



No adverse events were observed in clozapine-treated patients on extended hematologic monitoring intervals during the coronavirus pandemic in four psychiatric centers in Japan

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Abstract

Aim: As an emergency measure during the coronavirus disease pandemic, the monitoring interval for clozapine use was temporarily extended beyond the regulatory requirement in Japan, which is the safest monitoring interval worldwide. In this study, we aimed to explore the effect of this measure on patients undergoing clozapine treatment.

Methods: This retrospective chart review study included patients with treatment-resistant schizophrenia (TRS) who were undergoing clozapine treatment at four psychiatric institutions in Japan. Demographic characteristics and clinical information of these patients were collected on April 27, 2020, when Japanese psychiatrists were virtually allowed to prescribe clozapine beyond the regulatory requirement. Furthermore, information of adverse events related to the emergency measure was collected and analyzed.

Results: Of the 41 patients with TRS included in this study, 19 patients underwent extended hematological monitoring during clozapine treatment. No psychiatric or hematological adverse events were observed in the patients during the extended monitoring interval.

Conclusion: This study suggested that there were few adverse events of clozapine-treated patients related to emergency measures in Japan. However, hematological monitoring intervals during clozapine treatment have been emergently extended worldwide; hence, it is necessary to verify the results of these measures.

KEYWORDS

clozapine, coronavirus, COVID-19, schizophrenia, treatment-resistant schizophrenia

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1 | INTRODUCTION

Clozapine is currently the most effective antipsychotic for treatment-resistant schizophrenia (TRS).¹ The clinical guidelines in several countries,^{2,3,4} including Japan,⁵ recommend clozapine for the management of TRS. Although clozapine treatment is clinically useful, it is associated with agranulocytosis, a serious life-threatening adverse event.⁶ Hence, frequent hematological monitoring is needed during clozapine treatment for early detection of agranulocytosis. The regulatory requirement for hematological monitoring during clozapine treatment in Japan is the most frequent and safest worldwide.

In Japan, the hematological monitoring interval is regulated at a maximum of 7 days when the clozapine treatment period is 1–26 weeks and a maximum of 14 days when the period exceeds 26 weeks.⁷ The frequency of hematological monitoring adopted in a relatively large number of countries is weekly for the first 18 weeks and once a month thereafter.¹

One of the reasons for the strict national regulations regarding the monitoring of patients undergoing clozapine treatment could be a higher frequency of clozapine-induced agranulocytosis reported in Japanese clinical trials than in clinical trials from Europe and the United States.⁸ Another reason is the late launch of clozapine in Japan. In Japan, clozapine has been available since 2009; hence, the experience of psychiatrists regarding clozapine treatment is limited.¹ However, prescribing data have been accumulated for >10 years, and no deaths due to agranulocytosis in >1800 clozapine-treated cases were reported in a postmarketing surveillance in Japan.⁹ To reduce the burden on patients undergoing frequent hematological monitoring, the necessity of reconsidering the hematological monitoring interval during clozapine treatment has been discussed in Japan.¹⁰

An outbreak of coronavirus disease (COVID-19) emerged in China in the late 2019 and became a pandemic by 2020. Under these circumstances, on March 23, 2020, the document “Clozapine - Emergency protocol for: Patients on monthly monitoring”¹¹ published by the Royal College of Psychiatrists recommended to extend the hematological monitoring interval for patients undergoing clozapine treatment and meeting the following criteria: drug continuation for >1 year, absolute neutrophil count never <2000/ μ L, no safe access to hematological testing, and a high risk of deterioration of psychosis after discontinuing clozapine treatment.

Subsequently, the consensus statement on the use of clozapine during the COVID-19 pandemic¹² was published online on April 3, 2020. It recommended that the frequency of hematological monitoring during clozapine treatment can be reduced to once every 3 months.

In Japan, on April 10, 2020, the document titled “Requests for the emergency measures regarding monitoring interval of clozapine use when requesting to refrain from going out or invoking lockdown instruction by the government”¹³ was submitted to the officer in charge of the Ministry of Health from the chief directors of four academic societies—the Japanese Society of Psychiatry and Neurology, the Japanese Society of Clinical Neuropsychopharmacology, the

Japanese Society of Neuropsychopharmacology, and the Japanese Society of Schizophrenia Research.

