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## A Decrease of Neutrophils After COVID-19 Vaccination in a Treatment-Resistant Patient With Schizophrenia Taking Clozapine

### To the Editors:

Clozapine (CLZ) not only is effective in 30% to 60% of patients with treatment-resistant schizophrenia (TRS)<sup>1</sup> but also carries the risk of adverse drug reactions.<sup>2</sup> Because neutropenia associated with CLZ is reported in 3.8% of patients and agranulocytosis is estimated to be 0.4%, absolute neutrophil count (ANC) monitoring is required during continuous administration of CLZ.<sup>3,4</sup> The coronavirus disease 2019 (COVID-19) pandemic raises concerns about the continued administration of CLZ in TRS patients with COVID-19.<sup>5</sup> Although patients with COVID-19 infection frequently experience lymphopenia but not neutropenia,<sup>6,7</sup> transitory drops in neutrophil counts in TRS patients were reported recently.<sup>8,9</sup> COVID-19 vaccinations are administered worldwide and effective for the prevention of COVID-19 infection,<sup>10</sup> but there is no report about the relationship between neutropenia after COVID-19 vaccination during CLZ treatment. We experienced a TRS patient with 5 years' CLZ administration who showed a transient decrease of the absolute white blood cell (WBC) count and ANC after administration of COVID-19 vaccinations (Pfizer/BioNTech).

### CASE PRESENTATION

A 45-year-old woman first experienced auditory hallucination and persecutory delusion at 20 years old. She had a 25-year history of schizophrenia (*International Classification of Diseases, Tenth Revision*) characterized by auditory hallucinations and persecutory delusions that had resulted in disruption to her education, family life, and employment. Haloperidol and risperidone were partially effective at first, but

**TABLE 1.** Change of Absolute WBC and Neutrophil Count After First or Second COVID-19 Vaccination ( $\times 10^9/L$ )

	Before	First Vaccination			Second (Day 21)	
	(Day 0)	Day 3	Day 7	Day 10	Day 24	Day 28
Absolute WBC	3.86–7.42	3.16	3.83	4.24	3.03	4.37
Absolute neutrophil	2.20–3.86	1.90	2.69	3.14	1.92	2.97

she stopped them. Her symptoms became worse, and she made several attempts at suicide. Treatment with 16 mg blonanserin for 8 weeks, 20 mg olanzapine for 12 weeks, 6 mg risperidone for 12 weeks, and 24 mg aripiprazole for 16 weeks was ineffective, and a regimen of 112.5 mg/day CLZ with 200 mg/d lithium carbonate was initiated when she was 41 years old. This decreased her hallucinations and delusions, and her suicidal thoughts disappeared. She continued her part-time job for the next 4 years. Her absolute WBC count every 2 weeks was usually from 3.86 to 7.42  $\times 10^9/L$ , and her ANC was from 2.20 to 3.86  $\times 10^9/L$ . She did not have a history of COVID-19 infection or allergy.

Table 1 shows the changes in her WBC count and ANC. When the first COVID-19 vaccination (0.5 mL; Pfizer/BioNTech) was administered, her only subjective adverse effect was arm pain for 3 days. Three days after the COVID-19 vaccination, her absolute WBC suddenly dropped to 3.16  $\times 10^9/L$ , and her ANC also dropped to 1.90  $\times 10^9/L$ . At 7 days after the first vaccination, these values had returned to the normal range. A second COVID-19 vaccination of 0.5 mL was administered 3 weeks after the first vaccination. The WBC suddenly dropped to 3.03  $\times 10^9/L$  and neutrophils to 1.92  $\times 10^9/L$  3 days after the second vaccination. Seven days after the second vaccination, they had returned to the normal range. There was no fever, flu-like symptoms, sweating, or tachycardia, which are suggestive of infection, and the CLZ regimen was stable before and after the vaccination. Following the regulations of the Clozaril Patient Monitoring Service Japan, because her ANC dropped from green ( $>2.00 \times 10^9/L$  ANC) to dark amber (from 1.99 to 1.50  $\times 10^9/L$  ANC), she required blood tests twice as frequently for 26 weeks. She gave written consent to publish the case report.

There were 5 cases of leukopenia (1 fatal) and 36 cases of neutropenia after COVID-19 vaccinations (Pfizer/BioNTech) in the United Kingdom spontaneous reports received between August 12, 2020, and January

9, 2021 for the mRNA Pfizer/BioNTech vaccine. In our patient, neutropenia was transient without developing agranulocytosis.

