PSYCHIATRIA ET NEUROLOGIA JAPONICA

Debate

Can the Examination Interval during Clozapine Administration be Extended?: Discussion of Experience in Temporarily Extending the Examination Interval under the Declaration of Emergency to Prevent the Spread of the Novel Coronavirus

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Abstract

Clozapine is a clinically useful drug for patients with treatment-resistant schizophrenia; however, it has a serious side effect of agranulocytosis. Therefore, for its early detection and improved prognosis, frequent blood monitoring is required. Under the government-issued declaration of emergency to prevent the spread of the novel coronavirus, the blood monitoring interval for clozapine in Japan was temporarily extended. In this article, we outlined clozapine treatment overseas, described the circumstances leading to extension of the blood monitoring interval under the declaration of emergency in Japan, and discussed the situation in our department and the need to prolong the examination interval during clozapine administration. The spread of the novel coronavirus was unprecedented and the implementation of preventative measures took time. However, we expect the relevant organizations to promptly respond to the next epidemic. In addition, the permanent extension of the examination interval during clozapine administration needs to be discussed in general.

Keywords：schizophrenia, clozapine, COVID-19

Introduction

Clozapine is the only drug currently approved for the treatment of treatment-resistant schizophrenia. A network meta-analysis of patients with schizophrenia reported that clozapine had the highest efficacy compared with other antipsychotics in improving overall psychiatric symptoms 3). There is a large body of high-quality evidence that clozapine treatment is beneficial compared with other treatments. The current situation is that "treatment-resistant schizophrenia = clozapine treatment" in all guidelines in various countries, and The Japanese Society of Neuropsychopharmacology's "Guidelines for the Pharmacological Treatment of Schizophrenia" also states that clozapine treatment in treatment-resistant schizophrenia is useful and strongly recommended 9).

Although clozapine is a clinically useful drug, it has a serious side effect of agranulocytosis. Thus, blood monitoring is required for the early detection of agranulocytosis or its signs, and the prevention of a serious prognosis when it occurs 9). In Japan, the Clozaril Patient Monitoring Service (CPMS) is in operation. Clozapine should be administered to registered patients at registered medical institutions and pharmacies with physicians and pharmacists registered with the CPMS only when all the criteria specified in the CPMS, such as blood tests, are met 10). Clozapine was launched in Japan in 2009, but the use of clozapine has a higher threshold for treatment than other antipsychotics for several reasons, including concerns about serious side effects, the registration system at medical institutions, and the burden of collaboration with hematologists and frequent blood monitoring 5). It is estimated that only 3-4% of patients with treatment-resistant schizophrenia receive clozapine treatment 5). Among the aforementioned reasons, frequent blood monitoring is considered to be a major burden for patients and medical personnel, especially since it increases the number of medical examinations.

In Japan, the maximum interval between tests of leukocyte and neutrophil levels is 7 days for clozapine treatment from 1 to 26 weeks, and 14 days for treatment longer than 26 weeks (however, if leukocyte and neutrophil levels fall below the prescribed values, testing is required twice a week) 10). The protocol for blood glucose and HbA1c testing requires blood glucose measurements at a minimum interval of 14 days for protocol C (diabetes or strongly suspected diabetes), with a

longer interval (up to 84 days) if blood glucose and HbA1c levels are closer to the normal type. Therefore, many outpatients on clozapine therapy require visits and blood tests every 14 days to determine leukocyte and neutrophil levels.

Clozapine is used in about 100 countries around the world, and all of them require periodic blood tests, but only the United States, the United Kingdom, Australia, Canada, South Korea, and Japan have a CPMS (or similar) system in place 12). The major difference between Japan and other countries is that in those countries, blood testing is basically left to health care providers, and, not only in countries that do not implement a CPMS-like system, but even in those that do, warnings by CPMS (or similar) centers are loose. For example, in the U.S., warnings are issued only 45 days after the test date has passed, and in Korea, only patient registration is performed and blood tests are not checked 12). There is no need to report violations to the regulatory authorities or to have the registration of a medical institution or health care professional revoked, as is the case in Japan. On the other hand, many generic versions of clozapine are sold overseas, and each distributor has its own CPMS (or similar) center. Therefore, even if the registration is revoked by one company, it is possible to use another company's product 11). In addition, in Japan, diabetes mellitus is a major cause of death and disability. Diabetes mellitus is a contraindication in principle in Japan, but is not a contraindication in other countries, and no other country has implemented blood glucose monitoring.

