From the Department of Severe Mental Illness at Mental Health Care Organization North-Holland North, Heerhugowaard, Netherlands

White Blood Cell Monitoring During Long-Term Clozapine Treatment

Dan Cohen, M.D., Ph.D.

Marcel Monden, M.D.

Late-onset agranulocytosis is rare during treatment with clozapine, especially in monotherapy. The authors describe a case of agranulocytosis that emerged after 19 years of continuous clozapine monotherapy. The discovery of the agranulocytosis was due to the lifelong white blood cell counts that are now required for clozapine treatment. Despite the fact that this requirement probably saved the life of this patient, this monitoring is not evidence-based because the incidence of agranulocytosis does not exceed that of conventional antipsychotic drugs, for which no such requirement exists. For mentally competent and adequately informed patients, the Netherlands Clozapine Collaboration Group now permits quarterly monitoring after the first 6 months of clozapine treatment.

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Case Presentation

"Mr. L," a white male, was first seen in 1990 when he was 23 years old. He was dependent on several substances, mainly heroin, which he used intravenously. He was acutely psychotic with paranoid delusions that made him threaten and attack passers-by. After he set fire to his house, he was involuntarily admitted to the acute ward of a psychiatric hospital.

Mr. L was diagnosed with paranoid schizophrenia and opium abuse according to DSM-IV criteria. He was started on clozapine in April 1990, after a trial of depot flupentixol (50 mg every 2 weeks) proved ineffective for his delusional thinking and aggressive behavior. A satisfactory therapeutic response was achieved with a dosage of 250 mg/day (plasma level, 160 μg/L), resulting in complete remission of his psychosis and opioid addiction. This beneficial response was maintained for 19 years with the same dosage of clozapine. Lorazepam (2.5 mg) was used occasionally for the treatment of anxiety.

Before the initiation of clozapine, Mr. L's WBC count was 4.2×10^9/L, and it remained above 4.0×10^9/L during clozapine treatment until February 2007, when it decreased to 3.7×10^9/L with a neutrophil count of 1.9×10^9/L; there were no changes in other leukocytes. In February 2009, the patient's WBC count suddenly decreased to 2.5×10^9/L with a neutrophil count of 1.3×10^9/L, and in April 2009 it decreased further to 1.9×10^9/L with a neutrophil count of 1.0×10^9/L, a lymphocyte count of 0.6×10^9/L, a monocyte count of 0.3×10^9/L, an eosinophil count of 0.0×10^9/L, and a basophil count of 0.0×10^9/L. In the same week, the patient developed laryngitis with a temperature of 40.2°C and was admitted to the hospital. The patient was treated with phenethicillin (500 mg daily), and the consultant hematologist advised immediate discontinuation of clozapine. After 2 days, the fever abated and the patient was discharged. The consultant hematologist advised a drug-free period, during which the patient was seen twice a week by a psychiatrist (M.M.). A week after the discontinuation of clozapine, the patient's WBC count increased to 3.5×10^9/L, and 3 weeks later to 4.7×10^9/L. Treatment was started with aripiprazole (45 mg/day) and lorazepam (5 mg/day). Since then, the patient has remained in full remission without relapse of the psychosis or substance abuse. His WBC count was 5.9×10^9/L in May 2011.

Discussion

Eight fatal cases of agranulocytosis in Finland (1) prompted the worldwide ban of clozapine. The drug was subsequently reintroduced for the treatment of refractory schizophrenia (2) with the stipulation that WBC and absolute neutrophil counts should be performed regularly to enable the early detection of treatment-emergent leukopenia and agranulocytosis. Since the incidence of leukopenia is highest in the first year of treatment, and especially in the first 6 months, regulatory authorities have made WBC and neutrophil counts mandatory. In Europe, WBC and neutrophil counts must be performed weekly during the first 18 weeks and at least every 4 weeks thereafter through treatment (3). In the United States, weekly WBC and neutrophil counts are required during the first 26 weeks and biweekly counts during the second 26 weeks and every 4 weeks thereafter through treatment (4). The

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TABLE 1. Reports of Late-Onset Neutropenia or Agranulocytosis

Treatment and Study	Treatment Duration	WBCs/mm^3	Neutrophils/mm^3	Comedication
Clozapine monotherapy				
Tamam et al. (6)	2 years	2,400	1,100	
Latif et al. (7)	6 years	2,800	1,700	
Raja et al. (8)	10 years	2,200	650	
Sedky et al. (9)	11 years	1,300	154	
Nongpiur et al. (10)	11 years	2,500	1,000	
This case	19 years	1,900	1,000	
Clozapine polypharmacy				
Bhanji et al. (11)	17 months	2,900	1,000	Olanzapine, quetiapine, risperidone, valproate
Godleski and Sernyak (12)	22 months	2,500	376	Risperidone
Raveendranathan et al. (13)	24 months	2,200	198	Risperidone
Thompson et al. (14)	3 years	5,840	1,420	Sertraline, valproate
Peacock and Gerlach (15)	48 months	2,000	460	Thioridazine, valproate
Small et al. (16)	4 years	1,800	200	Benazepril, haloperidol, olanzapine
Sénéchal et al. (17)[a]	5 years 7 years	5,200 5,700	1,200 700	Haloperidol, valproate Haloperidol, methotrimeprazine, risperidone, valproate
Patel et al. (18)	69 months	1,500	0	Lithium, risperidone
Panesar et al. (19)	9 years	2,700	500	Ethambutol, isoniazid, rifampicin, pyrazinamide
Tourian and Margolese (20)	10 years	n.a.	200	Lamotrigine
Kutscher et al. (21)	10 years	2,400	1,750	Azithromycin, citalopram, cyclobenzaprine, doxazosin, esomeprazole

[a] The two periods of neutropenia occurred in the same patient.

detection of late-onset leukopenia or agranulocytosis constitutes the main argument in favor of lifelong WBC monitoring, but the validity of this argument has been questioned (5).