International regulations regarding the use of CLZ vary significantly. The Japanese regulations are among the most stringent, requiring an absolute WBC  $4.00 \times 10^9/L$ , ANC  $2.00 \times 10^9/L$ , and hospitalization at initiation.<sup>11</sup> The United Kingdom, Canada, and Australia require an absolute WBC  $3.50 \times 10^9/L$  and ANC  $2.00 \times 10^9/L$ .<sup>11</sup> In the United States, absolute WBC monitoring is not required, and an ANC  $1.50 \times 10^9/L$  is acceptable. In the United States, the criteria of the CLZ Risk Evaluation and Mitigation Strategy are the lowest of most countries: with mild neutropenia ( $1.00\text{--}1.49 \times 10^9/L$ ), patients continue treatment with blood tests 3 times weekly until ANC  $\geq 1.50 \times 10^9/L$ . Once ANC  $\geq 1.50 \times 10^9/L$ , the patient is returned to the last “normal range” ANC monitoring interval. Community initiation of CLZ in these countries is also possible.<sup>11</sup> In Japan, when the absolute WBC count is less than  $4.00 \times 10^9/L$  or ANC is less than  $2.00 \times 10^9/L$  (medium amber), patients are required to take blood tests 2 times a week until returning to the normal range. At less than absolute WBC  $3.50 \times 10^9/L$  or ANC  $2.00 \times 10^9/L$  (dark amber), they continue to take blood tests every week for 26 weeks even after returning to the normal range. In addition, at less than WBC  $3.00 \times 10^9/L$  or ANC  $1.50 \times 10^9/L$ , CLZ is withdrawn.

The risk of stopping CLZ may be greater than the risk of agranulocytosis, especially if CLZ has been used for at least 6 months to a year.<sup>12</sup> In Japan, very restrictive cutoffs including those for absolute WBC and ANC monitoring and the requirement to initiate CLZ in a hospital are used. However, the regulation by the Clozaril Patient Monitoring Service should be flexible in the case of vaccination. Clinicians should be able to decide in consultation with the patient whether national rules about WBC constraints and cessation of CLZ are too stringent and should be followed or not. If the decision is to disregard the regulations, the patient should be informed that this is off-label use.

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## A Case of Hyperpyrexia Associated With Risperidone Microspheres for Injection (II)

**To the Editors:**

Risperidone is a commonly used atypical antipsychotic in managing psychosis,<sup>1</sup> and risperidone microspheres for injection is the first long-acting atypical antipsychotic injection. Since its postmarketing in North America in 2004, its safety and efficacy have been further verified.<sup>1,2</sup> Risperidone microspheres for injection (II) was launched in China in March 2021. As reported in previous studies, the use of atypical antipsychotics may modulate individual body temperature.<sup>3–5</sup> Except neuroleptic malignant syndrome (NMS), hyperpyrexia is a rarely reported adverse event because of atypical antipsychotic treatment. Herein, we present a case of hyperpyrexia associated with risperidone microspheres for injection.

**CASE REPORT**

A 17-year-old drug-naive female adolescent was admitted to our hospital on June 24, 2021, because of “auditory hallucination, persecutory delusion, feeling of being monitored for over 2 months.” No psychological inducement was reported before her onset of illness. Her emotion was flat and had no history of depressive or (hypo)manic episodes. Self-injurious behavior by cutting the wrist

was also observed. She failed to continue her study at school and was taken to our hospital by her parents. After admission, physical examinations of the nervous system were negative. History of psychoactive substance use was denied. No fever, headache, nausea, or disturbance of consciousness was observed during the illness course. Cranial magnetic resonance imaging was normal. Routine and biochemistry examination, as well as antibodies of autoimmune encephalitis, of cerebrospinal fluid was negative. A baseline score of the Positive and Negative Syndrome Scale (PANSS) was 128. According to the criteria of *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, the patient was given a diagnosis of schizophrenia. Given her lack of insight, the long-acting risperidone microspheres for injection (II) monotherapy was prescribed and was injected on June 28 at the right deltoid muscle with a dose of 25 mg. No redness or swelling appeared at the injection site. Although psychotic symptoms gradually improved and the PANSS score reduced to 95, this patient developed fever on the evening of July 8, 10 days after the first injection of risperidone microspheres. At the same night, the patient also experienced transient, mild runny noses and scratchy throats, which disappeared spontaneously the next day. In addition, there were no signs and symptoms of NMS, such as tachypnea, tachycardia, disturbance of consciousness, rigidity, or elevated creatine kinase levels. Her body temperature rose to a maximum of 39.4°C and dropped to normal with oral acetaminophen treatment. No symptoms and signs related to infection were observed. Blood routine test and C-reactive protein, as well as computerized tomography scanning of the lung, were also normal. Her fever recurred continuously for 4 days, and no antibiotic was used as lack of evidence of infection. Consultation of the Infection Department indicated the possibility of drug fever and recommended the discontinuation of the suspected drug. Therefore, the second injection of risperidone microspheres was canceled and replaced by oral aripiprazole for antipsychotic treatment, the dose of which was gradually titrated up to 17.5 mg per night. In the next week, no fever was observed, and the PANSS score was 81 on July 15. The patient was then discharged. In the first 2-week follow-up visit, the patient was free from fever and her psychotic symptoms further improved. The dynamic change of body temperature was shown in Figure 1.

**DISCUSSION**

Herein, we report a case of hyperpyrexia secondary to treatment with risperidone microspheres for injection, which has the