A preliminary study of association of genetic variants with early response to olanzapine in schizophrenia

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INTRODUCTION

Schizophrenia affects many aspects of mental function-cognition, perception, behavior, and emotion, leading to debilitating severe mental illness. Response to treatment in schizophrenia is heterogeneous. "Atypical" or second-generation antipsychotics, mainstay of the treatment for schizophrenia, have improved its long-term prognosis and reduced side effects such as extrapyramidal symptoms and tardive dyskinesia. Olanzapine is considered more effective among the second-generation antipsychotics, but it can cause weight gain and metabolic side effects.

Background: Treatment response can be predicted in schizophrenia by DNA information in the drug metabolism pathways. This study aimed to examine clinical characteristics and genetic determinant(s) of early response to olanzapine treatment in schizophrenia using specified drug metabolizing genes.

Materials and Methods: Consenting participants (n = 33) suffering from schizophrenia were diagnosed on Diagnostic Interview for Genetic Studies. Oral olanzapine was administered in an incremental dose up to 10 mg (2 weeks) and 20 mg (6 weeks). All participants were tested on Positive and Negative Syndrome Scale, Clinical Global Impressions, and Global Assessment of Functioning at 0, 2, and 6 weeks. Side effects were also evaluated. After 2 weeks, 11 (33.33%) fulfilled criteria for early response, whereas 17 (51.52%) responded at 6 weeks. We investigated the contribution of clinical factors and five polymorphisms (rs2740574, rs2470890, rs762551, rs3892097, and rs1065852) in predicting response to olanzapine at 2 and 6 weeks of treatment with a standard dose.

Results: Severity of positive symptoms at baseline was associated with response at 2 weeks (P = 0.01) while higher scores on Scale for the Assessment of Negative Symptoms (SANS) at baseline was associated with response at both 2 (P = 0.04) and 6 weeks (P = 0.03). None of the five single nucleotide polymorphisms (SNPs) selected were significantly associated with response to olanzapine.

Conclusions: Olanzapine is an effective and safe drug. Positive and Negative Syndrome Scale positive score and SANS score were variably associated with response at 2 and/or 6 weeks. Replicate studies with bigger sample size are warranted for conclusive results in the Indian population for genetic association.

Key words: Drug metabolizing genes, genotypes, olanzapine, responders, schizophrenia
Substantial heterogeneity has been observed in olanzapine response. Such differences are influenced by a number of factors such as duration and severity of illness, duration of treatment, average drug dose, and compliance-related factors. Environmental (smoking and diet), demographic (sex and ethnicity), illness-related (illness onset and duration and comorbidities), and genetic factors contribute to this variability.\(^{[5]}\) Comparatively few Asian studies investigating the efficacy and tolerability of olanzapine, especially among Indians, have been reported.\(^{[6-8]}\) Cytochrome P450 3A4 is one of the most abundant P450s expressed in the liver, metabolizing more than 50% of all known drugs.\(^{[9]}\) The gene is inducible and wide interindividual variation (up to 40-fold) exists in the level of expression, but few significant functional polymorphisms which could explain this variability have been found.

Olanzapine is metabolized primarily by CYP1A2\(^{[10]}\) and to a lesser extent by CYP2D6.\(^{[11]}\) In vitro studies suggest that olanzapine is metabolized to N-desmethylolanzapine by the action CYP1A2.\(^{[12]}\) This metabolite is correlated significantly with olanzapine clearance rates in vitro.\(^{[13]}\) CYP1A2*1F polymorphism may be associated with olanzapine serum concentrations, which can influence response to treatment in schizophrenia.\(^{[14]}\) CYP1A2 1545 C > T was found to be associated with schizophrenia; however, it was rendered insignificant after corrections for multiple comparisons.\(^{[10]}\)

