Use of Cytokines in Clozapine-Induced Agranulocytosis

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Objective: To report and review the use of cytokines for the treatment of clozapine-induced neutropenia.

Method: Case report and review of literature.

Results: Cytokines, granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), appear to shorten the duration of clozapine-induced neutropenia.

Conclusions: G-CSF or GM-CSF therapy should be considered in patients with profound neutropenia of prolonged duration (high-risk neutropenia).

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Key Words: clozapine, neutropenia, G-CSF, review

Clozapine is an atypical neuroleptic agent that has shown efficacy in schizophrenic patients refractory to other neuroleptic drugs. It has been impressive in both symptom resolution and improvement in the quality of life (1). Its novel pharmacological profile, lack of extrapyramidal effects, and therapeutic benefit in tardive dyskinesia have resulted in the expansion of the indications for clozapine to include schizoaffective and other affective disorders (for example, psychotic depression) as well as psychosis in patients with dementia and Parkinson’s disease (2–4). It has been administered to a wide range of age groups, from adolescents to the elderly, to patients with concomitant medical illnesses, and in combination with various other drugs (2,3,5). The most serious adverse effect of clozapine remains drug-induced agranulocytosis.

The incidence of agranulocytosis with clozapine treatment has been estimated to be as high as 1% to 2%. As a result of strict monitoring requirements, however, the actual incidence was found to be 0.8% after the first year of treatment and 0.92% after 18 months (6). The greatest risk appears to be within 4 to 18 weeks after the initiation of the drug (7), but a small risk of agranulocytosis continues throughout the course of treatment.

Drug-induced agranulocytosis is a potentially life-threatening blood dyscrasia characterized by profound neutropenia. The hematologic condition shows an absence of granulocytes in the peripheral blood and bone marrow, with relative sparing of erythroid and megakaryocytic elements. With few exceptions (8), the reduction in white cell count (< 2.0 × 10⁹/L or 2000 cells/mL) accompanies the reduction in neutrophils (< 0.5 × 10⁹/L or 500 cells/mL). In most cases of agranulocytosis, the neutrophil count declines gradually and may be detected before dropping below 1.5 × 10⁹/L (1500 cells/mL), but in some cases the fall is precipitous (9). As neutrophils are critical in host defence to microbial infection, their depression may result in rapidly spreading and overwhelming infections. The risk of infection in these patients is directly related to the duration of neutropenia and the rate of decline of granulocytes. In patients with acute leukemia (10), the incidence of severe infection increases rapidly when the absolute neutrophil count (ANC) is less than 0.1 × 10⁹/L (100/mm³) for more than 14 days. The mortality in the neutropenic patients with sepsis may approach 50% (7), particularly if the infection is unrecognized and antibiotic therapy is delayed.

Until the availability of hematopoietic growth factors, management of the agranulocytic condition has been largely supportive. The use of recombinant human granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF), in an attempt to speed recovery time following agranulocytosis, provides...
clinicians with alternative strategies of management. Originally marketed to hasten marrow recovery and reduce infection rates in patients receiving myelosuppressive chemotherapy (11) or bone marrow transplants (12), there are now an increasing number of reports of the successful use of these cytokines in the treatment of drug-induced agranulocytosis. Both GM-CSF and G-CSF have the ability to stimulate the proliferation and differentiation of myeloid precursor cells in the bone marrow (13–15). It has also been suggested that G-CSF enhances mature neutrophil function, improving chemotaxis and increasing phagocytosis and oxidative burst (16). G-CSF is lineage specific in that it has been shown to have minimal direct in vivo and in vitro effect on the production of other hematopoietic cell types (6). In this report we describe a case of drug-induced agranulocytosis treated with G-CSF and summarize the literature on clozapine-induced neutropenia treated with cytokines. Management strategies for drug-induced agranulocytosis are proposed. Our report adds to the increasing body of evidence suggesting the utility of cytokines in the management of clozapine-induced agranulocytosis.

