Clozapine Rechallenge After Neutropenia or Leucopenia

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Abstract: To rechallenge with clozapine for a patient who previously has experienced neutropenia or leucopenia or during clozapine treatment is a difficult clinical decision. Herein, we analyzed the results of such a rechallenge in 19 patients. We analyzed all the reports, from the database of the pharmacovigilance department of the Argentine National Administration of Drugs, Foods, and Medical Devices, of patients who were rechallenged with clozapine after a leucopenia or a neutropenia. Nineteen cases of rechallenge after leucopenia or neutropenia were reported between 1996 and 2014. One third of the patients re-exposed to clozapine developed a new hematologic adverse reaction. The second blood dyscrasia was less severe in 83% of the cases and had a shorter median latency as compared with the first (8 weeks vs 182 weeks, $P = 0.0045$). There were no significant differences for demographic and clinical characteristics of patients who developed a second dyscrasia as compared with those who did not. The present study shows that almost 70% of the patients rechallenged with clozapine after a leucopenia or a neutropenia did not develop a new hematological adverse effect, whereas the remaining 30% had a faster but less serious neutropenia.

Key Words: clozapine, rechallenge, neutropenia, risk factors

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Clozapine is a second-generation or *atypical* antipsychotic drug used for the treatment of patients with refractory schizophrenia, persistent suicidal behavior, or intolerance to the adverse effects of other antipsychotic drugs (especially adverse effects on motility).[1–3] The use of clozapine has several important adverse effects, some of which are life threatening. These include a dose-dependent risk of epileptic seizures, potentially severe inhibition of bowel function, and possible carditis and cardiomyopathy.[4] The most prevalent and dangerous adverse effects with clozapine are blood dyscrasias like leucopenia, neutropenia, and agranulocytosis.[5–11]

A complex scenario that occurs in clinical practice is when a patient treated with clozapine develops a hematologic adverse effect, and clozapine has to be discontinued. After discontinuation, there are 2 possibilities. First, clozapine may be changed to another antipsychotic that is not chemically related. This decision is associated with relapse in almost 80% of the patients,[12] and patients previously treated with clozapine usually experience severe relapses. A second alternative is to rechallenge the patient with clozapine; however, there is sparse support for this option given its infrequency. Work by Dunk et al[13] has the largest number of cases evaluating the rechallenge with clozapine. Findings from this work suggested the rechallenge with clozapine increased the risk of a second faster and more severe hematological adverse effect.[13]

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In the present study, a case series of patients rechallenged with clozapine after a neutropenia or leucopenia was analyzed based on data recorded by the Argentinian Clozapine Monitoring System overseen by the Argentine National Administration of Drugs, Foods, and Medical Devices (ANMAT).[14]

METHODS

Rechallenge Process in Argentina

Four pharmaceutical companies (ie, Fabra, IVAX-Argentina, Novartis, Rospaw) market clozapine in Argentina, and each have their own patient monitoring program within their pharmacovigilance department. The notification of any hematological adverse effects during clozapine treatment to the ANMAT is mandatory. The ANMAT Monitoring Program for the management of hematologic adverse effects states that if the white blood cell count (WBC) is less than 3000 cells/μL and/or the absolute neutrophil count is less than 1500 cells/μL, medication should be discontinued, and patients should be monitored every 24 hours.[14] Rechallenge with clozapine is an off-label process undertaken by a medical decision and under its own responsibility. Information specific to rechallenge is reported by doctors or by pharmaceutical companies to the ANMAT and recorded in their pharmacovigilance department. Hematologic monitoring during the re-exposure to clozapine was performed with the same frequency as in the first exposure, weekly for the first 18 weeks and monthly thereafter.

Data Collection

All reports of patients who were rechallenged with clozapine after a leucopenia (<3000 cells/μL) or a neutropenia (<1500 cells/μL) during the previous clozapine exposure were obtained from the database of the pharmacovigilance department of ANMAT. Additional information such as demographic variables, hematological history, and concomitant treatments was requested from the 4 pharmaceutical companies in Argentina. Patients were required to have a break of at least 1 week between the 2 courses of treatment to be classified as rechallenge patients.[13]

Data Analytic Approach

Categorical measures are reported as frequency or percentage and compared with contingency tables (χ^2). Continuous measures are reported as means (SD) and compared by ANOVA methods (*t* test) or Wilcoxon rank sum test (Mann-Whitney *U* statistic) for non-normally distributed continuous data. Latency to blood dyscrasias was estimated by use of Kaplan-Meier survival analysis. Statistical significance required 2-tailed $P < 0.05$. All statistical analyses were conducted using SPSS 20 software (International Business Machines Corporation, Armonk, New York).