CYP2D6*4 (G > A) accounts for more than 75% of the poor metabolizer (PM) phenotype among Europeans. Its frequency is variable, ranging from 0.1 in Spaniards to 0.21 in Germans.\(^{[15]}\) The PM phenotype leads to higher drug concentrations in the plasma. Thus, it is a major determinant of the therapeutic efficacy and toxicity of the administered drug.\(^{[16,17]}\) CYP2D6 (*10 allele) and CYP1A2 (*1F allele) have been associated with the development of tardive dyskinesia in schizophrenia patients.\(^{[18]}\) CYP2D6*10 allele is important for the regulation of the activity of CYP2D6, which is involved in metabolism of risperidone.\(^{[19]}\) Among East Indians, CYP2D6*10 allele is a prevalent mutant allele.\(^{[20]}\) In Chinese patients treated with risperidone, CYP2D6*10 polymorphism 188C > T was found to be associated with weight gain.\(^{[21]}\)

The present study examined the role of clinical characteristics and few single nucleotide polymorphisms (SNPs) of drug-metabolizing genes from the cytochrome P450 family in early response to olanzapine among participants with schizophrenia.

**MATERIALS AND METHODS**

The study was carried out at the Department of Psychiatry, Center of Excellence in Mental Health, Post Graduate Institute of Medical Education and Research-Dr. Ram Manohar Lohia Hospital (PGIMER-Dr. RMLH), New Delhi, from November 2015 to March 2017. Consecutive patients with schizophrenia, seeking treatment at the department, were invited to participate in an open-label trial for a period of 6 weeks by their treating physicians. Those who agreed were enrolled after due written informed consent. All enrolled participants were between 18 and 65 years of age, with no history of substance abuse in the preceding 6 months, experiencing acute exacerbations when recruited. At study entry, patients were either drug naive or with treatment gap of minimum 2 weeks from any oral antipsychotic and minimum 6 weeks from any long-acting injectable antipsychotic. Those suffering from diabetes, hypertension, or any other neurological or medical conditions that could affect the outcome of antipsychotic treatment or the propensity to develop adverse effects were excluded from the study. Twelve participants were inpatients; the majority of the participants were treated in an outpatient setting. The Hindi version of the Diagnostic Interview for Genetic Studies\(^{[22,23]}\) was administered on all consented participants, and a consensus diagnosis was ascertained according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria.

Positive and Negative Syndrome Scale (PANSS),\(^{[24]}\) Clinical Global Impressions (CGI) Scale,\(^{[25]}\) and Global Assessment of Functioning (GAF)\(^{[26]}\) scales were used to evaluate the efficacy of treatment and functioning of the patient. Abnormal Involuntary Movements Scale (AIMS),\(^{[27]}\) Barnes Akathisia Rating Scale (BARS),\(^{[28]}\) and Simpson Angus Scale (SAS)\(^{[29]}\) were used to monitor side effects. All scales, except DIGS (only at baseline), were administered at baseline, at 2, and 6 weeks. Ethical approval was obtained from the Institutional Review Boards and Institutional Ethics Committee at PGIMER-Dr. Ram Manohar Lohia Hospital and University of Delhi before the study initiation.

**Clinical evaluation**

The efficacy index was defined as the difference between PANSS scores at baseline and after 2 and 6 weeks of treatment. It was used as an outcome variable for multivariate analysis. To enable comparisons with published studies, responders were defined at 2 weeks as at least 20% improvement on PANSS\(^{[30]}\) or improvement in CGI of at least three points; and at 6 weeks as at least 30% reduction on PANSS\(^{[30]}\) or at least 2-point decrease in CGI-S in patients with baseline between 5 and 7, or at least 1-point decrease in CGI-S in patients with baseline between 2 and 4.\(^{[31]}\)

The baseline, week 2, and week 6 data have been included in the present analysis.

**Clinical and laboratory parameters**

Physical examination, including pulse rate, height, weight, body mass index (BMI), hip circumference, waist circumference, waist-hip ratio, and blood pressure, was assessed at baseline, 2, and 6 weeks. BMI was calculated using the formula: BMI = weight/(height mm\(^2\)).\(^{[32]}\) Complete blood count, liver function test, and kidney function test were
done at baseline, 2, and 6 weeks. Fasting and postprandial blood sugar, lipid profile including high-density and low-density lipoproteins (HDL and LDL), total cholesterol, and serum triglycerides were done at baseline and 6 weeks. ECG was done at baseline and 6 weeks.

