

Clozapine-induced myocarditis: Follow-up for 3.5 years after successful retrial

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Abstract

Schizophrenia patients have significantly lower life expectancy than the general population. Clozapine is the most effective antipsychotic to reduce the mortality rate in these patients. Here, we report a schizophrenic patient with clozapine-induced myocarditis and successful retrial. In the first trial, clozapine was discontinued due to myocarditis. In the second trial, the titration rate was slower, and sodium valproate was not coadministered with clozapine. The patient has not developed myocarditis over 3.5 years of observation. It may be possible to take clozapine for a long time even after clozapine-induced myocarditis, and thus improve the life expectancy of schizophrenia patients.

KEYWORDS

clozapine, life expectancy, myocarditis, retrial, sodium valproate

1 | INTRODUCTION

Life expectancy at age 20 years is >20 years shorter in schizophrenia patients than the general population.¹ Long-term cumulative exposure to any antipsychotics reduced the mortality rate in schizophrenia patients.¹ Clozapine is associated with significantly lower long-term all-cause mortality rate than other antipsychotics in schizophrenia, so continuous clozapine treatment is important.² Here, we describe a Japanese man who developed myocarditis after clozapine administration and in whom subsequent retrial with the drug was successful for 3.5 years.

2 | CASE REPORT

A man in his late 20s treated for schizophrenia for >10 years was admitted to Asahi General Hospital due to severe auditory hallucinations and delusions, which did not respond to antipsychotics,

including olanzapine (15 mg), blonanserin (24 mg), and aripiprazole (30 mg). He was a nonsmoker with body mass index (BMI) 25.4. Routine physical and laboratory examinations revealed tachycardia, with pulse 107 beats per minute (bpm). Clozapine was started at 12.5 mg (day 1) and increased gradually: 12.5 mg for 4 days, 25 mg for 3 days, 50 mg for 4 days, 75 mg for 4 days, 100 mg for 1 day, and 50 mg for 1 day. Coadministration of sodium valproate (600 mg) and cross-tapering blonanserin (8–16 mg) and flunitrazepam (1 mg) was performed. His psychiatric symptoms improved markedly. On day 15, he developed high-grade fever (39.3°C), tachycardia with pulse 112 bpm, leukocytosis (9500 cells/μL), and elevated C-reactive protein (CRP, 4.40 mg/dL). On day 17, he experienced chills, and elevated high-sensitive troponin I (356.3 pg/dL, normal range ≤30). Ejection fraction (EF) on echocardiogram was 51%. Clozapine was discontinued due to suspected clozapine-induced myocarditis. On day 18, troponin I was markedly elevated (3168.8 ng/mL). Electrocardiogram (ECG) revealed nonspecific ST-T changes on II, III, aVF, V4–V6 (Figure S1). Echocardiogram showed left ventricular

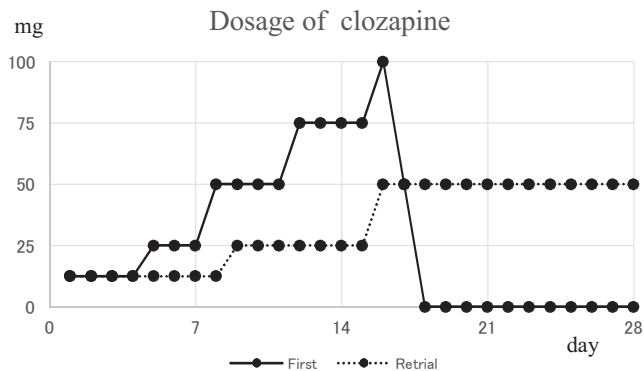


FIGURE 1 The figure shows the dosage of clozapine from days 1 to 28 of the first and second trials. Clozapine was titrated from 12.5 to 25 mg per 3-4 days initially but was titrated from 12.5 to 25 mg per 7-8 days in the retrial

hypertrophy and mild pericardial effusion. Cardioangiography (CAG) showed no coronary artery obstruction or narrowing. Antibodies to coxsackievirus, echovirus, and influenza virus were negative. Chest X-ray and cardiac magnetic resonance imaging (MRI) showed no abnormalities (Table 1).