Case Report

A 41-year-old male with an 18-year history of schizophrenia had been treated with numerous antipsychotics and was eventually switched to clozapine. His white blood count (WBC), hemoglobin, and platelets were monitored weekly. His baseline WBC was normal. Approximately 7 months after the initiation of clozapine, he became neutropenic: his WBC fell to 2.4×10⁹/L; his ANC was 0.3×10⁹/L. Clozapine was discontinued immediately, and he was placed in reverse isolation. Four days later, his WBC fell further to 1.3×10⁹/L and the granulocyte count was 0.1×10⁹/L. Within 3 days, he developed a dry cough, sore throat, and a fever of 38.5°C and was transferred to our centre. On admission, his WBC was 0.8×10⁹/L and ANC was 0. Systems review and examinations revealed no obvious focus for infections. Blood, urine, and sputum cultures were all negative. He was treated with the intravenous antibiotics gentamicin and cefotaxime, and his fever resolved in 24 hours. He was switched to oral ciprofloxacin 3 days later, but daily WBC showed no signs of improvement. Eleven days after the initial documentation of neutropenia, his ANC remained 0, so a sternal bone marrow aspiration was performed, revealing an abundance of myeloid precursors consistent with early marrow recovery. He was started on subcutaneous G-CSF (10 µg/kg/day). After 2 doses of G-CSF, a rise in ANC from 0 to 0.4×10⁹/L was observed. Three days after the initiation of G-CSF, his WBC rose to 23×10⁹/L, and the ANC was 4.8×10⁹/L. G-CSF was discontinued. He was discharged 2 days later with a WBC of 30.9×10⁹/L and ANC of 12.7×10⁹/L.

Discussion

We describe a case of late-onset, clozapine-induced agranulocytosis treated with G-CSF. Historically, spontaneous recovery has taken 14 to 30 days after the withdrawal of clozapine (17). In this case, G-CSF was initiated 11 days after documentation of neutropenia and discontinuation of clozapine. G-CSF appeared to speed the recovery process, with a significant increase of ANC from 0.0×10⁹/L to 4.8×10⁹/L documented 3 days after the initiation of the cytokine. Other reports have shown similar effects of G-CSF in the acceleration of neutrophil recovery time within 6 to 11 days after the initiation of the growth factor (13,17–26). In this case study, the rapid increase of neutrophils just 3 days after the initiation of treatment with G-CSF is likely due to the fact that G-CSF was initiated during early marrow recovery, rather than when the marrow was hypoplastic.

G-CSF is a human glycoprotein hormone that acts to stimulate proliferation and differentiation of committed myeloid progenitor cells of the neutrophil lineage. An increase in neutrophil production with the cytokine of approximately 9 to 10 times results from increased input of precursor cells into the myeloblast compartment, increased number of divisions during neutrophil development, and shortening of the time required for neutrophil maturation (14). G-CSF has been shown to be beneficial in a randomized placebo-controlled study in patients receiving myelosuppressive chemotherapy for small-cell lung cancer (11). When administered 24 hours after chemotherapy, G-CSF was shown to reduce the duration and severity of neutropenia, in turn reducing hospitalizations and antibiotic usage. The optimal schedule for G-CSF administration has not been established in chemotherapy-induced neutropenia or other forms of agranulocytosis. For clozapine-induced agranulocytosis, it is usually given subcutaneously in doses of 4 to 10 µg/kg/day (20) and discontinued 24 hours after the ANC is above 0.5×10⁹/L (500/mm³) and signs of infection have resolved. Side effects to G-CSF, which tend to occur infrequently, include headache and mild bone pain, particularly at higher doses (19). These effects can be readily treated with acetaminophen.

The use of G-CSF for other neutropenic states, including congenital and idiopathic chronic neutropenias, is less well studied. It has shown a remarkable degree of efficacy in patients with congenital neutropenias (27) and a small series of patients with cyclic neutropenia (28). In Canada, it is approved for use in patients with severe chronic neutropenia. A number of case reports suggest that G-CSF can significantly decrease the duration of clozapine-induced agranulocytosis. A review of the literature on the use of cytokines for clozapine-induced agranulocytosis showed that the use of G-CSF (filgrastim) or GM-CSF successfully resolved the neutropenia within an average of 8 days and
shortened recovery time by about 50% (Table I). The evidence supporting the use of hematologic growth factors in drug-induced agranulocytosis remains confined to anecdotal reports (29). Based on the number of reports and the prolonged neutropenia normally associated with clozapine, the support for the use of cytokines in this condition is relatively strong. Although a series of case reports does not constitute proof of efficacy of the agent, it appears unlikely that a prospective randomized trial for this disorder will be conducted. Several questions regarding the use of G-CSF or GM-CSF in the treatment of drug-induced agranulocytosis remain unanswered, including the timing of the initiation of growth factor.

Clozapine is thought to induce agranulocytosis through an immune-mediated mechanism (30,31), although a toxic mechanism induced by its metabolite N-dimethyl clozapine against myeloid precursors is postulated by some investigators (31). The drug appears to trigger the development of antibodies against human leukocyte antigens (HLA) on bone marrow progenitor cells with sparing of the stem cell compartment. HLA are critical in the regulation of immune responsiveness and are associated with susceptibility to disease. An association between expression of HLA B16 allele and the risk of clozapine-induced agranulocytosis has been suggested (32), but has not been confirmed by other studies (33). Cross-reactivity between clozapine and other classes of neuroleptics has not been observed (34). Rechallenge of 9 patients with clozapine-induced leukopenia or agranulocytosis brought on a rapid recurrence of these reactions. The shortened latency period of the second reaction is consistent with an immune-mediated mechanism (6).

