P.0166

NEUROSCIENCE APPLIED 1 (2022) 100112 100264

Inflammatory profiles predict treatment outcome to simvastatin in a randomized controlled trial for patients with schizophrenia spectrum disorders

C. Schiweck [1], M. Aichholzer [2], S. Gangadin [3], L. de Wit [4], R. Kahn [4], I. Sommer [5], H. Drexhage [6]. [1] *Goethe University Frankfurt- University Hospital Frankfurt, Department for Psychiatry- Psychosomatics and Psychotherapy, Frankfurt am Main, Germany;* [2] *Goethe University Frankfurt- University Hospital Frankfurt, Department for Psychiatry- Psychosomatics and Psychotherapy-, Frankfurt, Germany;* [3] *Department of Biomedical Sciences of Cells & Systems- University Medical Centre Groningen UMCG, Groningen, Netherlands- The;* [4] *Icahn School of Medicine at Mount Sinai, Department of Psychiatry, New York- NY, United States;* [5] *University Medical Centre Groningen UMCG- University of Groningen, Department of Biomedical Sciences of Cells & Systems, Groningen, Netherlands- The;* [6] *Erasmus MC, Department of Immunology, Rotterdam, Netherlands- The*

Introduction: Chronic low-grade inflammation can be observed in several psychiatric disorders, including Schizophrenia Spectrum Disorders (SSD). This non-specificity makes applicability as diagnostic biomarker rather unlikely, but inflammatory proteins could have potential as stratification biomarkers for treatment selection. Simvastatin can cross the blood brain barrier and has, among others, anti-inflammatory properties. A recently published randomized, double-blind controlled clinical trial found no overall benefit of an add-on statin treatment compared to placebo [1]. However, baseline inflammatory profiles were not taken into account for analysis.

Aim: To reanalyse the treatment response to simvastatin using stratification for baseline inflammatory profiles.

Methods: Monocyte gene expression of 60 patients (30 in the placebo group, 30 in the 40mg simvastatin group, duration 24 months) was obtained using qPCR on frozen PBMCs. High sensitive interleukin 6 (hs-IL-6) was obtained using enzyme-linked immunosorbent assay, T regulatory (Tregs) and T helper 17 (Th17) cells were obtained with Fluorescence-activated cell sorting analysis. Patient clusters were identified using hierarchical clustering of ddCT values at baseline. Gene expression and clinical characteristics were compared between groups using Kruskal Walli's test and Dunn's test as follow-up. Generalized linear mixed models were used to assess change on the Positive and Negative Syndrome Scale (PANSS) scores and the Calgary Depression Scale for Schizophrenia (CDSS) over time, including a random intercept, the inflammatory cluster group, the treatment (placebo vs. simvastatin) and the timepoint (baseline to 24 months), and a three-way interaction. Additionally, baseline scores of PANSS or CDSS respectively were used as covariate.

Results: Two patient profiles were identified based on the cluster of typical inflammatory genes: patients with upregulated (n=18) or downregulated gene expression (n=42). Patients in the upregulated group also had the highest levels of hs-IL-6 (vs. controls: z=2.37, p=0.024; vs. downregulated: z=2.40, p=0.065), higher Th17 cells vs. controls: (z=2.31, p=0.02; vs. downregulated: z=1.90, p=0.057) and higher Tregs (vs. controls: z=3.88, p<0.001; vs. downregulated: z=2.40, p=0.016). Preliminary results showed a significant patient group x timepoint x treatment interaction for PANSS total scores (F=2.15, df=6, p=0.049). Post-hoc contrasts revealed a significant reduction in PANSS scores only for patients with inflammatory gene expression in the simvastatin condition: The reduction occurred from 6 months onwards and reached significance at 1 year (t=2.92, df=256, p.adj=0.013) and 24 months (t=3.87, df=258, p.adj<0.001). Patients with downregulated gene expression in the simvastatin group showed no significant improvement at 1 year (t=-0.97, df=258, p.adj=0.561), but a small significant improvement at 24 months (t=3.061, df=260, p.adj=0.026). Patients in the placebo group did not show any variation. Between-group comparisons at 12 months were not significant. Inflammatory gene expression at baseline was also associated with improved depression scores as measured by the CDSS (timepoint x group interaction, F=2.94, df=3, p=0.034). Post-hoc results revealed consistent reductions from 6 months (t=2.79, df=165, p=0.012) up until 24 months (t=4.63, df= 165, p<0.001).

Conclusions: Simvastatin as add-on therapy may have a small additional benefit for patients with inflammatory signatures. Higher baseline scores of inflammation in patients with SSD may be associated with improvement of depressive symptoms during treatment as usual.

