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SHORT COMMUNICATION

Pharmacogenetic study of the effects of raloxifene on negative symptoms of postmenopausal women with schizophrenia: A double-blind, randomized, placebo-controlled trial

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Abstract
Several double-blind clinical trials have reported improvement in positive, negative and cognitive symptoms of schizophrenia with raloxifene, a selective receptor estrogen modulator. However, there are some inconsistencies in replicating findings between studies of different countries. The failure to replicate these findings may result from genetic factors that could explain some of the variability in the treatment response. However, pharmacogenetic studies exploring this topic in women with schizophrenia are lacking. We aimed to conduct an exploratory pharmacogenetic analysis of a double-blind, randomized, parallel, placebo-controlled study of 24 weeks' duration of raloxifene aiming to improve negative symptoms in postmenopausal women with schizophrenia. Four single nucleotide polymorphisms (SNPs) were studied: rs9340799, rs2234693 and rs1801132 in the Estrogen Receptor 1 (ESR1) gene, and rs1042597 in the UDP-glucuronosyltransferase 1A8 (UGT1A8) gene. Sixty-five postmenopausal women with schizophrenia (DSM-IV) were randomized to either 60 mg/day adjunctive raloxifene (36 women) or adjunctive placebo (29 women). Psychopathological symptoms were assessed at baseline and at weeks 4, 12, and 24 with the Positive and Negative Syndrome Scale (PANSS). Of the four studied SNPs, the rs1042597 variant in the UGT1A8 gene was associated with a different treatment response in negative symptoms with raloxifene treatment, whereas the rs2234693 variant in the ESR1 gene was associated with a distinct response in general psychopathology. In conclusion, our study suggests that genetic variants in *UGT1A8* and *ESR1* genes modulate the treatment response to adding raloxifene to antipsychotic treatment in postmenopausal women with schizophrenia.

1. Introduction

Estrogens are effective in improving psychotic symptoms (Kulkarni et al., 2008), although their use in long-term treatment has been limited by their potentially negative effect on breast and uterine tissue (Chlebowski et al., 2009). This has led to investigating the use of selective estrogen receptor modulators (SERM) such as raloxifene to improve symptoms without these side effects in reproductive tissues. Double-blind clinical trials have demonstrated improvement of symptoms of schizophrenia with raloxifene, including positive symptoms (Kianimehr et al., 2014; Usall et al., 2011), negative symptoms (Usall et al., 2015, 2011), general psychopathology (Kulkarni et al., 2010; Usall et al., 2011) and cognitive abilities (Huerta-Ramos et al., 2014; Weickert et al., 2015). Although our group conducted two previous clinical trials (Usall et al., 2015, 2011) reporting improvement in negative symptoms with 60 mg/day of raloxifene in postmenopausal women with schizophrenia, these positive results have not been replicated in other clinical trials using 60 mg (Kulkarni et al., 2010) or 120 mg (Kianimehr et al., 2014; Kulkarni et al., 2010; Weickert et al., 2015) of raloxifene. Differences between trials in terms of selection criteria of patients or raloxifene dose may explain the lack of consistency among studies. The failure to replicate these findings may also result from a lack of pharmacogenetic studies. Genetic factors (i.e. genetic variants in candidate genes related to estrogen receptors or raloxifene metabolism) may help to shed light on the variability in the treatment response. However, no pharmacogenetic studies have explored whether genetic variants modulate the raloxifene response in women with schizophrenia.

In our last Stanley Medical Research Institute funded trial we aimed to conduct a pharmacogenetic study exploring single nucleotide polymorphisms (SNPs) in two candidate genes related to raloxifene: the Estrogen Receptor 1 (*ESR1*) and the UDP-glucuronosyltransferase 1A8 (*UGT1A8*). Variants in the *ESR1* gene, which are thought to contribute to the risk of schizophrenia (Weickert et al., 2008), have been reported to be associated with SERM response in patients with breast cancer (Madeira et al., 2014) and osteoporosis (Heilberg et al., 2005; Zavratnik et al., 2010). The *UGT1A8* gene is another candidate gene, as the major metabolic pathway of raloxifene is glucuronidation at 6- and/or 4'-positions, which is mainly catalyzed by the *UGT1A8* enzyme. Raloxifene is transformed into water-soluble, excretable metabolites, and therefore functional allelic variants of *UGT1A8* may influence the clinical response and bioavailability of medicines metabolized mainly by *UGT1A8* (Kokawa et al., 2013).

Four single nucleotide polymorphisms (SNPs) in two candidate genes were studied: rs9340799, rs2234693 and rs1801132 located in *ESR1* and rs1042597 in *UGT1A8* gene. Although the study was focused on negative symptoms, data on positive psychotic symptoms and general psychopathology were also explored.

2. Experimental procedures

2.1. Sample

Participating women were recruited from mental health centers and various long-stay hospital units (non-acute patients) at Parc Sanitari Sant Joan de Déu, Hospital Universitari Institut Pere Mata, and the Corporació Sanitària Parc Taulí. Of 78 patients randomized,

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