A diagnosis of myocarditis was made, and the patient was moved to the ICU on day 18. No specific treatment was required. Myocarditis improved rapidly after clozapine cessation, and he was returned to the psychiatric ward on day 24 and discharged from hospital on day 67. However, his auditory hallucinations and delusions were exacerbated after discharge, and he was readmitted on day 77. After explaining the risks, benefits, and alternative therapies, the patient and his parents consented to clozapine retrial from day 89 with a gradual increase in dosage: 12.5-37.5 mg per 1-2 weeks up to 275 mg on day 220 (Figure 1). Olanzapine (20 mg) and flunitrazepam (2 mg) were also administered on the day of retrial, and tapered off over 3-6 weeks. The clozapine dosage on day 240 (day of discharge) was 200 mg. After discharge, clozapine was administered at 150-300 mg, and there has been no recurrence of myocarditis for 3.5 years.

3 | DISCUSSION

Clozapine-associated myocarditis is diagnosed by clinical findings, AND histological evidence of myocarditis, OR (a) elevated serum troponin I or T or CK-MB concentrations, (b) ECG changes, (c) evidence of heart failure on chest X-ray, (d) left or right ventricular systolic dysfunction on echocardiogram, or (e) evidence of myocarditis on MRI.³

In this case, maximum body temperature and pulse first showed abnormalities with elevation of white blood cells (WBC) and CRP. Subsequently, troponin I and CK-MB were elevated. Simultaneously, ECG showed nonspecific ST-T changes and echocardiogram revealed left ventricular hypertrophy and mild pericardial effusion with temporary EF depression. Normal CAG findings excluded coronary

diseases. The coronary and clinical findings suggested myocarditis due to clozapine as viral infections were excluded.

Systematic survey showed that 83% of cases of clozapine-induced myocarditis occurred between days 14 and 21 of treatment with the drug.⁴ In our patient, myocarditis occurred on day 15. Elevation of eosinophil count, an indicator of clozapine-associated myocarditis, tends to be delayed for ≤ 7 days after troponin I/T peak³; eosinophil count elevation was also delayed in our patient. Myocarditis improved after cessation of clozapine, supporting a diagnosis of clozapine-induced myocarditis.

Rapid dose titration, concomitant sodium valproate administration, and older age are risk factors for clozapine-associated myocarditis.⁵ Cumulative clozapine dose >920 mg over 1-9 days doubled the risk associated with <500 mg.⁵ In this case, the cumulative clozapine doses were 225 and 125 mg at first and second administrations, respectively. Neither showed rapid titration. However, Sarathy et al⁶ reported a case of retrial requiring slower titration than our second trial. Slower titration may help to avoid myocarditis. Our patient's only risk factor was sodium valproate coadministration, which may inhibit clozapine metabolism.⁷ Successful rechallenge was likely due to slower titration and cessation of sodium valproate.

The rate of clozapine administration in schizophrenic patients is lower in Japan (0.6%) than other developed countries (5%-30%).⁸ The Ministry of Health, Labour and Welfare is promoting the adoption of clozapine for schizophrenic patients. As psychiatrists and patients consult general practitioners (GPs) for signs and symptoms, including fever of unknown origin (FUO), more GPs will examine schizophrenic patients taking clozapine in future. Although most FUOs in patients taking clozapine are benign, myocarditis and secondary infections due to neutropenia must be excluded.⁹

Life expectancy in schizophrenia patients is reduced partly because of cardiovascular diseases and suicide.^{1,2} Continuous clozapine was reported to reduce the all-cause mortality rate in schizophrenia patients.² The patient described in this report took clozapine for 3.5 years after the retrial. The figures in previous reports were for periods of less than 3 years or were unlisted.^{6,10} Retrial of clozapine is under discussion.¹⁰ This case suggested that even after clozapine-induced myocarditis, clozapine may be taken for a long time to improve life expectancy in schizophrenia patients.

4 | CONCLUSIONS

We reported a case of clozapine-induced myocarditis with successful reintroduction of clozapine. Rechallenge succeeded due to slower titration and cessation of sodium valproate. Clozapine may be taken for a long time even after clozapine-induced myocarditis to improve life expectancy in schizophrenia patients.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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