The usual inspection intervals 11) for each country implementing a CPMS (or similar) system are shown in Table 1. Once a certain period of time has elapsed after the introduction of clozapine, the testing interval will be every 4 weeks except in Japan, where the interval is every 2 weeks, which is the most safety-conscious interval. It has been pointed out that the background to the establishment of such a safety-conscious testing interval is that the frequency of clozapine-induced agranulocytosis observed in Japanese clinical trials and clinical studies was higher than that reported in Europe and the United States up to that time 14). However, the frequency of clozapine-induced agranulocytosis in Japan as of 2017 was approximately 0.8%, which is not significantly different from the frequency assumed in the West 14). It has been pointed out that there is a need for active consideration of test intervals during clozapine administration 4)14). Many clinicians may have doubts about the current

situation in which the maximum interval between examinations is 2 weeks, which imposes a burden on medical practitioners who are forced to see patients frequently, and also imposes a heavy burden on patients who are forced to visit the hospital frequently. Since the launch of clozapine in 2009, more than 10 years of prescribing experience and data have been accumulated in Japan, and we ourselves have been wondering whether we could consider extending the examination interval by making use of this experience and data.

Since then, a new type of coronavirus infection has spread throughout the world, including to Japan, leading to the declaration of a state of emergency by the Japanese government. Under the emergency declaration, the interval between tests during clozapine administration was effectively extended in Japan, including at the Department of Neurology and Psychiatry, Osaka University Hospital (hereafter referred to as "our department"). This inspired us to reexamine the possibility of extending the interval between tests. In this article, we describe the measures taken to extend the examination interval during clozapine administration in the world at the time of the spread of the novel coronavirus infection, the measures taken to extend the examination interval in Japan, and our own experience. We discuss the necessity of extending the examination interval during clozapine administration.

I. Testing intervals during clozapine administration in other countries in response to the spread of novel coronaviruses

Regarding the global response to the restrictions imposed by the spread of the novel coronavirus infection, a document entitled "Clozapine: Emergency protocol for patients on monthly monitoring" 15) was published on March 23, 2020, at the Institute of Psychiatry, UK, and mentioned the possibility of extending the testing interval up to 12 weeks for patients treated with clozapine who meet certain requirements. Subsequently, in the Consensus on the Use of Clozapine published on April 3 of the same year 13), it was recommended that the testing interval be every three months. On April 16 of the same year, the New York State Office of Mental Health in the U.S. posted a letter 7) endorsing prescribers' adherence to the aforementioned consensus recommendations 13).

(The document was linked from the American Psychiatric Association's Practice Guidance for COVID-19 page.)

Although it is difficult to obtain a complete picture of clozapine treatment

worldwide because of the involvement of multiple pharmaceutical companies, including generic companies, it is assumed that these trends have led to the acceptance of longer intervals between tests.

II. Requests from academic societies regarding examination intervals in Japan and subsequent responses

With the spread of the novel coronavirus infection, we have often received requests from patients receiving clozapine treatment and their families to extend the intervals between visits to our outpatient clinic due to concerns about the risk of infection. Under these circumstances, on April 10, 2020, The Japanese Society of Psychiatry and Neurology, Japanese Society of Clinical Neuropsychopharmacology, The Japanese Society of Neuropsychopharmacology, and Japanese Society of Schizophrenia Research submitted "The Request for Urgent Action Regarding Clozapine Testing Intervals in the Event of a Request for Voluntary Refraining from Going Out or Lockdown Orders" 8) to the Director of the Drug Safety Division and the Director of the Drug Evaluation and Control Division, Pharmaceuticals and Consumer Health Bureau, Ministry of Health, Labour and Welfare under the names of the presidents of the four societies. The request was made to extend the intervals between blood monitoring tests for patients receiving treatment with clozapine when certain conditions are met, because the act of visiting a medical institution itself poses a risk of community-acquired and nosocomial infections to patients in the community due to the spread of the novel coronavirus infection. This is a Japanese recommendation based on the fact that, as mentioned above, after an emergency situation was declared, the United Kingdom extended the testing interval to a maximum of 12 weeks (84 days) to reduce patients' exposure to novel coronaviruses when certain requirements are met ((1) granulocytes have never been below 2,000/microL in the past, (2) safe visits to registered medical facilities are difficult, and (3) there is a high possibility of symptom exacerbation if clozapine treatment is discontinued). In this proposal, the following requirement was added to the above three requirements set by the British Psychiatric Institute: After the government declares a state of emergency based on the Special Measures Law, the governor of the prefecture where the patient resides or where the registered medical institution is located has issued a request to refrain from leaving the house or a lockdown order. Therefore, the total number of requirements is now four. In addition, in

this proposal, regarding the inspection interval, considering that the usual inspection interval in Japan is 14 days maximum, which is half of the inspection interval in the UK, the extended inspection interval is also half, up to a maximum of 42 days.