This document, in consideration of the maximum recommended hematological monitoring interval of 14 days during clozapine treatment in Japan, which was half of that recommended in the United Kingdom in normal circumstances, recommended an extension of the monitoring interval of up to 42 days when the clinical criteria proposed by the Royal College of Psychiatrists¹¹ were met. An additional condition that emergency measures must be conducted under the lockdown or any similar instruction by the government was included in the abovementioned Japanese academic societies’ document.¹³ This extended monitoring interval was also half of that recommended in the United Kingdom during the COVID-19 pandemic.

Subsequently, all doctors certified to prescribe clozapine received an e-mail from the center-in-charge of clozapine use in Japan on April 27, 2020, and the hematological monitoring interval during clozapine treatment was virtually extended up to 42 days.

However, the effect of this emergency measure on patients undergoing clozapine treatment is uncertain. Hence, in this study, we aimed to explore the psychiatric and hematological adverse events in patients undergoing extended hematological monitoring during clozapine treatment due to the COVID-19 pandemic and verify the validity of this urgent measure based on retrospective chart review in four psychiatric centers in Japan.

2 | METHODS

2.1 | Participants

This retrospective chart review study included patients with TRS undergoing clozapine treatment at four psychiatric institutions in Japan—Osaka University Hospital (OUH), Osaka Psychiatric Medical Center (OPMC), Asakayama General Hospital (AGH), and Kosaka Hospital (KH). All patients were diagnosed with TRS based on the Japanese clinical guidelines⁷ by certified psychiatrists and prescribed clozapine. Demographic characteristics and clinical information of these patients, including age, sex, usage, and duration of clozapine treatment, were collected on April 27, 2020, when Japanese psychiatrists were virtually allowed to prescribe clozapine beyond the regulatory requirement.

2.2 | Definitions of treatment-resistant schizophrenia

Clozapine was prescribed for patients with TRS. The diagnostic criteria of TRS included poor response and tolerance to other antipsychotics based on the clozapine pharmaceutical reference in Japan.⁷ The poor response criterion was defined as the failure to respond (never reached ≥ 41 points in the Global Assessment of Functioning) to a sufficient dose (>600 mg/d chlorpromazine equivalent) of at

least two well-tolerated antipsychotics with sufficient treatment duration (at least 4 weeks).¹⁴ The poor tolerance criterion was defined as the failure to adequately respond to monotherapy of at least two antipsychotics due to failure in increasing the adequate treatment dose for reasons such as the occurrence or worsening of moderate or severe tardive dyskinesia, tardive dystonia, or other tardive extrapyramidal symptoms or occurrence of uncontrollable parkinsonism, akathisia, or acute dystonia.¹⁴

2.3 | Statistical analyses

We used the chi-square test and Fisher's exact test to compare the demographic and clinical data of patients treated at the four psychiatric centers and analyze the adjusted standardized residuals. Analysis of variance was used to determine whether differences existed among the four psychiatric centers with regard to patient characteristics, and the Bonferroni post hoc test was used for adjusting multiple comparison situations. The threshold for significance was set at $P = .05$. Statistical analyses were conducted using SPSS software version 25.0.

3 | RESULTS

The demographic and clinical characteristics of patients with TRS undergoing clozapine treatment on April 27, 2020, are shown in Table 1. The Japanese government declared a state of emergency from April 7, 2020, in the Osaka Prefecture, where the psychiatric centers of this study are located. The state of emergency was lifted on May 21, 2020. As of April 27, 41 outpatients with total TRS were being treated with clozapine at OUH ($N = 9$), OPMC ($N = 16$), AGH ($N = 11$), and KH ($N = 5$). Almost all ($N = 40$, 97.5%) patients were treated with clozapine due to poor response to antipsychotics, and only one patient was treated with clozapine due to poor tolerance. Sex, age, and clozapine dosage were not statistically different among patients treated at the four institution. However,

a significant difference was observed in the duration of clozapine therapy ($P = .019$); patients treated at OUH had significantly longer duration of clozapine therapy than those treated at AGH and KH ($P = .049$ and $P = .038$, respectively, after Bonferroni correction). Among the 41 outpatients, 37 (90.2%) patients met the recommended conditions proposed by the Japanese academic societies¹³; however, four (9.8%) patients did not meet the absolute neutrophil requirements. The proportion of patients who met the condition for extending the monitoring interval varied in each center ($P = .016$); a significantly smaller proportion of patients met the condition for extending the monitoring interval at OUH than at other institutions ($P = .0035$). Of the 37 patients who were eligible for extension, 19 (51.4%) patients underwent extended hematological monitoring during clozapine treatment beyond the regulated 14 days. The conduction rate of the extension measures varied among the psychiatric centers ($P = .007$); the rate was significantly large at OUH ($P = .0047$), whereas it was small at OPMC ($P = .0026$). No psychiatric or hematological adverse events were observed in these patients. Fortunately, none of these outpatients developed COVID-19 during the state of emergency.