**Dosing schedule**
Participants were administered 10 mg/day of olanzapine at onset. At the end of 2 weeks, they were assessed for response and side effects, and those qualifying as good responders were continued on the same dose. Nonresponders had their dose increased up to 20 mg/day of olanzapine, until 6 weeks. During the entire study period, participants did not receive any other antipsychotic medication or other medications, which could have altered the results of the study. However, benzodiazepines were used in cases of acute exacerbations not controlled by olanzapine (n = 7). Since a caregiver always accompanied the patient, tablets were given to the caregiver and a tablet count to assess the degree of compliance was carried out at follow-up. Throughout the trial, only one brand of olanzapine, bought commercially from different chemists, was used.

**Genetic analysis**
Blood was drawn at study initiation and at the end of the study. Peripheral blood (5–10 ml) was drawn from each subject recruited in this study, and genomic DNA was isolated at the Department of Genetics, University of Delhi, South Campus, using the phenol–chloroform method. SNPs from CYP genes were assayed using restriction fragment length polymorphism (RFLP).[33] Four polymorphic markers from three genes, namely CYP1A2 1545 C > T (15:74755085 and rs2470890), CYP1A2*1F A > C (15:74749576 and rs762551), CYP2D6*4 1846 G > A (22:42128945 and rs3892097), and CYP2D6*10 T > C (22:42130692 and rs1065852) were tested using RFLP. One SNP CYP3A4*1B A > G (7:99784473 and rs2740574) was genotyped by sequencing [Table 1]. The choice of all these markers was based on their functional significance and literature support.[10,14-21] PCR conditions, primer sequences, restriction enzymes used, and allele sizing are given in Table 1.

**Statistical analysis**
Efficacy parameters were compared using Mann–Whitney’s U-test. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 20.0.[34] Hardy–Weinberg equilibrium and association for the five markers were assessed using Pearson’s Chi-square method in Plink[35] (http://pngu.mgh.harvard.edu/purcell/plink/). Power was calculated using power and precision software (http://www.power-analysis.com).

**RESULTS**
Out of a total of 45 subjects assessed initially, 7 refused to participate due to personal reasons. A total of 38 persons
with schizophrenia were enrolled, but 5 of them were lost to follow-up (went back to village, could not be contacted at follow-up, and refused after first follow-up), so final analysis was conducted from the data of remaining 33 subjects. Among the participants, there were 17 males and 16 females. The mean age of the subjects was 36.85 years, 21 of them were ever married and 12 were never married. They were living in own home with spouse and/or children (n = 15) or in home of parents or children (n = 14). They had average 7.88 years of schooling and were mostly working as housewives, operators, laborers, or were not employed. Their average age of onset of psychotic symptoms was 28.12 years.

**Therapeutic response**

On the basis of at least 20% improvement in PANSS score at 2 weeks and at least 30 percent improvement on PANSS at 6 weeks, 11 (33.33%) showed early response at the end of 2 weeks, whereas 17 participants (51.52%) responded at 6 weeks. All those who responded at 2 weeks (n = 11) continued to respond even at 6 weeks. In addition, six other participants who did not respond at 2 weeks responded later at 6 weeks. Mean score of CGI-S was 4 at baseline, which improved to 3.70 at the end of 2 weeks and to 3.06 at the end of 6 weeks. It suggests that there was change in category of severity from “moderately ill” to “mildly ill” within the first 2 weeks of treatment.

Effect size was calculated by Cohen’s D method. At 2 and 6 weeks, the effect size of PANSS (total) was −1.65 and −3.92, respectively, suggesting severity of illness decreased significantly. It was −0.89 and −0.96 for PANSS (positive), −0.96 and −2.37 for PANSS (negative), and −1.38 and −3.13 for PANSS (general). Similarly, effect size was also calculated for CGI and GAF and was found to be −0.49 at the end of 2 weeks and −1.53 at the end of 6 weeks for CGI and 0.76 at the end of 1 week and −1.53 at the end of 6 weeks for GAF. These findings suggest that there was improvement in the symptoms as per all the scales used, both at 2 and 6 weeks. Improvement was greater at the end of 6 weeks than at the end of 2 weeks [Table 2].