Despite a postulated immunologic destruction of myeloid progenitors induced by clozapine, the ability of G-CSF to increase the input of precursor cells into the myeloblast compartment likely accounts for its beneficial effects on neutrophil recovery. Thus, although the mechanism of clozapine-induced agranulocytosis differs from the direct toxic effects of chemotherapy, its rationale for use in this condition is similar.

**Monitoring and Management Strategies for Clozapine-Induced Agranulocytosis**

Heightened awareness of clozapine-induced agranulocytosis has led to the institution of weekly monitoring protocols to identify this condition early. Despite these measures, there were 386 cases of agranulocytosis with 12 fatalities reported in the United States between 1990 and 1994 (17,30). Between March 1991 and December 1994 in Canada, 3704 patients received clozapine, with incidence of reported agranulocytosis of 0.67% (males, 0.41%; females, 1.17%). There was one reported death, but its relationship to clozapine was unconfirmed (A. Sawtell, Sandoz, Canada, personal communication). A review of 656 patients on clozapine in Denmark showed no difference in the patient gender or dose of

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**Table I**

<table>
<thead>
<tr>
<th>Case Report</th>
<th>Clozapine Treatment</th>
<th>Pretreatment WBC/ANC (\text{ANC}&lt;0.1)</th>
<th>Days to Recover</th>
<th>Cytokine Dose Duration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>33-year-old female</td>
<td>10 weeks</td>
<td>ANC less than 0.05 for 10 days</td>
<td>12</td>
<td>G-CSF 10 µg/kg (\times 8) days then 10 µg/kg for total of 10 days (\text{a})</td>
<td>Nelson H 1993 (13)</td>
</tr>
<tr>
<td>Report of 3 cases; 3 male</td>
<td>7 to 11 weeks</td>
<td>ANC from 0 to 2.0</td>
<td>10 – 12</td>
<td>G-CSF 300 µg/day (\times 5) to 8 days (\text{b})</td>
<td>Lamberti JS and others 1995 (17)</td>
</tr>
<tr>
<td>30-year-old female</td>
<td>7 weeks</td>
<td>WBC 0.6, ANC less than 0.5 for 9 days</td>
<td>11</td>
<td>G-CSF 300 µg/day (4-8 \text{ µg/kg}) (\times 3) days then 400 µg/(\text{d}) for a total of 10 days (\text{c})</td>
<td>Raison CL and others 1994 (18)</td>
</tr>
<tr>
<td>Report of 4 cases; 3 male 1 female</td>
<td>mean of 18 weeks</td>
<td>ANC less than 0.1 for at least 3 days</td>
<td>6 – 11</td>
<td>G-CSF 300 to 600 µg/(\text{d}) started within 48 hrs (\text{d})</td>
<td>Gerson SL and others 1992 (20)</td>
</tr>
<tr>
<td>28-year-old male</td>
<td>7 weeks</td>
<td>WBC 2.0, ANC 0.26</td>
<td>5</td>
<td>GM-CSF 150 µg q 12h (\times 6) days then 75 µg bid (\times 3) days (\text{e})</td>
<td>Barnas C and others 1992 (21)</td>
</tr>
<tr>
<td>Report of 5 cases; 4 male 1 female</td>
<td>4 to 14 weeks</td>
<td>ANC 0.007 to 0.3</td>
<td>6 – 13</td>
<td>G-CSF 300 to 900 µg/day (\text{f})</td>
<td>Guillon G and others 1994 (22)</td>
</tr>
<tr>
<td>32-year-old male</td>
<td>55 days</td>
<td>WBC 2.1, ANC 0.504</td>
<td>11</td>
<td>G-CSF 300 µg (\times 6) days (\text{d})</td>
<td>Ryabik BM and others 1993 (23)</td>
</tr>
<tr>
<td>45-year-old male</td>
<td>7 weeks</td>
<td>WBC 1.1, ANC 0</td>
<td>8</td>
<td>GM-CSF 3 µg/kg/day (\times 4) days (\text{b})</td>
<td>Oren R and others 1993 (24)</td>
</tr>
<tr>
<td>48-year-old female</td>
<td>27 days</td>
<td>WBC 0.3 for 9 days</td>
<td>14</td>
<td>G-CSF 10 µg/kg (\times 6) days (\text{b})</td>
<td>Weide R and others 1992 (25)</td>
</tr>
<tr>
<td>64-year-old female</td>
<td>21 months</td>
<td>ANC less than 0.1</td>
<td>10</td>
<td>G-CSF 300 µg/day (\times 7) days (\text{b})</td>
<td>Geibig CB and others 1993 (26)</td>
</tr>
</tbody>
</table>