Subsequently, in an e-mail dated April 27, 2020, the CPMS Center sent a "Request to Healthcare Professionals" to CPMS-registered healthcare professionals, emphasizing that since the content of the recommendations of the academic societies constitutes a deviation from the attached document and CPMS regulations, it is the responsibility of the prescribing physician to decide whether to extend the intervals between tests based on the academic societies' recommendations. Prescribing physicians should carefully and thoroughly evaluate the risks and benefits of each case and make a decision. We were notified that it would not be reported as a CPMS violation if the test interval was extended in accordance with this emergency response. This effectively allowed the testing interval to be extended up to a maximum of 42 days during clozapine administration.

III. Practical Response in Our Department

Osaka Prefecture, where our department is located, was designated as an emergency area by the government from April 7, 2020 to May 21, 2020. Nine patients with treatment-resistant schizophrenia were treated with clozapine as outpatients in our department as of April 2020, all of whom had been on clozapine therapy for more than 52 weeks. All patients met the "criteria for poor reactivity" 9) and No patients were introduced to clozapine because they met the "criteria for intolerance" 9). Information on outpatients receiving clozapine treatment as of April 27, 2020, as reported by the CPMS center, is shown in Table 2. Six patients met the recommendations and could receive an extension of the interval up to 42 days, while three patients could not receive an extension of the interval due to granulocyte requirements. Four of the six patients who were deemed eligible for extension actually had their intervals extended to 42 days, and the remaining two patients had their intervals extended to 28 days due to reasons such as the succession of the physician in charge. However, the emergency declaration was lifted in Osaka Prefecture on the next outpatient day, so the examination interval was restored to 14 days. Fortunately, none of the nine clozapine-treated outpatients in our department contracted the novel coronavirus infection while the state of emergency was declared, and none of

the patients whose intervals were extended experienced adverse events such as worsening psychiatric symptoms or abnormal laboratory values. Written consent for case reporting was obtained from all nine patients mentioned in this report, and privacy was carefully protected in the case descriptions.

IV. Discussion

This report describes our experience with the use of clozapine in our department under a state of emergency declared in response to the spread of the novel coronavirus infection, as well as global trends. During the spread of the novel coronavirus infection, patients and their families often requested longer intervals between tests. The extended examination intervals are in line with social conditions that encourage patients to refrain from leaving the house, and I got the impression that patients and their families were generally favorable to the extended intervals. The patients were able to reduce their burden by reducing the number of visits to the hospital, and the medical personnel were able to reduce their burden by reducing the number of medical examinations and the associated inputting of laboratory values due to the extended examination intervals.

As described in the recommendations 8), the incidence of agranulocytosis and granulocytopenia caused by clozapine was high during the first 18 weeks of treatment and significantly decreased thereafter, with new cases of agranulocytosis and neutropenia becoming rare, especially after 52 weeks 6). On the other hand, as also recommended by the academic societies, patients taking clozapine generally have a higher risk of pneumonia and associated death 1), and have a higher frequency of risk factors associated with severe novel coronavirus infection (physical complications, obesity, smoking history, and others) 7), suggesting that it is important that patients receiving clozapine therapy, in particular, should reduce their exposure to novel coronaviruses. A study published after the recommendations of the Japanese Society reported that patients taking clozapine were significantly more susceptible to the novel coronavirus infection than patients taking other antipsychotic drugs 2). Although the outlook for the prevalence of the novel coronavirus infection in the future is uncertain, at least in the "with corona era", it is reasonable to reduce the intervals between hospital visits of patients taking clozapine to reduce their exposure to novel coronaviruses.

Compared with other countries, the testing interval in Japan is set

according to the most safety-conscious standard. If no adverse events have occurred in Japan as a result of the extension of the test interval at this time, we can consider extending the test interval on a regular basis. In fact, in the United States and the United Kingdom, for example, the testing interval has already been extended compared to that at the time of the launch of clozapine as experience with its use accumulates 4). On the other hand, although not related to the novel coronavirus infection, there was a patient who was unable to take clozapine for one day because public transportation was stopped due to a natural disaster, making it difficult for the patient to go to our department on the day of the examination (the patient was able to be prescribed clozapine after examination the next day, but his insomnia and mental condition worsened after discontinuing clozapine). Although it is obvious that clozapine treatment carries a risk of fatality and requires careful follow-up, if requirements are set such as 52 weeks after the start of clozapine treatment, for example, there may be room for consideration of flexible measures such as allowing prescriptions for several days as an emergency measure when the patient is unable to come to the hospital.