Mann–Whitney’s U-test was applied to compare the various parameters among the two groups (responders and nonresponders at 2 and 6 weeks) as the sample size was small and was not normally distributed. Years of schooling were found to be statistically different among responders and nonresponders at 6 weeks (P = 0.01); responders being less educated than nonresponders. The total score of Scale for the Assessment of Negative Symptom (SANS) at the end of 2 weeks was 45.76 ± 13.60 and 36.13 ± 12.56 for responders and nonresponders, respectively. The SANS score at baseline was significantly different between responders and nonresponders (P = 0.04), suggesting responders had higher score on SANS at baseline. At 6 weeks, the total score of SANS was 45.76 ± 13.60 and 36.13 ± 12.56 for responders and nonresponders, respectively (P = 0.02), similar to the results at 2 weeks. There was significant difference in baseline PANSS positive score between responders and nonresponders at 2 weeks (P = 0.01); responders having more positive symptoms than nonresponders at baseline. Rest of the PANSS scores were not significantly different between responders and nonresponders of either 2 or 6 weeks [Table 3].

**Side effects**

At 2 and 6 weeks, none of the participants had side effects as measured by AIMS. Two participants developed tremors at 2 weeks, while at 6 weeks, one developed tremors and one other participant developed rigidity of wrist joint, as evaluated on SAS. While on BARS, none of the participants had side effects at 2 weeks and two of them developed akathisia at 6 weeks. The mean increase in BMI was 0.45 ± 0.62 and 1.06 ± 0.93 at 2 and 6 weeks, respectively. At 6 weeks, the mean change in fasting blood sugar, post prandial blood sugar, HDL, and LDL was 1.94 ± 5.08, 0.79 ± 5.10, 0.03 ± 1.67, and 0.79 ± 4.89, respectively.

SNP rs2740574 was monomorphic in the study and therefore was excluded from further analysis. All SNPs were in Hardy–Weinberg equilibrium [Table 4]. Test of association was performed using Fisher’s exact test as the sample size was small. There was no association of the common drug-metabolizing genes and response to olanzapine in schizophrenia at both 2 and 6 weeks [Table 4]. Allele frequency differences were observed between responders and nonresponders but were not significant. Allele frequency differences were observed among different populations and have been listed in Table 4.

| Table 2: Effect sizes of outcome variable at 2 and 6 weeks |
|---------------------------------|
| **Variable** | **Baseline** | **At 2 weeks** | **At 6 weeks** | **Effect size** |
|----------------|-------------|----------------|----------------|----------------|
| **Means±SD** | **At 2 weeks** | **At 6 weeks** | **At 2 weeks** | **At 6 weeks** |
| PANSS (positive) | 22.39±3.80 | 19.00±3.26 | 14.03±3.13 | −0.89 | −2.20 |
| PANSS (negative) | 22.48±2.45 | 20.12±2.00 | 16.67±3.35 | −0.96 | −2.37 |
| PANSS (general) | 33.48±3.53 | 28.61±4.49 | 22.45±4.49 | −1.38 | −3.13 |
| PANSS (total) | 78.36±6.44 | 67.73±6.93 | 53.15±7.99 | −1.65 | −3.92 |
| CGI | 4.00±0.61 | 3.70±0.88 | 3.06±0.75 | −0.49 | −1.53 |
| GAF | 24.45±6.07 | 29.06±5.88 | 37.82±7.21 | 0.76 | 2.20 |

SD – Standard deviation; PANSS – Positive and Negative Syndrome Scale; GAF – Global Assessment of Functioning; CGI – Clinical Global Impression
**DISCUSSION**

We defined early response as at least 20% improvement on PANSS at 2 weeks and at least 30% improvement on PANSS at 6 weeks. Two-week criterion was based on Kinon et al., who defined early response as ≥20% improvement in the baseline PANSS at week 2 and ≥40% reduction in the PANSS at 3 months.[27] Emsley et al. defined response as improvement in the PANSS total score of ≥20% and assessed response at weekly interval in 400 patients of first episode schizophrenia.[28] Correll et al. defined improvement of ≥20% from baseline every week till 4 weeks on the Brief Psychiatric Rating Scale score.[28] Crespo-Facorro et al. defined response as ≥40% improvement in the BPRS total score from baseline studied in 172 patients.[29] Using our criterion at 6 weeks more than half of the participants (51.52%) showed response to treatment. In the shorter term, at 2 weeks, 33.33% had "responded."

