD subjects

![Graph showing the improvement in anhedonia symptoms over time for placebo and Sirukumab 50 mg groups.](image)

- **Number of Patients**
  - Placebo (N=47) 46
  - Sirukumab (N=47) 47

- **Visit**
  - Baseline
  - Week 1 (DB)
  - Week 4 (DB)
  - Week 8 (DB)
  - Week 12 (DB)
  - Week 15 (DB)
  - Week 22 (FU)

- **Least Squares Mean Changes (±SE)**

- *p=0.014
Study results summary

- Lack of efficacy using a “general” depression scale despite adequate suppression of peripheral inflammatory biomarkers
- Lack of an enrichment biomarker to identify responders
- Promising signal on an anhedonia scale
- Positive effect on anhedonia is plausible from a biological standpoint
- Previous positive studies with monoclonal antibodies used depression rating scales that emphasize anhedonia, such as the HADS
Is there a path forward for drugs which target anhedonia?

- **Regulatory hurdles**: showing that anti-anhedonic effects are not part of a general antidepressant effect to avoid pseudo-specificity

- **Development hurdles**: does a drug improve anhedonia in subjects with MDD only or improve anhedonia across different diagnosis?

- **Payers hurdles**: how do we show quantifiable value for anhedonia to payers?
  - What is the burden of untreated anhedonia?

- **Prescribers hurdles**: do they see anhedonia as an area of unmet need? How do they identify subjects with anhedonia?