Managing clozapine-induced neutropenia and agranulocytosis

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Mr. S, age 43, has schizophrenia and been stable on clozapine for 6 years after several other antipsychotic regimens failed. Mr. S also has a history of hypertension, dyslipidemia, and gastroesophageal reflux disorder. His medication regimen includes clozapine, 400 mg/d, lisinopril, 20 mg/d, atorvastatin, 40 mg/d, omeprazole, 40 mg/d, and a multivitamin. During routine blood monitoring, Mr. S shows a significant drop in absolute neutrophil count (ANC) (750/µL) (reference range, 1,500 to 8,000 µL). Mr. S, who is African American, has no history of benign ethnic neutropenia (BEN) or ANC <1,000/µL. While reviewing his chart, clinicians note that Mr. S had an ANC of 1,350/µL 3 years earlier in 2013. Because a complete workup reveals no other cause for this lab abnormality, we determine that it is clozapine-induced. Mr. S’s physician asks about treatment options that would allow him to stay on clozapine.

Because of clozapine’s efficacy in treatment-resistant schizophrenia, many psychiatrists aim to manage patients who develop abnormal laboratory values without discontinuing clozapine. This article will examine the evidence behind 2 potential management strategies.

Clozapine-induced neutropenia

Clozapine was approved in 1989 for managing treatment-resistant schizophrenia after demonstrating better efficacy than chlorpromazine. However, the adverse effects of neutropenia (white blood cell count [WBC] <3,000/µL) and agranulocytosis (ANC <500/µL) leading to death were reported in later studies. One study in the United Kingdom and Ireland reported a prevalence of 2.9% for neutropenia and 0.8% for agranulocytosis among patients taking clozapine. Because of this risk, the FDA mandated WBC and ANC monitoring before initiating clozapine and periodically thereafter. In October 2015, the Risk Evaluation and Mitigation Strategies program for clozapine updated recommended ANC levels and eliminated WBC monitoring. ANC monitoring frequencies are summarized in the Table (page 52).

The exact mechanism of clozapine-induced neutropenia is unknown, although it is possible it stems from the drug’s effect on white blood cell precursors. Neutropenia

Practice Points

• There is lack of evidence for long-term use of filgrastim for clozapine-induced neutropenia and agranulocytosis; short-term treatment is recommended.
• There is potential risk of lithium masking the preliminary state of neutropenia leading to severe agranulocytosis.
• Patients who experience neutropenia with clozapine are at an increased risk for a repeat neutropenia on rechallenge.
typically appears within 3 months of clozapine initiation; however, delayed cases have been reported. Additionally, the risk is higher in certain patient populations (African heritage, Yemenite, West Indians, and Arab). Patients with a lower ANC at clozapine initiation and advanced age appear to be at higher risk.²

Filgrastim

The use of granulocyte-colony stimulating factor, such as filgrastim, often is viewed as a “rescue” treatment. Filgrastim’s mechanism of action is related to neutrophil production and proliferation. Several articles from the 1990s reported efficacy in the short-term management of low WBC or ANC. However, few articles, mainly case reports, have looked at long-term use of these agents. One article examined 3 patients, average age 45, who developed neutropenia during clozapine treatment.³ Filgrastim at an average dosage of 0.6 to 0.9 mg/week was
used successfully. The dosage was reduced to 0.3 mg/week in 1 patient, although neutropenia returned.

Because of the lack of literature regarding long-term therapy, it is recommended to consider short-term treatment with filgrastim to normalize ANC after a severe drop in a symptomatic patient. Physicians also must consider the potential barriers to filgrastim treatment including adverse effects, such as allergic reactions, bone pain, and thrombocytopenia, and high cost.

**Adjunctive lithium**

Lithium could cause leukocytosis, which could balance neutropenia induced by clozapine. One of the largest studies evaluating lithium therapy with clozapine-induced neutropenia and agranulocytosis studied 25 patients taking clozapine with a previous “red result” (WBC <3,000/μL, ANC <1,500/μL, or platelets <50,000/μL). Lithium treatment was started before or simultaneously with the reinitiation of clozapine in most patients; the remaining patients started treatment at a later date. Only 1 of 25 patients experienced a repeat “red result.” The average lithium level was 0.54 mEq/L.

It is important to remember that initiating adjunctive lithium carries risk. Adverse effects include gastrointestinal upset, tremors, polyuria, polydipsia, and nephrotoxicity.

Additionally, there is risk that lithium simply masks the preliminary states of neutropenia leading to a more severe agranulocytosis without warning. Again, the mechanism of action of clozapine-induced neutropenia is thought to be related to the drug’s effect on WBC precursors. The mechanism of lithium-induced leukocytosis is unknown, therefore it’s possible that lithium will not protect a patient from clozapine-induced neutropenia or agranulocytosis, and can lead to serious adverse events.

When deciding whether to rechallenge a patient on clozapine who had a prior episode of moderate or severe neutropenia or agranulocytosis, a risk vs benefit discussion is necessary. One study found that 20 of 53 patients (38%) experienced a repeat dyscrasia when rechallenged. Of these patients, most experienced a lower ANC that presented faster and took longer to resolve. If a patient has experienced true agranulocytosis, the recommendation is to not rechallenge clozapine.

**References**