With respect to years of school attended, there was no significant difference between responders and nonresponders at 2 weeks. However, at 6 weeks, more years of schooling was a predictor of nonresponse (P = 0.01). This finding is in contrast with the study by Diaz et al. which found lower education level as one of the risk factors for not achieving clinical remission during the 1st year of treatment in schizophrenia.[30] This difference may be arbitrary because we observed response at very early stage of treatment (at 6 weeks). One more study also suggested that education level was one of the predictor of unfavorable long-term outcome.[31]

Severity of illness was rated on PANSS. There was a significant difference on PANSS positive score between responders and nonresponders at 2 weeks (P = 0.01), with responders having more positive symptoms than nonresponders at baseline. Rest of the PANSS scores was not significantly different. It suggests that severity of positive symptoms, as measured on PANSS, may be a predictor of response at least at 2 weeks, but not at 6 weeks since we could not replicate the same result at 6 weeks.

In our small sample, PANSS total and general scores at baseline did not determine response to olanzapine at 2 or at 6 weeks. Case et al. reported that higher PANSS score is a predictor of poor treatment response.[32] Robinson et al. also found that patients with more severe positive symptoms are less likely to respond.[33] Another study reported that severity of general and positive symptoms but not the negative symptoms at baseline was better predictor of clinical response.[34]

In our study, the average weight and BMI of the participants increased at both 2 and 6 weeks, consistent with other
studies. However, change in weight or BMI was not found to be significantly associated with response both at 2 and 6 weeks. Effect size was also calculated for various physical parameters. It was significantly high for BMI at the end of 6 weeks only ($P = 0.32$). Most physical parameters remained similar after 2 and 6 weeks, suggesting that olanzapine is a safe drug.

Our study found increase in fasting and postprandial blood sugar levels at the end of 6 weeks; however, it was not statistically different among responders and nonresponders. This finding has been reported in previous studies as well. There was no significant change in HDL level of the subjects at 6 weeks, reported in another Indian study. We observed nonsignificant motor side effects in our sample at both 2 and 6 weeks.

Various pharmacogenetic studies have investigated the role of genes in predicting treatment response in patients diagnosed with schizophrenia. SNPs have been the main focus of pharmacogenetics research in schizophrenia. Olanzapine has been studied in a few of these studies, but none of the studies have tried to explore genetic correlates of early response to olanzapine in schizophrenia. None of the SNPs we selected were significantly associated with response to olanzapine probably because of the small sample size. Small observations such as presence of TT genotype in only nonresponders were seen for rs2470890.

**CONCLUSIONS**

We established in the study that olanzapine is a safe and effective drug, showing early response in schizophrenia. SANS score at baseline was found to be a predictor of early response at 2 weeks ($P = 0.04$) and 6 weeks ($P = 0.02$). PANSS positive score at baseline was found to be a predictor of response at 2 weeks ($P = 0.01$) and years of schooling were associated with response at 6 weeks ($P = 0.01$). In this pilot study of Cytochrome P450 genes (CYP1A2 rs2470890, rs762551; CYP2D6 rs1065852, rs3892097; CYP3A4 rs2740574) in a limited sample size of 33 subjects, no significant finding was observed for olanzapine response in schizophrenia. TT genotype was found in only nonresponders for rs2470890. Other SNPs which were not studied in this research could also play a role. A larger cohort and analysis with more genes is warranted for a conclusive result.

**Acknowledgment**

I express my sincere regards to Dr. Rajesh Nagpal for his time and immense help in improving the reliability of this study.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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