Psychiatry Research 279 (2019) 389–390

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Letter to the Editor

The lack of association between COMT rs4680 polymorphism and symptomatic remission to olanzapine monotherapy in male schizophrenic patients: A longitudinal study

Despite numerous antipsychotic medications, many patients with schizophrenia respond poorly to treatment. As dopamine is a target for all antipsychotics, and deficits in cognition modulated by genes regulating dopaminergic system are frequent in schizophrenia, our study focused on the possible association between catechol-O-methyltransferase (COMT rs4680) gene variants and symptomatic remission to olanzapine monotherapy, defined according to the "Remission in Schizophrenia Working Group" /RSWG/ criteria (Andreasen et al., 2005). The functional COMT Val158Met (rs4680) polymorphism (a G/A substitution resulting in valine (Val) to methionine (Met) change, and consequently lower COMT activity in the Met carriers) has been studied as a possible candidate gene in treatment response or resistance in schizophrenia, but with inconsistent results (Huang et al., 2016). Since patients included in previous studies were not separated by gender (Sagud et al., 2018), received different antipsychotics (Huang et al., 2016), and criteria for treatment response or remission were different (Andreasen et al., 2005), we hypothesized that COMT rs4680 genetic variants will be associated with remission (according to RSWG criteria) after 6-months monotherapy with olanzapine in male patients with schizophrenia.

The study included 150 male patients with a DSM-IV diagnosis of schizophrenia, age range 19 to 60 years (median 33, IQR 28–42), monotherapy with olanzapine (5–20 mg/d), acute exacerbation of schizophrenia, and Caucasian ethnicity living in Croatia. Exclusion criteria were: serious somatic illnesses, neurologic disorders, previous therapy with clozapine, electroconvulsive therapy, and a history of drug use during the previous 6 months. Remission was defined according to RSWG criteria, i.e. reduction to mild levels on the key 8 symptoms on the PANSS scale (items P1, P2, P3, N1, N4, N6, G5, G9) for at least 6 months (Andreasen et al., 2005). Patients were divided into remitted and non-remitted groups. Genotyping of COMT Val158Met polymorphism (rs4680) was performed using Taqman-based allele-specific PCR assay (assay ID: C_25746809_50) and the procedure described by Applied Biosystems (Applied Biosystems, Foster City, CA). The results were analyzed using ANOVA, Mann-Whitney test, odds ratios with 95% confidence intervals, Pearson's χ^2test, and univariate logistic regression. G*Power 3 Software determined the required sample size and statistical power (set at 0.800), with $p = 0.05$; and medium effect sizes: for regression, Mann-Whitney test, and χ^2 test, the required sample sizes were 68, 102 and 108, respectively. As the study included 150 subjects, it had an adequate number of subjects.

Out of 150 male patients with schizophrenia, 5 dropped out, and symptomatic remission was achieved in 45 patients (31%). Remitted patients had significantly (Mann–Whitney test) lower baseline PANSS total ($U = 1427$; $Z = -3.519$, $P < 0.001$; AUC = 0.33), PANSS negative ($U = 1285.5$; $Z = -4.139$, $P < 0.001$; AUC = 0.29), and PANSS general psychopathology ($U = 1407.5$; $Z = -3.604$, $P < 0.001$; AUC = 0.31) scores compared to non-remitted patients. Smoking status was not associated with remission since smokers had similar odds (univariate logistic regression) to achieve symptomatic remission as non-smokers (OR = 1.6; 95% CI = 0.74–3.36). Only a small proportion of patients (21.3%) were treated with different antipsychotics 4–6 months before the study. These patients had 0.8 times smaller odds for achieving remission, compared to those who did not receive antipsychotic therapy during this period (OR = 0.2; 95% CI = 0.006–0.58). In line with previous remission rate (Terzic et al., 2016), 31% of our patients achieved symptomatic remission, which was not affected by smoking, previous antipsychotic treatment, but was related to reduced baseline illness severity, longer treatment duration or illness course, a higher number of hospitalizations, and high dropout rates (AlAqeel and Margolese, 2012; Andreasen et al., 2005).

COMT rs4680 genotypes significantly deviated ($P = 0.007$, χ^2test) from Hardy Weinberg equilibrium (HWE) in remitted patients. At baseline, carriers of the COMT Val/Met genotype, in contrast to Met/Met carriers ($P = 0.230$), had more than three times (univariate logistic regression) greater odds (OR = 3.3; 95% CI = 1.14–9.32) for achieving symptomatic remission ($P = 0.027$) than patients with the Val/Val genotypes. However, this positive significant association, that might predict remission, was not confirmed with further analyses. Namely, carriers of the COMT Val or Met allele had similar ($P = 0.282$) odds (OR = 1.31; 95% CI = 0.80–2.16) to achieve remission at baseline. The distribution of the COMT genotypes ($\chi^2 = 5.366$; df = 2; $P = 0.068$) or alleles ($\chi^2 = 0.903$; df = 1; $P = 0.342$) did not differ significantly (χ^2test) between remitted and non-remitted patients. After treatment, COMT rs4680 was not associated with symptoms of schizophrenia in 45 remitted patients, since PANSS total, positive, negative and general psychopathology scores did not differ significantly ($P > 0.05$, ANOVA) between carriers of the COMT genotypes or alleles.