4 | DISCUSSION

In this retrospective chart review, we analyzed the clinical data of patients with TRS undergoing clozapine treatment at four psychiatric centers in Japan under the emergency state declared the government against the COVID-19 pandemic. The differences in the conduction rate of the extension measures for clozapine monitoring among surveyed institutions could be reflecting the difference in patients' background (such as the duration of clozapine treatment and proportion of patients who met the condition for extending the monitoring interval) and the position of hospital (OUH is attached to a university; thus, there are many patients in other clinical departments, yielding increased contact opportunities among patients). Additionally, according to doctors in charge of these patients, the following reasons for not extending monitoring intervals were

TABLE 1 Summary of clozapine-treated outpatients in each hospital as of April 27, 2020

| | OUH | OPMC | AGH | KH | P value |
|--|---------|-----------|----------|--------|-------------------|
| Number of patients (M/F) | 9 (5/4) | 16 (11/5) | 11 (3/8) | 5(1/4) | .103 |
| Mean age (y) | 44.4 | 40.1 | 33.8 | 41 | .193 |
| Mean clozapine dosage (mg/d) | 422 | 378 | 335 | 385 | .618 |
| Mean duration of clozapine therapy (mo) | 83.6 | 57.3 | 45.5 | 34.6 | .019 |
| Number of patients with qualification for expanded monitoring interval | 6 | 16 | 11 | 4 | .016 ^a |
| Actual number of patients undergoing expanded monitoring | 6 | 4 | 7 | 2 | .007 ^b |
| Number of psychiatric or hematological adverse events | None | None | None | None | |

Abbreviations: AGH, Asakayama General Hospital; KH, Kosaka Hospital; OPMC, Osaka Psychiatric Medical Center; OUH, Osaka University Hospital.

^aCalculated based on proportion of all patients in each hospital.

^bCalculated based on proportion of qualified patients for expanding interval in each hospital.



mentioned: patients or patients' family wishing to visit the hospital as usual in spite of the COVID-19 pandemic, patients frequently visiting the hospital for occupational therapy, and unstable psychiatric symptoms of patients.

No psychiatric or hematological adverse events in patients undergoing extended hematological monitoring during clozapine treatment were observed in this study.

The regulatory requirement for hematological monitoring during clozapine treatment in Japan is the most frequent (at least once every 2 weeks) worldwide. One of the reasons for this strict regulation was the high frequency of clozapine-induced agranulocytosis in Japanese clinical trials.⁸ However, in 2017, the frequency of clozapine-induced agranulocytosis dropped to approximately 0.8%, which was similar to that reported in Europe and the United States.⁸ The baseline risk of severe neutropenia during clozapine administration was estimated to be 1.3% overall, with peak risk around 1 month after initiation and substantial decline in risk at 18 weeks.¹⁵ Afterward, the risk of neutropenia was estimated to be 0.70/1000 patient-years for the clozapine treatment period of 6-12 months and 0.39/1000 patient-years after 12 months from clozapine initiation.¹⁶ This risk was considered very similar to that with other first-generation antipsychotics (0.1-1.1/1000 patients-years).¹⁶ However, the therapeutic approach for drug-induced agranulocytosis had progressed compared to that in the 1960-1970s, when clozapine was developed and verified worldwide. Patients treated with hematopoietic growth factors were reported to have a shorter duration of neutropenia and a lower proportion of infectious or fatal complications than patients without treatment.¹⁷ The restrictions on clozapine use were originally stricter in Japan than in other countries; thus, the hematological monitoring interval during clozapine treatment in Japan was only extended to a level similar to that in other countries due to emergency measures against the COVID-19 pandemic. No particular adverse events were observed in this study. Hence, this study suggests that hematological monitoring interval during clozapine treatment should be reappraised¹⁸ as frequent monitoring is a cause for clozapine underutilization in Japan.¹