\(\text{a}\) Nielson H 1993 (13) \(\text{b}\) Lamberti JS and others 1995 (17) \(\text{c}\) Raison CL and others 1994 (18) \(\text{d}\) Gerson SL and others 1992 (20) \(\text{e}\) Barnas C and others 1992 (21) \(\text{f}\) Guillon G and others 1994 (22) \(\text{g}\) Ryabik BM and others 1993 (23) \(\text{h}\) Oren R and others 1993 (24) \(\text{i}\) Weide R and others 1992 (25)
clozapine in patients with or without agranulocytosis; 60% of the patients, however, were receiving at least one other psychotropic drug (5).

Careful monitoring, although essential in reducing the risk, will not entirely eliminate the problem of clozapine-induced agranulocytosis. The population using clozapine may be particularly at risk because of their underlying illness (20) and poor compliance with neutropenic precautions. The relative risk of agranulocytosis must be compared with the 10% to 15% risk of suicide in patients with schizophrenia (35).

A gradual, progressive decline in WBC or ANC should alert clinicians to the possible early development of this complication. Other markers in the complete blood count may include a rapid fall in neutrophils (even if the total WBC remains above 3500/mm³), the presence of immature myeloid forms, or eosinophilia (8). Eosinophilia was observed to precede the development of agranulocytosis in a Finnish study (36), but has not been a consistent marker for this complication (37). Should eosinophilia occur in association with leukopenia, dermatologic symptoms, or fever, discontinuation of clozapine is recommended (38).

In all cases of neutropenia, any medications that can potentially produce agranulocytosis should be discontinued. For patients with mild neutropenia (ANC >1.5 × 10⁹/L), the risk of infection is low (39,40). These patients should have their granulocyte count monitored until recovery. For moderate levels of neutropenia (ANC 0.5 × 10⁹/L to 1.5 × 10⁹/L), more frequent monitoring for the development of infection and neutrophil recovery is recommended. Reverse isolation precautions are recommended by some studies when the ANC is less than 0.5 × 10⁹/L, although others have argued about the actual benefits and efficacy of this approach (41,42). Any neutropenic patient who develops a fever should have prompt initiation of empiric broad-spectrum antibiotics, which are generally continued until neutropenia and signs of infection resolve.

For patients with severe neutropenia (ANC <0.5 × 10⁹/L), we recommend that a bone marrow aspiration be performed to rule out other causes of bone marrow failure. If marrow shows recovering myeloid activity and the patient has no signs of infection, it may be appropriate simply to observe the patient, as neutrophil recovery is likely imminent (1 to 3 days) (29). If, however, the patient is infected or has a hypoplastic marrow, it is likely that the neutropenic phase will be prolonged (>7 days), and the initiation of the growth factor G-CSF or GM-CSF should be considered. Doses have varied from 4 to 10 µg/kg for G-CSF and 3 to 10 µg/kg for GM-CSF, with no direct correlation between dose and time for neutrophil recovery (29). Despite the high cost of hematopoietic growth factors, their use in high-risk patients may be warranted because of their potential to shorten the neutropenic period, decrease morbidity, and reduce hospitalization time.

We recommend that the use of cytokines be reserved for this subgroup of patients at highest risk of infection and, therefore, with greatest potential for benefit from this newly available therapy.

**Clinical Implications**

- Clozapine-induced agranulocytosis may be prolonged and is associated with significant morbidity and mortality.
- Careful monitoring of blood counts while on clozapine is mandatory.
- In high-risk neutropenic patients, use of cytokines may shorten the neutropenic period and reduce hospitalization time.

**Limitations**

- Even with cytokines, neutropenia may take up to 2 weeks to resolve.
- Efficacy of cytokines for clozapine-induced neutropenia is based solely on case reports.
- A cost–benefit analysis for the use of cytokines in this condition remains to be determined.

**References**

Résumé

Objectif : Compte rendu et examen de l’utilisation des cytokines afin de traiter la neutropénie provoquée par la clozapine.

Méthode : Exposé de cas et examen de la littérature.

Résultats : Les cytokines, le facteur stimulant les colonies de granulocytes (G-CSF) et le facteur stimulant les colonies de granulocytes-macrophages (GM-CSF) semblent réduire la durée de la neutropénie provoquée par la clozapine.

Conclusion : Il faudrait envisager le traitement au G-CSF ou au GM-CSF chez les patients qui présentent une neutropénie grave et dont la durée est prolongée (neutropénie à risque élevé).