A Case of Agranulocytosis Secondary to Rechallenge With Clozapine Following Severe Neutropenia During Previous Therapy

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Data providing information on outcome in patients rechallenged with clozapine after previous agranulocytosis during clozapine treatment are scarce.[1,2] Clinicians have been urged to publish their cases, since a greater number of cases in the literature may enable the detection of plausible risk factors.

We report the case of a 46-year-old man diagnosed with paranoid schizophrenia and uncontrollable violent behavior who was rechallenged with clozapine after a severe neutropenia during previous therapy.

Case report. When Mr A was admitted to the Refractory Psychosis Unit of our hospital in July 2010, he was taking clozapine 300 mg/d, extended-release quetiapine, olanzapine, haloperidol, lactitol, and omeprazole. He had been taking clozapine for approximately 2 years when admitted to our hospital, and his serum clozapine level was 370 ng/mL. The patient's hematologic parameters at the time were within normal values: absolute neutrophil count (ANC) = 5×10^9/L, hemoglobin 13.4 g/dL, platelets = 192×10^9/L. In addition to his mental illness, he had a past history of resolved alcohol dependence, asymptomatic hemosiderosis, and psychogenic polydipsia. He was also a heavy smoker.

Despite the complex polypharmacy regimen, his psychopathologic state was unsatisfactory. Thus, monotherapy with clozapine was considered, with the dose gradually increased until it was 900 mg/d on October 8, 2010, at which time his serum clozapine level was 423 ng/mL. After 2 weeks of no response, paliperidone up to 15 mg/d was added. The treatment was not effective, so cyproterone was added to restrain his violent behavior. This combination was yielding positive results, but, unfortunately, on January 3, 2011, an ANC of 0.3×10^9/L was found. After consultation with the internal medicine service regarding the clinical situation, clozapine treatment was stopped and granulocyte colony-stimulating factor (G-CSF) was prescribed. No clinical symptoms derived from the neutropenia were recorded.

After treatment with G-CSF, the neutropenia resolved completely (ANC = 20.5×10^9/L on January 9) within 9 days. However, without clozapine and despite the use of high-dose olanzapine, the patient's psychopathologic state worsened rapidly.

After considering the individual's prior response to clozapine and the magnitude of his deterioration upon stopping treatment, the psychiatrist decided to reintroduce clozapine on February 23, 2011. Clozapine was cautiously reintroduced, reaching a dose of 300 mg/d after 3 weeks, while all of the other drugs were maintained equally. One month later, on March 28, Mr A developed agranulocytosis, with an ANC of 0×10^9/L. He was transferred to the internal medicine service, where the neutropenia resolved completely after he received treatment with G-CSF once again (recovery in 10 days). During this period, he suffered from catheter-related suppurative phlebitis in his forearm, which resolved with antibiotic therapy.

As found in previous studies,[1] the second blood dyscrasia occurred more rapidly, lasted a bit longer, and was more severe than the first blood dyscrasia. The case was reported to the Basque Centre of Pharmacovigilance (Galdakao, Spain), where an objective causality assessment using the modified Karch-Lasagna probability scale[3] suggested that the agranulocytosis was definitely related to clozapine.

This case adds to the scarce body of evidence available regarding clozapine rechallenge in patients who have suffered a previous neutropenia. Rechallenge is potentially dangerous, at least for patients who have a history of severe clozapine-related agranulocytosis. If rechallenge is considered, addition of prophylactic G-CSF seems advisable, although no conclusive evidence of its effectiveness is available.[4]

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Conflicts of interest: None reported.
Funding/support: None reported.
J Clin Psychiatry 2011;72(12):1659 (doi:10.4088/JCP.11cr07263)