DOI: 10.1111/ijcp.14441

LETTER

Psychiatry

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

# The potential interaction between COVID-19 vaccines and clozapine: A novel approach for clinical trials

Dear Editor,

COVID-19 infection-related clozapine intoxication could be induce post-infection cytokine release, downregulation of the metabolism of clozapine in the cytochrome P450 (CYP) system through CYP1A2.[1] We thought that COVID-19 vaccination would induce a similar effect on serum concentration of clozapine. We would like to examine the potential interaction between clozapine and COVID-19 vaccines from different perspectives.

Vaccines could trigger immune responses and alter the metabolism of the drugs. As an illustration, mRNA COVID-19 vaccines which are BNT162b2 and mRNA-1273 brought out strong CD4+ and CD8+ T-cell and antibody responses. The increase of these cells is led to produce cytokines, especially interferon-gamma by T lymphocytes. However, T-cell responses are not have demonstrated only by mRNA vaccines that are mentioned above. COVID-19 vaccine (ChAdOx1 nCoV-19) which is vector-based had been caused similar responses too. In this connection, cytokines such as IFN-γ could lead to decreased expression of CYP enzymes in an in vitro study.[2]

On the other hand, COVID-19 (inactivated) vaccine did not induce T-cell response in the preclinical studies with mice and non-human primates, also T-cell responses were not evaluated in the human Phase I clinical trials. Differently, the recombinant protein vaccine from Matrix™-M adjuvanted (NVX-CoV2373) demonstrated multifunctional CD4+ T-cell responses, although determined CD8+ T-cell responses were not available.[3]

An in vitro study with human hepatocytes stated that IFN-γ could decrease the efficacy of CYP1A2 and CYP3A4 isoenzymes. Nevertheless, the production of IFN-γ could not affect all the CYP enzymes, wherein in vitro studies showed that human hepatocytes treated with IFN-γ had decreased CYP1A2, CYP3A4 expressions but it is not affected on the expression of CYP2C9, CYP2C19, and CYP2C18 isoenzymes.[2]

Clozapine is one of the most efficient antipsychotics available for people with schizophrenia spectrum disorders and is the only effective medication in treatment-resistant schizophrenia. CYP1A2, CYP2D6 and CYP3A4 isoenzymes are related to clozapine metabolism. However, in clozapine metabolism, the major CYP isoform is CYP1A2 and the activity of this isoenzyme is an important determinant of clozapine dose.[4]

In addition, to support the idea of cytokines could elicit reduced expression of CYP enzymes, we would like to discuss interferon-beta (IFN-β) administration in COVID-19 treatment and its effect on CYP enzymes. The COVID-19 Treatment Guidelines Panel advises against the use of interferons (IFNs) for severe or critical COVID-19 treatment, except in a clinical trial.[5] Because, IFNs are a vital part of the innate cytokine response to viral infection, actually, IFN-α/β and IFN-γ were initially defined as antiviral but IFNs have many different important activities in the immune system such as enhancement of dendritic cell reactions and in promoting the survival of activated lymphocytes, stimulate macrophage function and cytokine production regulation throughout the immune reaction.[6]

The IFN-γ and IFN-β have different mechanisms of action but we would like to emphasize the similarity of enzyme system alteration. The same CYP enzyme system also influenced theophylline metabolism that resulted in the reduction of the theophylline clearance (CYP1A2 substrate) by IFN-β. However, because of a possible risk of additive haematological toxicity with co-administration, additional monitoring should be considered.[7]

According to Kow et al, most of the COVID-19 vaccines could downregulate CYP1A2 and CYP3A4 enzymes and increased IFN-γ had reduced expression of CYP1A2 and CYP3A4 which are also involved in clozapine metabolism.[2] Another striking results of Raaska et al study demonstrated that influenza vaccination using conventional trivalent influenza vaccine (inactivated) does not affect serum concentration of clozapine. However, infection-related increase in CRP may be associated with elevated serum concentration of clozapine.[8] The latest case report confirms this hypothesis. Deborah et al demonstrated that administration of mRNA COVID-19 vaccine (BNT162b2) could cause increased clozapine and CRP levels.[9]

In conclusion, the literature which we discussed above assert that COVID-19 vaccines have strong antibody responses, and this would lead to potential interactions with some drugs as well as clozapine. The possibility of elevated serum concentration of clozapine will result in unplanned treatment cessation because of possible CYP downregulation. Thus, relapse in psychotic symptoms may occur as a result of withdrawal of clozapine. Therefore, followed by COVID-19 vaccine administration, the clinicians should beware of such potential interactions and monitor absolute neutrophil counts and clozapine serum concentrations closely in patients using clozapine. We could not suggest that concomitant with clozapine treatment and COVID-19 vaccines are contraindicated. Thus, COVID-19 vaccination should be encouraged in patients prescribing clozapine treatment. Further studies are needed to evaluate the impact of duration, dose, prescribed concomitant drugs and their interaction with patients' individual (age, gender, genetic polymorphism, etc), environmental (obesity, smoking, etc) and laboratory parameters

  

(CRP, absolute neutrophil counts, leucocyte levels and clozapine serum concentrations) on examining the potential interactions between types of COVID-19 vaccine and clozapine.

## ACKNOWLEDGEMENT

Not available.

## DISCLOSURE

The authors declared no conflict of interest.

## DATA AVAILABILITY STATEMENT

Not available.

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