References

[1] Iris E Sommer, Shiral S Gangadin, Lot D de Witte, Sanne Koops, C van Baal, Sabine Bahn, Hemmo Drexhage, N E M van Haren, Wim Veling, R Bruggeman, Peter Martens, Sybren Wiersma, Selene R T Veerman, Koen P Grootens, Nico van Beveren, Rene S Kahn, Marieke J H Begemann, Simvastatin Augmentation for Patients With Early-Phase Schizophrenia-Spectrum Disorders: A Double-Blind, Randomized Placebo-Controlled Trial, Schizophrenia Bulletin, Volume 47, Issue 4, July 2021, Pages 1108–1115, https://doi.org/10.1093/schbul/sbab010

No conflict of interest

doi: https://doi.org/10.1016/j.nsa.2022.100264

P.0167

NEUROSCIENCE APPLIED 1 (2022) 100112 100265

Revisiting the neurodegenerative-developmental hypotheses in the neurobiology of resistance to treatment in schizophrenia with serum IGF-1 levels and retinal layers

U.H. Yesilkaya [1], O. Sahmelikoglu Onur [1], O.P. Akarsu Acar [2], D.F. Goy [3], I.U. Onur [2], N. Karamustafalioglu [4]. [1] *Bakirkoy Research &- Training Hospital for Psychiatry- Neurology&-Neurosurgery- 3thPsychiatry, Psychiatry, Istanbul, Turkey;* [2] *Sadi Konuk Training and Research Hospital, Ophthalmology, Istanbul, Turkey;* [3] *Bakirkoy Research &- Training Hospital for Psychiatry- Neurology&-Neurosurgery- 12thPsychiatry, Psychiatry, Istanbul, Turkey;* [4] *Bakirkoy Research &- Training Hospital for Psychiatry- Neurology&-Neurosurgery- 16thPsychiatry, Psychiatry, Istanbul, Turkey*

Background: Schizophrenia is a progressive chronic mental disorder that affects approximately 1% of the population and is usually first identified during late adolescence and young adulthood [1]. It is generally agreed that schizophrenia is caused by a combination of many factors, such as neuroanatomical deformities, abnormalities in neurotransmitters and the immune system, as well as inflammation [2]. Although many hypotheses have been asserted over the years, the neurodegenerative and neurodevelopment hypotheses have retained focus; nonetheless, no consensus has been reached.[1]. Since IGF-1 plays a central role in development both at prenatal and postnatal period, it has been widely investigated in the context of the neurobiology of neurodevelopmental disorders [3]. In additon optical coherence tomography (OCT) is referred to as a "window into the brain". Therefore, retinal pathology can be observed in central nervous system diseases[4]. It was applied in neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease leading to interesting and reproducible findings [5]. In the present study, we aimed to investigate these two main hypotheses in both schizophrenia and treatment resistant schizophrenia. We evaluated OCT, which has been applied to neurodegenerative disorders in recent years, and serum IGF-1 levels, which is known to play a role in neurodevelopment processes.

Methods: Thirty-nine patients under remission from schizophrenia, 43 treatment resistant schizophrenia (TRS) patients and 40 healthy controls were included in the study. All patients were recruited and evaluated over a period of 13 months. Symptoms at the time of evaluation were assessed twice using BPRS, PANSS, CGI, and GAF scales by an experienced psychiatrist in accordance with Andreaseen's remission criteria and TRIPS group resistance criteria. OCT was carried out on all participants. Blood samples were collected to determine fasting glucose, LDL, HDL, Triglyceride, total cholesterol, fasting, insulin, GH and IGF-1 levels in all participants.

Result: IGF-1 levels were lower in patients in the remitted schizophrenia group compared to the TRS patients. In addition, the Inferior retinal nerve fiber layer (NFL) Superior NFL and Global NFL were thinner in all schizophrenia patients (TRS or remitted) than the control group. Fasting blood glucose and LDL levels were higher in remitted schizophrenia patients compared to healthy controls. Moreover, LDL levels of the remitted schizophrenia group were higher than the TRS group while the fasting blood glucose levels did not show any significant difference. In a regression model, serum IGF-1 was significantly associated with treatment resistance while the Inferior NFL, Superior NFL and Global NFL were significantly associated with schizophrenia.

Conclusion: The present study showed that OCT measurements and IGF-1 levels support the neurodegenerative hypothesis in the pathogenesis of both remitted schizophrenia and TRS. Additionally, while IGF-1 levels could significantly[SB1] predict resistance to treatment, superior RNFL, inferior RNFL and global RNFL thickness could significantly predict schizophrenia. Our data may contribute to a better understanding of treatment resistant pathogenesis, better follow-up and treatment and especially to the personalization of treatment in schizophrenia.

References

[1] Owen, M. J., Sawa, A., & Mortensen, P. B. (2016). Schizophrenia. The Lancet, 388(10039), 86–97. https://doi.org/10.1016/S0140-6736(15)01121-6 [2]