Continuing Clozapine Treatment in Acute Psychosis With Neutropenia

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Treatment-resistant schizophrenia, or lack of response to treatment, was first described in 1988.1 It is defined as schizophrenia symptoms treated in three phases with different antipsychotics at adequate doses for at least 6 weeks per phase without at least a 20% reduction in symptoms. About one-third of patients with schizophrenia are diagnosed with the treatment-resistant form of the disorder,2 reflecting two illness subtypes: treatment-resistant schizophrenia and treatment-responsive schizophrenia.3

Clozapine is the best evidence-based therapeutic option with an indication for treatment-resistant schizophrenia.4 Results of multiple clinical studies suggest that clozapine is effective in reducing hospital admissions, suicidality, and aggressive behavior when compared with other antipsychotics.5,6 However, it could lead to serious hematological side effects, such as neutropenia or agranulocytosis. According to previous consensus,7 discontinuation of clozapine is recommended with the occurrence of neutropenia, when the white blood cell (WBC) count falls below 3×10³/uL or the absolute neutrophil count falls below 1.5×10³/uL during first-time clozapine use. After considering the benefits and risks, rechallenge after complications are resolved has been occasionally attempted for patients with psychotic symptoms.8

We describe the case of a patient who developed neutropenia after starting clozapine. The patient’s treatment team continued clozapine at lower doses combined with typical antipsychotics. After closely monitoring her absolute neutrophil count, her psychotic symptoms improved without another episode of neutropenia or agranulocytosis.

CASE REPORT

A 41-year-old unemployed, single Asian woman presented to our clinic. She had a history of schizoaffective disorder, with onset at age 27. She had been treated with antipsychotics and mood stabilizers, including haloperidol, sulpiride, clonazepam, quetiapine, olanzapine, risperidone, paliperidone, and aripiprazole, since age 37 but with inadequate treatment response, thereby fulfilling the criteria for treatment-resistant or refractory psychosis.9 She was a hepatitis B carrier with a history of diabetes mellitus under regular medication. No family history of psychosis and no previous head trauma or other organic brain disorders were reported. She had been living in a halfway house in recent years and was hospitalized in the acute psychiatric ward approximately once every 2 years for exacerbated psychosis with disturbing behavior. She refused treatment with ECT.

Despite compliance with the treatment regimen, the patient’s symptoms worsened. Consequently, her treatment team decided to start her on clozapine (50 mg/day) during outpatient assessment, which was 6 days before her hospital admission. Laboratory assessment indicated normal WBC and neutrophil counts (6.23×10³/uL and 3.95×10³/uL, respectively). On admission, which was day 6 of clozapine use, her dosage was titrated to 100 mg/day, with close monitoring, and the patient’s WBC and neutrophil counts were 3.14×10³/uL and 1.66×10³/uL, respectively. On day 7, a drop was detected in both WBC (2.78×10³/uL) and neutrophil (1.48×10³/uL) counts, without any subjective discomfort or signs of infection. Her score on the Naranjo Adverse Drug Reaction Probability Scale was 7, corresponding to a probable adverse clozapine-associated effect of neutropenia.10 The patient maintained clozapine use at lower doses (75 mg/day), after the potential benefits and risks were weighed. Her WBC and neutrophil counts were closely monitored twice a week during the first 2 weeks, and the counts remained within the normal range (4.28×10³/uL and 6.72×10³/uL, respectively, on day 8). The treatment team tapered clozapine to 50 mg/day and combined it with trifluoperazine (5 mg/day) during the third week because the patient began to experience a sore throat and cough.

She was asymptomatic after 4 weeks of treatment and was discharged from the hospital with improved psychotic symptoms. She received regular outpatient follow-up for several months. She remained in remission without any adverse effects under the same regimen, with regular monitoring of her WBC count (>4×10³/uL) and without another episode of neutropenia or agranulocytosis.

DISCUSSION

The above case of treatment-resistant schizophrenia provides a strategy for managing neutropenia during clozapine use by tapering the dosage and combining it with typical antipsychotics. However, continuing clozapine treatment is potentially risky when hematological side effects occur.
Clozapine-induced neutropenia can be divided into three types: pseudo, benign, and malignant. The malignant type raises serious concerns and can necessitate discontinuing clozapine use. Risk factors for developing neutropenia in patients taking clozapine include younger age and male sex, and it also has a higher potential occurrence among people of African origin. Clozapine is virtually the only medication with an evidence-based effect on refractory psychosis. Therefore, under certain conditions, clozapine rechallenge is considered to be the only effective treatment. The risks and benefits of rechallenge and any other options must be weighed carefully. Clozapine has been successfully rechallenged with lithium or granulocyte colony stimulating factor (G-CSF).

Rechallenge of clozapine with lithium to increase the neutrophil count and total WBC count may be beneficial. A brief review suggested that continuing clozapine treatment with lithium in patients with schizophrenia with neutropenia or leukopenia may be a successful strategy. Increased side effects related to lithium and clozapine were not observed.

Clozapine has also been successfully rechallenged after neutropenia in combination with G-CSF. However, the method of use of G-CSF—whether as a single or occasional dose or in regular prophylactic use—was uncertain. Moreover, the risk of side effects caused by G-CSF, including bone pain and autoimmune disorders, should be considered.

One study reported that clozapine, compared with other antipsychotics, is known for contributing to higher risk for neutropenia, even when patients are receiving a number of drugs or have an underlying undetected hematological disorder. Concomitant drug therapy and drug-drug interactions may be underestimated. There are few studies on continuing clozapine use without adjuvant medication. A case report demonstrated that rechallenge with clozapine after 2 days had no adverse effects. One study suggested that clozapine bioactivation caused dose-dependent inhibition of stromal viability, eventually resulting in the death of human bone marrow stromal cells in vitro. Another study showed that clozapine-related neutropenia through cell apoptosis was caused by cells binding nitrenium molecules in vitro and characterized by dose-dependent toxicity.

The present case report adds to the limited evidence on continuing clozapine treatment for psychosis with neutropenia. After considering the benefits and risks of administering nonantipsychotic medication, such as lithium or G-CSF, the treatment team successfully used lower doses of clozapine, combined with typical antipsychotics, in a patient with treatment-resistant schizophrenia following an episode of neutropenia. For optimal treatment of refractory schizophrenia, further investigations should focus on innovative, evidence-based pharmacological strategies.

**REFERENCES**


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