Adjunctive minocycline for major depressive disorder:
Characterisation of peripheral immune-inflammatory profile

Walker AJ [1], Bortolasci C [2], Mohebbi M [1,3], Ashton M [1,4,5], Kanchanatawan B [6], Singh A [1], Ng C [5], Mahli G [7,8], Dowling N [5], Maes M [6], Walder K [2], Berk M [1,4,9,10,11], Dean OM [1,4,9].

[1] IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, VIC, Australia; [2] Metabolic Research Unit, School of Medicine, Deakin University, Geelong, VIC, Australia; [3] Biostatistics Unit, Faculty of Health, Deakin University; [4] The Florey Institute for Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia; [5] Department of Psychiatry, The Melbourne Clinic, The University of Melbourne, Richmond, VIC, Australia; [6] Department of Psychiatry, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [7] Discipline of Psychiatry, Sydney Medical School, The University of Sydney, Sydney, NSW, Australia; [8] CADE Clinic, Department of Psychiatry, Royal North Shore Hospital, St. Leonards, NSW, Australia; [9] Department of Psychiatry, Royal Melbourne Hospital, The University of Melbourne, Parkville, VIC, Australia; [10] Orygen Youth Health Research Centre, Parkville, VIC, Australia; [11] Centre for Youth Mental Health, The University of Melbourne, Parkville, VIC, Australia.

Background

Primary treatments for major depressive disorder (MDD) are useful, however shortfalls remain in both remission and recovery [1].

The identification of biological markers that relate to treatment response may improve understanding of the pathophysiology of MDD and assist with this shortfall [2].

Inflammation is now known to play a role in the pathophysiology of MDD, leading to clinical trials of adjunctive treatments that target these pathways [3].

Minocycline has been shown to modify the immune-inflammatory processes, however its effects on the inflammatory profile of participants with MDD are unknown [4].

Aim: This study aims to address a secondary outcome of a clinical trial by assessing inflammatory biomarkers in collected peripheral blood samples.

Methods

This current study is a secondary analysis of peripheral blood samples collected from patients during a randomised placebo-controlled trial evaluating 12 weeks of adjunctive minocycline (200 mg/day) in addition to treatment as usual (ACTRN12612000283875) [5].

Samples were collected from consenting participants at baseline (week 0), and at the end of treatment (week 12).

Of the 71 participants that completed the trial, at least one serum aliquot was available for 47 of the participants. Placebo group *n*=24 (13f/11m), and the minocycline group *n*=23 (13f/10m).

Samples were assessed for an array of 46 inflammatory analytes including cytokines, chemokines and acute-phase reactants using Myriad RBM's InflammationMAP®

Composite Z-scores were calculated for detectable immune-inflammatory analytes, and statistical analyses were conducted using SPSS Statistical Package version 25.0 by an investigator blinded to treatment.

Preliminary analysis included generation of descriptives, and subsequent Spearman's nonparametric correlation analysis to assess analyte group profile at baseline and endpoint. Measures of depression (MADRS) and anxiety (HAMA) were included to assess treatment response.

Preliminary Results

Spearman's Correlation (ρ) - Baseline

Spearman's Correlation (ρ) - Follow-up, week 12

Key: -1.000 / -0.750 / -0.500 / -0.250 / 0.000 / 0.250 / 0.500 / 0.750 / 1.000

Statistical significance: **p < 0.01**; p < 0.05; *p < 0.08*; p > 0.08

Discussion & Future Directions

Studies have often focused their biomarker investigations on a common few immune-inflammatory markers (e.g. interleukin-6, C-reactive protein, tumor necrosis factor alpha). To date, such an approach has offered limited therapeutic insight [6].

The current study is employing broader quantitative approaches including multiplexed immunoassays to better characterise the inflammatory profile of participants in a clinical trial of minocycline for MDD.

Of the 46 analytes assessed, 27 were detectable in over 90% of the samples evaluated. IL-1β was detectable in 80%, IL-8 in 70%, and IL-15 in 60% of samples.

16 analytes were detectable in <50% of the samples (FIBRN, GM-CSF, IFNγ, IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12p70, IL-17, MIP-1α, TNFα, TNFβ). Due to low detection rates these were excluded from analysis.

This preliminary data will be used to conduct further analyses (mediator and moderator analysis, and partial least squares regression – with projection to latent structures) to assess how the quantified analytes relate to the primary clinical outcomes.

Funding & Acknowledgements

References

[1] Akil et al. *Neurosci Biobehav Rev.* 2018:84.
[2] Miller AH, Maletic V, Raison CL. *Biol. Psychiatry.* 2009:65.
[3] Berk M et al. *BMC Med.* 2013:11.
[4] Dean OM et al. *CNS Drugs.* 2012:26.
[5] Dean OM et al. *Aust N Z J Psychiatry.* 2017:51
[6] Berk M, Walker AJ, Nierenberg A. *JAMA Psychiatry.* 2019:76.

Abbreviations: AAT - alpha-1-antitrypsin ; A2Macro - alpha-2-macroglobulin ; B2M - beta-2-microglobulin ; BDNF - brain-derived neurotrophic factor ; CRP - C-reactive protein ; C3 - complement C3 ; CCL11 - eotaxin-1; FVII - factor VII; FRTN - ferritin ; - fibrinogen; GM-CSF - granulocyte-macrophage colony-stimulating factor ; HAMA – Hamilton anxiety rating scale (change in total score); HAPT - haptoglobin; ICAM-1 - intercellular adhesion molecule 1 ; IFNγ - interferon gamma ; IL-1α - interleukin 1 alpha ; IL-1β - interleukin 1 beta ; IL-1RA - interleukin-1 receptor antagonist ; IL-2 - interleukin-2 ; IL-3 - interleukin-3 ; IL-4 - interleukin-4 ; IL-5 - interleukin-5 ; IL-6 - interleukin-6 ; IL-7 - interleukin-7 ; IL-8 - interleukin-8 ; IL-10 - interleukin-10 ; IL-12p40 - interleukin-12 subunit p40 ; IL-12p70 - interleukin-12 subunit p70 ; IL-15 - interleukin-15 ; IL-17 - interleukin-17 ; IL-18 - interleukin-18 ; IL-23 - interleukin-23 ; MADRS - Montgomery–Åsberg Depression Rating Scale (change in total score); MIP-1α - macrophage inflammatory protein-1 alpha ; MIP-1β - macrophage inflammatory protein-1 beta ; MMP-3 - matrix metalloproteinase-3 ; MMP-9 - matrix metalloproteinase-9 ; MCP-1 - monocyte chemotactic protein 1 ; SCF - stem cell factor ; RANTES - t-cell-specific protein RANTES (also CCL5); TIMP1 - tissue inhibitor of metalloproteinases 1 ; TNFα - tumor necrosis factor alpha ; TNFβ - tumor necrosis factor beta ; TNFR2 - tumor necrosis factor receptor 2 ; VCAM-1 - vascular cell adhesion molecule-1 ; VEGF - vascular endothelial growth factor ; VDBP - vitamin d-binding protein ; vWF - von willebrand factor.