This episode was unprecedented, and it took 21 days from the declaration of a state of emergency by the government on April 7, 2020, to the CPMS response on April 27 of the same year. We would like to see further studies by academic societies and the Ministry of Health, Labour and Welfare so that we can respond promptly in the event of another outbreak of the novel coronavirus infection.

Conclusion

In this article, we reviewed the situation of clozapine treatment overseas, introduced the circumstances that led to the extension of blood monitoring intervals in Japan under the government's declaration of a state of emergency following the spread of the novel coronavirus infection, described the situation in our department, and discussed the appropriateness of testing intervals during clozapine administration based on our experience. The appropriateness of the intervals between blood tests during clozapine administration was also discussed based on the experience of our department. Although the spread of the novel coronavirus infection was unprecedented and it took time for the government to take action, we hope that the organizations concerned will consider taking prompt action in the event of another outbreak of the novel coronavirus infection, and we hope that

this article will provide an opportunity to reconsider the appropriateness of intervals between tests during clozapine administration.

There are no conflicts of interest to disclose in connection with this paper.

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表 1　クロザピンの通常の検査間隔

	アメリカ	イギリス	オーストラリア	カナダ	韓国	日本
検査間隔	週 1 回/6 ヵ月間 2 週 1 回/6 ヵ月以降 4 週 1 回/1 年以降	週 1 回/18 週間 2 週 1 回/18 週以降 4 週 1 回/1 年以降	週 1 回/18 週間 4 週 1 回/18 週以降	週 1 回/26 週間 2 週 1 回/26 週以降 4 週 1 回/52 週以降	週 1 回/18 週間 4 週 1 回/18 週以降	週 1 回/26 週間 2 週 1 回/26 週以降

（文献 11 をもとに著者作成）

Table 1: Normal testing intervals for clozapine

United States / United Kingdom / Australia / Canada / South Korea / Japan

Test interval

Once a week / 6 months

Once every 2 weeks / 6 months or later

Once every 4 weeks / 1 year or later

Once a week / 18 weeks

Once every 2 weeks / 18 weeks or later

Once every 4 weeks / 1 year or later

Once a week / 18 weeks

Once every 4 weeks / 18 weeks or later

Once a week / 26 weeks

Once every 2 weeks / 26 weeks or later

Once every 4 weeks / 52 weeks or later

Once a week / 18 weeks

Once every 4 weeks / 18 weeks or later

Once a week / 26 weeks

Once every 2 weeks / 26 weeks or later

(Prepared by the author based on Reference 11)

表 2　緊急事態宣言下のクロザピン治療中の当科外来患者

	年齢	性別	内服量	内服期間	検査間隔延長
症例 1	20 歳代	男	350 mg	3 年 9 ヵ月	可能
症例 2	30 歳代	女	400 mg	6 年 1 ヵ月	可能
症例 3	30 歳代	男	400 mg	8 年 0 ヵ月	不可*
症例 4	40 歳代	男	600 mg	9 年 5 ヵ月	可能
症例 5	40 歳代	女	300 mg	6 年 7 ヵ月	不可*
症例 6	40 歳代	男	600 mg	8 年 8 ヵ月	可能
症例 7	50 歳代	男	400 mg	9 年 2 ヵ月	可能
症例 8	50 歳代	女	150 mg	2 年 6 ヵ月	可能
症例 9	60 歳代	女	600 mg	8 年 6 ヵ月	不可*

*顆粒球が 2,000/μL を下回った既往があるため延長不可

Table 2: Outpatients in our department on clozapine treatment under emergency declaration

Age / Sex / Dose / Duration / Extended examination interval

Case 1: 20s, male, 350 mg, 3 years and 9 months, possible

Case 2: 30s, female, 400 mg, 6 years and 1 month, possible

Case 3: 30s, male, 400 mg, 8 years and 0 months, not possible*

Case 4: 40s, male, 600 mg, 9 years and 5 months, possible

Case 5: 40s, female, 300 mg, 6 years and 7 months, not possible*

Case 6: 40s, male, 600 mg, 8 years and 8 months, possible

Case 7: 50s, male, 400 mg, 9 years and 2 months, possible

Case 8: 50s, female, 150 mg, 2 years and 6 months, possible

Case 9: 60s, female, 600 mg, 8 years and 6 months, not possible*

*No extension due to a history of granulocyte counts below 2,000/μL.