We searched PubMed for studies published between January 1980 and September 2012, using the following terms: clozapine, late onset, agranulocytosis. To date, 16 patients have been reported to have developed agranulocytosis after the early high-risk period, with incidences from 17 months to 11 years. To our knowledge, our patient, with an apparent onset after 19 years of treatment, is the latest onset. This is only the sixth case of late-onset agranulocytosis during clozapine monotherapy reported (Table 1). After withdrawal of clozapine, our patient's WBC count increased within 7 weeks to 5.9×10^9/L and his neutrophil count to 3.9×10^9/L, and both have remained stable since then (>3 years). The stable but low total WBC and neutrophil counts during clozapine therapy can, with hindsight, be explained as being due to a constant but mild clozapine-induced suppression of WBCs during the 19 years of clozapine treatment.

Although the majority of the reported cases, both early and late onset, involved cotreatment with somatic or psychiatric medications (22–24), it remains extremely difficult to prove that a given drug increases the risk of neutropenia or agranulocytosis in clozapine treatment when used as comedication. For example, although valproate was used as comedication in two cases of early-onset (23, 24) and four of 10 cases of late-onset polypharmacy-induced neutropenia or agranulocytosis, no such cases were reported in 34 patients treated for at least 4 weeks with a combination of clozapine and valproate (25). In some cases, however, the relation between comedication and onset of agranulocytosis seems clear-cut. For instance, in one case, agranulocytosis developed after addition of risperidone after 22 months of uncomplicated clozapine monotherapy (12).

We found only five cases of late-onset neutropenia that developed after a maximum of 11 years of clozapine monotherapy. Our patient developed agranulocytosis after 19 years of clozapine monotherapy; no concomitant medication was involved, and after discontinuation of clozapine, the patient's WBC count recovered within a week.

Prolonged (>6 months) treatment with clozapine has not been found to carry a greater risk of neutropenia than does treatment with conventional antipsychotics (5). Two recent studies have also addressed this issue. One study (26) addressed the question of whether clozapine use is associated with an increased incidence of neutropenia. Ninety-five new clozapine users (86.6% with diagnoses of schizophrenia, schizoaffective disorder, or bipolar disorder) were compared with 884 non-clozapine users (65% with diagnoses of other disorders, treated with first-generation antipsychotics for schizophrenia, selective serotonin reuptake inhibitors for major depression, and benzodiazepines for anxiety disorder). The 24-month incidence of neutropenia was 6.3% (95% CI=2.3–11.7) in the clozapine group and 5.9%

TABLE 2. Incidence of Clozapine-Associated Agranulocytosis per 1,000 Patient-Years[a]

Country	≤18 Weeks	19–52 Weeks	≥52 Weeks
United States (28)	3.39–6.93	0.37–0.40	0.11–0.39
United Kingdom (28)	20.4–24.8	1.16–1.52	0.31–0.59
Australia (28)	8.27	2.17	0.52
South Korea (27)	12.35	2.48	1.03

[a] Some of the data presented in this table first appeared in Schulte (5).

(95% CI=4.4–7.5) in the non-clozapine group. In the clozapine group, all cases occurred within the first year of treatment (range, 37–338 days) and in the non-clozapine group during the 2 years (range, 2–711 days) of treatment. In the second study, by Kang et al. (27), during 11 years of follow-up, 54 cases of agranulocytosis occurred among 6,782 clozapine users, with 29 cases (53%) occurring within the first 18 weeks and 40 (74%) within the first year of treatment. The 14 remaining cases occurred during the 13,594 years of cumulative exposure, corresponding to an incidence of 1.03 per 1,000 patient-years (Table 2). Although the incidence of agranulocytosis during long-term clozapine treatment (1 per 1,000 patient-years) reported by Kang et al. is twice as high as that reported in other countries (Table 2), it is comparable to the incidence of 0.1–1.4 reported for conventional antipsychotics (5). This suggests that the risk of agranulocytosis during long-term treatment with clozapine is similar to that with other antipsychotic drugs.

Conclusions

We thus have a paradox: timely detection of agranulocytosis, the result of the requirement for lifelong WBC counts in clozapine therapy, probably saved this patient's life. However, WBC monitoring after the first 6 months of clozapine treatment is not evidence-based because the incidence of agranulocytosis does not exceed that of conventional antipsychotics, for which no such requirement exists. For mentally competent and adequately informed patients who request it, the Netherlands Clozapine Collaboration Group (29) permits lowering the frequency of blood tests to four times a year, which may be a reasonable compromise.

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Clinical Guidance: Frequency of Blood Tests in Clozapine Treatment

Late-onset agranulocytosis during clozapine treatment is rare. A literature search by Cohen and Monden revealed only 16 patients since 1980 who developed agranulocytosis more than a year after beginning clozapine treatment. They report an additional case, appearing 19 years after the start of clozapine monotherapy. The majority of cases involved co-treatment with other medications, including valproate, but no specific drug has been shown to increase risk. The incidence of agranulocytosis during long-term clozapine treatment is only 1 case per 1,000 patient-years, which is comparable to rates for typical antipsychotics. Whereas the U.S. requires white blood cell and absolute neutrophil counts every 4 weeks after the first year of treatment, the Netherlands now permits informed mentally competent patients to lower the frequency of blood tests to four times a year.