Our results revealed that COMT rs4680 genetic variants are not associated with symptomatic remission in schizophrenia. Additionally, COMT rs4680 genetic variants are not related to symptoms of schizophrenia evaluated by the PANSS in remitted patients. These results agree with the lack of association between genetic polymorphisms in dopaminergic system, including COMT rs4680, with remission (Terzic et al., 2016), but are not in line with the association between Met/Met genotype and faster reduction of negative symptoms during olanzapine treatment (see Hang et al., 2016). Divergent results could be explained by the different study designs, small sample sizes, ethnic differences in the genotype frequency, different medications, different criteria for remission/response, large heterogeneity across studies, and population stratification (Hang et al., 2016). This longitudinal study tried to control for most of these confounders. Our negative findings might be explained by the study limitations: a small number of remitted patients ($N = 45$), and COMT genotype's deviation from HWE in the remitted group. Strengths of the present longitudinal study include 6 months' olanzapine monotherapy, inclusion of only male ethnically

https://doi.org/10.1016/j.psychres.2019.04.028
Received 30 April 2019; Accepted 30 April 2019
Available online 01 May 2019

homogenous Caucasian patients with schizophrenia, allelic and genotypic analysis, and the use of RSWG criteria.

Although COMT rs4680 has been reported to be associated with treatment response in schizophrenia (Huang et al., 2016), we report a lack of association between COMT rs4680 and schizophrenia symptoms or symptomatic remission to long-term olanzapine monotherapy in male schizophrenic patients. These negative results should be confirmed in larger, well-powdered studies, evaluating gene-gene (Sagud et al., 2018) and gene-environment interactions to find reliable genetic markers of treatment outcome in schizophrenia.

Role of the funding source

This study was supported by the Croatian Ministry of Science, Education and Sport (grants 108-1083509-3513098-0982522-2455; and 098-0982522-2457), but it has no involvement in study design; in the collection, analysis and interpretation of data.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

Part of the statistical analysis was carried out by Biometrika Healthcare Research, Croatia. All authors contributed to and have approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.04.028.

References

AlAqeel, B., Margolese, H.C., 2012. Remission in schizophrenia: critical and systematic review. Harv. Rev. Psychiatry. 20, 281–297. https://doi.org/10.3109/10673229.2012.747804.

Andreasen, N.C., Carpenter, W.T.Jr., Kane, J.M., Lasser, R.A., Marder, S.R., Weinberger, D.R., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. Am. J. Psychiat 162, 441–449. https://doi.org/10.1176/appi.ajp.162.3.441.

Huang, E., Zai, C.C., Lisoway, A., Maciukiewicz, M., Felsky, D., Tiwari, A.K., Bishop, J.R., Ikeda, M., Molero, P., Ortuno, F., Porcelli, S., Samochowiec, J., Mierzejewski, P., Gao, S., Crespo-Facorro, B., Pelayo-Terán, J.M., Kaur, H., Kukreti, R., Meltzer, H.Y., Lieberman, J.A., Potkin, S.G., Müller, D.J., Kennedy, J.L., 2016. Catechol-O-methyltransferase Val158Met polymorphism and clinical response to antipsychotic treatment in schizophrenia and schizo-affective disorder patients: a meta-analysis. Int. J. Neuropsychopharmacol 19 pii: pyv132. https://doi.org/10.1093/ijnp/pyv132.

Sagud, M., Tudor, L., Perkovic, Nikolac, M., Uzun, S., Zivkovic, M., Konjevod, M., Kozumplik, O., Vuksan Cusa, B., Svob Strac, D., Mihaljevic-Peles, A., Rados, I., Mimica, N., Nedic Erjavec, G., Pivac, N., 2018. Haplotypic and genotypic association of catechol-O-methyltransferase rs4680 and rs4818 polymorphisms and treatment resistance in schizophrenia. Front. Pharmacol. 9, 705. https://doi.org/10.3389/fphar.2018.00705.

Terzic, T., Kastelic, M., Dolzan, V., Kores Plesnicar, B., 2016. Genetic polymorphisms in dopaminergic system and treatment-resistant schizophrenia Psychiatr. Danub 28, 127–131.

Maja Zivkovic[a,1,*], Alma Mihaljevic-Peles[a,1], Dorotea Muck-Seler[c], Marina Sagud[a], Lana Ganoci[a], Suzana Vlatkovic[b], Matea Nikolac Perkovic[c], Lucija Tudor[c], Nada Bozina[a], Nela Pivac[c,*]

[a] *University Hospital Centre Zagreb, Zagreb, Croatia*

[b] *University Psychiatric Hospital Vrapce, Zagreb, Croatia*

[c] *Rudjer Boskovic Institute, Zagreb, Croatia*

E-mail addresses: maja.zivkovic@kbc-zagreb.hr (M. Zivkovic), npivac@irb.hr (N. Pivac).

[*] Corresponding authors.

[1] Maja Zivkovic and Alma Mihaljevic-Peles contributed equally.