However, in a previous study, patients diagnosed with a mental disorder had an increased risk of COVID-19, especially in those diagnosed with schizophrenia.¹⁹ This could be explained by the overlapping biological factors of schizophrenia and COVID-19.¹⁹ One of the common biological factors was inflammation, which has been reported to play a role in the pathogenesis of schizophrenia²⁰ and in the systemic manifestations of COVID-19.²¹ In addition, patients with schizophrenia and COVID-19 were reported to have higher rate of mortality and hospitalization,¹⁹ which might have resulted from medical comorbidities and a variety of socioeconomic and disease-related factors.¹⁹ For instance, individuals with mental disorders have a higher risk of substance use disorders than the general population.¹⁹ In particular, tobacco smoking was highly prevalent among patients with schizophrenia compared to the general population,²² which accelerated the pulmonary pathology risk, leading to severe COVID-19.¹⁹ In addition, patients receiving clozapine were reported to be significantly more susceptible to COVID-19 than patients

receiving other antipsychotics.²³ Furthermore, clozapine-treated patients were reported to have a higher risk of pneumonia and pneumonia with fatal outcomes than patients treated with other second-generation antipsychotics.²⁴ Taken together, these results suggest the need for rigorous consideration of clozapine-treated patients during the COVID-19 pandemic. Thus, the Japanese emergency measures on clozapine monitoring against the COVID-19 pandemic were considered appropriate from the viewpoint of reducing hospital visits for clozapine-treated patients and thereby their chances of exposure to the virus.

COVID-19 imposed critical challenges for medical care worldwide.²⁵ The effects of the pandemic and related restrictions on healthcare contact are likely to be long-lasting and wide-ranging.²⁵ The restrictions related to the COVID-19 pandemic have urged clinicians and patients to reappraise medical care.²⁵ For instance, the pandemic situation allowed the consideration of novel blood monitoring via point-of-care devices, and the development and improvement of these devices could be important for improving access to clozapine.²⁶ Novel approaches for assessing patients with telemedicine have been rapidly adopted, allowing patients with symptoms of infection, whether due to suspected neutropenia or COVID-19, to contact a healthcare worker as soon as possible for further guidance without clinic visits.²⁶ It could be necessary to reconsider the clozapine treatment system, such as reconsideration of the hematological test system and monitoring frequency and remote examination for early detection of cold symptoms, for the coming time of coexistence with the novel coronavirus.

Hematological monitoring intervals during clozapine treatment have been extended worldwide during the COVID-19 pandemic based on the abovementioned documents.^{11,12} Thus, it is necessary to analyze the data of patients undergoing extended hematological monitoring during clozapine treatment in detail and carefully observe the occurrence of any adverse events, yielding new insights into clinical practice regarding clozapine treatment.

This study has several limitations. First, due to the retrospective nature of this study, the accuracy of patient information was based on the quality of the records in each institution's patient files. Second, this study included a relatively small sample size and limited number of institutions, especially limited to Osaka Prefecture in Japan; our findings could not reflect the general situation in Japan. Therefore, future studies including larger sample sizes and more institutions in Japan or the world are necessary. Another concern was the omission of inspection for COVID-19, particularly asymptomatic cases that could not be captured in regular clinical settings.

In conclusion, the hematological monitoring interval during clozapine treatment was temporarily extended beyond the regulatory requirement in Japan due to the COVID-19 pandemic. No psychiatric or hematological adverse events were observed in clozapine-treated patients in this study. Hematological monitoring intervals during clozapine treatment have been extended worldwide during the pandemic; hence, it is necessary to analyze the data of patients undergoing extended hematological monitoring interval

during clozapine treatment in detail and carefully verify the effects of these emergency measures.

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CONFLICT OF INTEREST

The authors of this article declare no conflict of interest.

AUTHOR CONTRIBUTIONS

MH, MF, and MI designed the study and wrote the protocol and first draft of the manuscript. MH, MF, KK, KY, YN, DN, SM, SK, TH, SN, AU, TS, KI, HT, AM, YT, NT, MS, YK, KK, and MH recruited and briefed patients and obtained informed consent. All authors collaborated in writing and editing the manuscript and approved the final draft.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

This study was approved by the Ethics Committee of Osaka University Hospital, Japan.

INFORMED CONSENT

The study protocol was fully explained to all patients by the doctors in charge before recruitment. Informed consent was obtained from all patients included in this manuscript, and privacy protection has been completely ensured in the case description.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

N/A.

ANIMAL STUDIES

N/A.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The raw data belonged to the present study cannot be made publicly available, because the disclosure of personal data was not included in the research protocol of the present study.

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