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RESEARCH LETTER

Haematological changes and adverse events associated with BNT162b2 mRNA COVID-19 vaccine in patients receiving clozapine—Findings from an audit

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Persons with severe mental illnesses (SMI) have higher risks of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19-related morbidity and mortality.[1] COVID-19 vaccination has been recommended for persons with SMI, including those on clozapine therapy.[1–3]

SARS-CoV-2 infection can result in elevated clozapine levels and toxicity in clozapine users but limited information is available on risk of COVID-19 vaccinations in clozapine users.[2] Thompson et al. reported a case of elevated clozapine levels presenting with delirium, increased falls and incontinence 4 days after receiving a dose of the BNT162b2 mRNA vaccine.[4] Others have postulated that elevated clozapine levels and toxicity may be related to the inhibition of CYP1A2 enzyme during inflammation.[2] Close monitoring for symptoms of clozapine toxicity after the vaccination was hence suggested.[4] The purpose of this research letter is to share our audit findings which assessed the haematological profile and other adverse events in patients on clozapine receiving the BNT162b2 vaccination.

In March 2021, a COVID-19 vaccination exercise was conducted in the Institute of Mental Health (IMH), Singapore. All institutionalised patients receiving clozapine treatment were screened and offered the BNT162b2 mRNA vaccine. Contraindications included patients who are immunocompromised, have severe allergies or bleeding risks that contraindicates intramuscular injection, or who are very frail (e.g., life expectancy <6 months). Consent was taken from patients, or their legal guardians if they lacked mental capacity. Only patients on clozapine who received the first vaccine dose were included in our audit.

The vaccine schedule consists of 2 intramuscular doses administered 21 days apart, with full blood count (FBC) monitoring within a week before the first dose and then a week after each vaccination. All patients were monitored for 30 minutes (for anaphylaxis or other discomfort) and then for 72 hours for any emergent adverse events after each vaccine dose.

All statistical analyses were performed using IBM SPSS Statistics for Mac, version 27 (IBM Corp., Armonk, NY). Paired Student's *T*-test, as well as repeated measures ANOVA test was used to compare haematological variables pre- and post-vaccination after logarithmic transformation was applied. McNemar's Test was used to compare the relative frequencies of total adverse events reported after each dose of vaccination. Statistical significance was set at $p < 0.05$.

A total of 127 and 124 patients on clozapine received the first and then the second dose of the vaccine respectively. The paired haematological indices of 127 patients

TABLE 1 Patients' haematological variables (Mean ± SD) before and after BNT162b2 mRNA vaccination

Haematological variables[a]	*n*	Pre-vaccination	1 week after 1st dose	1 week after 2nd dose	*p*[b]
WBC ($\times 10^3$/μl)	121[c]	7.92 ± 2.42	7.71 ± 2.24	7.53 ± 2.21	0.122
RBC ($\times 10^6$/μl)	121[c]	4.54 ± 0.48	4.52 ± 0.50	4.46 ± 0.51	0.826
Haemoglobin (g/dl)	121[c]	13.26 ± 1.35	13.18 ± 1.19	12.96 ± 1.34	0.776
Platelets ($\times 10^3$/μl)	121[c]	247.40 ± 67.48	251.15 ± 70.54	254.71 ± 70.37	0.523
MPV (fl)	119[d]	10.63 ± 1.02	10.53 ± 0.99	10.39 ± 0.95	0.550
Neutrophils ($\times 10^3$/μl)	121[c]	5.08 ± 2.02	4.87 ± 1.86	4.60 ± 1.83	0.226
Lymphocytes ($\times 10^3$/μl)	121[c]	1.85 ± 0.66	1.87 ± 0.66	1.90 ± 0.70	0.740
Monocytes ($\times 10^3$/μl)	121[c]	0.67 ± 0.25	0.79 ± 1.24	0.77 ± 1.00	0.681
Eosinophils ($\times 10^3$/μl)	121[c]	0.30 ± 0.28	0.30 ± 0.32	0.31 ± 0.24	0.723
Basophils ($\times 10^3$/μl)	121[c]	0.03 ± 0.01	0.04 ± 0.09	0.03 ± 0.01	0.975

Abbreviations: RBC, red blood cells; MPV, mean platelet volume; WBC, white blood cells.
[a]Log 10 transformation used for statistical analysis.
[b]*p* values obtained from repeated measures ANOVA test after controlling for age, sex and total daily clozapine dose.
[c]3 out of 124 were excluded from statistical analysis because of missing data.
[d]5 out of 124 were excluded from statistical analysis because of missing data ($n = 3$) and invalid MPV because of microcytosis ($n = 2$).

were not statistically significantly different between baseline and 1 week post first dose, except for a difference in the mean platelet volume (MPV) which is clinically insignificant. Post-second dose FBCs were missing for 6 patients as they did not receive the second vaccine dose (e.g., deemed clinically unfit for vaccination or patient declined) or were discharged. Comparing the three FBCs available for 121 patients who received both doses of the vaccine, no statistically significant differences were detected in their WBC, ANC and other haematological variables (see Table 1). Of note, there were no cases of agranulocytosis (i.e., ANC $\leq 0.5 \times 10^3$ μl) post-vaccination. Three patients had mild neutropenia (i.e., ANC 1.5–2.0 $\times 10^3$ μl). The low baseline neutrophil count of 1.74 $\times 10^3$/μl in a patient declined asymptomatically to 1.70 $\times 10^3$/μl after the first dose but normalised (to 2.19 $\times 10^3$/μl) after the second dose. Two other patients with a history of mild–moderate neutropenia (i.e., ANC 1.0–1.5 $\times 10^3$ μl) developed asymptomatic mild neutropenia after the second dose, which resolved within 1–2 months.

Of the 127 patients, 37 adverse events were documented post-vaccination among 30 patients (23.6%). There was no statistically significant difference in the frequency of adverse events between the first and second vaccine dose ($p = 0.405$). No cases of anaphylaxis occurred. Majority of the adverse reactions were mild. The top three adverse events were transient low-grade fever ($n = 13$), mild injection site reactions ($n = 10$), and behavioural disturbances ($n = 5$) that were consistent with the patients' long-standing behaviours and considered unrelated to the vaccine. One patient developed tachycardia 10 hours post-second dose but recovered after treatment for pneumonia and Klebsiella pneumoniae bacteraemia.

No major haematological adverse effects were detected in our audit data, nor were reported in the Interim Authorization Prescribing Information for the Pfizer-BioNTech COVID-19 Vaccine (17 January 2022 revision). We found one (0.8%) and two cases (1.7%) of asymptomatic mild neutropenia after the first and second dose respectively with spontaneous recovery, and all three cases had a history of granulocytopenia. Veerman et al similarly reported a low incidence of mild granulocytopenia (3% and 5%), after the first and second dose of the COVID-19 vaccinations respectively, without cause for additional monitoring.[5]

The strength of our audit is the inclusion of a baseline FBC and 72 hours post-vaccination monitoring for any adverse effects. We drew blood samples 1 week post-vaccination with considerations to the case report described by Thompson et al.[4] However, it was possible to have underestimated the incidence and severity of haematological or other adverse events as we only obtained 2 follow-up FBCs and captured adverse events only for 72 hours post-vaccination. We missed the post-second dose FBCs in 6 patients, and had no data of comorbidities and concurrent medications that might have affected the FBCs or adverse effects. Plasma clozapine and C-reactive protein levels were also not routinely performed in IMH. However, it is noteworthy that none of our patients developed myocarditis or clinical symptoms suggestive of clozapine toxicity such as oversedation, confusion or seizures within 72 hours post-vaccination. Lastly, our findings are based on the BNT162b2 mRNA vaccine and may not be generalisable for those who receive other brands or vaccines types.

In conclusion, the BNT162b2 mRNA vaccine appears safe for most patients on clozapine in our audit. We opine that additional haematological monitoring during

BNT162b2 mRNA vaccination is likely unnecessary, unless there are compelling clinical indications (e.g., for patients who developed an infection). Clinicians should not discontinue clozapine when there is a transient and asymptomatic decline in WBC/ANC above the red flag threshold. Given the risk that COVID-19 poses to patients on clozapine therapy, we support the use of mRNA vaccination as a strategy to reduce morbidity and mortality in those without contraindications.

AUTHOR CONTRIBUTIONS

Shuli Lim, Emily Liew, Amy Leo, Boon Tat Ng and Jimmy Lee contributed to the conception of this manuscript including the acquisition, analysis and interpretation of data. The main author would also like to thank her co-authors for proofreading of this manuscript. The final manuscript was discussed and approved by all authors to be published.

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CONFLICT OF INTEREST

Jimmy Lee has received honoraria from Otsuka Pharmaceuticals, Lundbeck Singapore, Janssen Pharmaceuticals and Sumitomo Pharmaceuticals. The other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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