RESULTS

We identified 19 cases of clozapine rechallenge after leucopenia or neutropenia treatment reported to the pharmacovigilance department of ANMAT between 1996 and 2014 (Table 1). Fifty-eight percent of patients were identified as men. The average patient age was 33.7 (8.7) years. The mean daily dosage of clozapine

TABLE 1. Description of the Patients Included in the Analysis

Patient	Sex	Age (y)	First Blood Dyscrasia					Second Blood Dyscrasia				
			Duration of Exposure (wk)	Severity of Dyscrasia	Cell Count (cells/μL)	Dosage (mg/d)	Alternative Explanation for Dyscrasia	Time to Rechallenge (wk)	Time to Recurrence After Rechallenge (wk)	Severity of Dyscrasia	Cell Count (cells/μL)	Follow Up (wk)
1	M	28	52	Moderate neutropenia	ANC,1173 WBC,5100	300	No	3	NR			272
2	M	29	83	Moderate neutropenia	ANC,1400 WBC,3500	200	No	568	NR			36
3	M	34	17	Moderate neutropenia	ANC,1419 WBC,3300	300	No	284	13	Moderate neutropenia	ANC,1242 WBC,4600	—
4	M	55	54	Moderate neutropenia	ANC,1416 WBC,2890	250	No	2	NR			144
5	F	36	58	Moderate neutropenia	ANC,1446 WBC, 2410	250	No	4	NR			164
6	F	26	3	Moderate neutropenia	ANC,1380 WBC,3730	200	No	Unknown	NR			84
7	M	41	14	Moderate neutropenia	ANC,1395 WBC,4500	300	No	1	NR			24
8	M	34	65	Moderate neutropenia	ANC,1295 WBC,3700	300	No	208	NR			64
9	M	33	20	Severe neutropenia	ANC,580 WBC,2900	600	Influenza vaccine	356	NR			32
10	M	20	12	Moderate neutropenia	ANC,1342 WBC,3440	NI	Valproic acid, benzodiazepine, gabapentin	1	2	Mild neutropenia	ANC,1850 WBC,4210	—
11	F	30	573	Moderate neutropenia	ANC,1224 WBC,3700	NI	Clotiapine, levomepromazine, zuclopenthixol, alprazolam	32	8	Mild neutropenia	ANC,1908 WBC,3600	—
12	M	36	156	Moderate leukopenia	ANC,2030 WBC 2900	250	No	5	3	Mild neutropenia	ANC,1638 WBC,3900	—
13	F	49	208	Moderate neutropenia	ANC,1287 WBC,3300	NI	Valproic acid, benzodiazepine	4	8	Mild neutropenia	ANC,1944 WBC,3600	—
14	F	35	210	Moderate neutropenia	ANC,1490 WBC,5730	NI	No	4	NR			48
15	F	22	288	Severe neutropenia	ANC,975 WBC,3900	350	No	8	13	Mild neutropenia	ANC,1722 WBC,4480	—
16	F	43	107	Moderate leukopenia	ANC,1650 WBC,2750	NI	No	68	NR			12
17	F	34	68	Moderate neutropenia	ANC,1435 WBC,4100	350	Carbamazepine, levomepromazine	188	NR			112
18	M	28	1	Moderate neutropenia	ANC,1480 WBC,4000	NI	No	1	NR			192
19	M	27	1	Moderate neutropenia	ANC,1408 WBC,4400	NI	Infection	2	NR			128

NI indicates not informed; and NR, no recurrence.

TABLE 2. Comparison of Blood Dyscrasias on First Exposure to Clozapine

	Patients Without Blood Dyscrasia on Rechallenge (n = 13)	Patients With Blood Dyscrasia on Rechallenge (n = 6)	*P*
Dyscrasia in first exposure			
Neutropenia, n (%)	12 (92)	5 (83)	$P = 0.5438^{\S}$
Leucopenia, n (%)	1 (8)	1 (17)	
Duration of clozapine treatment at time of dyscrasia, median (range), wk	54 (1–210)	182 (12–573)	$P = 0.1262^{\ddagger}$
Duration of break in clozapine treatment, median (range), wk	4.5 (1–568)*	6.5 (1–284)	$P = 0.8887^{\ddagger}$
Sex, female, n (%)	5 (39)	3 (50)	$P = 0.6594^{\S}$
Age, median (range), y	34 (26–55)	32 (20–49)	$P = 0.6599^{\ddagger}$
Age, mean (SD), y	34 (10.9)	32 (10.5)	$P = 0.5452^{\|}$

*No data recorded for 1 patient.
‡Wilcoxon signed rank test.
§Fisher exact test.
‖Student *t* test.

was 303.8 (100.9) mg. Patients were treated for a median (range) time of 58 (1–573) weeks before the first blood dyscrasia. At first blood dyscrasia, there were 17 cases (89%) of neutropenia. Approximately 88% of these cases were moderate (WBC of 3000–2000 cells/μL or absolute neutrophil count [ANC] of 1500–1000 cells/μL), 12% were severe (WBC < 2000 cells/μL; ANC, 1000–500 cells/μL), and no cases were mild. There were only 2 cases of leucopenia, both of which were moderate. Additional explanation for the dyscrasia was observed in 32% of the cases (Table 1). Almost one third of the patients re-exposed to clozapine developed a new hematologic adverse reaction (Table 1). The second blood dyscrasia was less severe in 83% of the cases. None of the patients re-exposed to clozapine were hospitalized or died during re-exposure.

There were no significant differences for demographic and clinical characteristics between patients who developed a second dyscrasia and those who did not (Table 2). Regarding the first blood dyscrasia, those who did not develop a second event had a shorter median latency (54 vs 182 weeks) compared with those who did; however, this difference was not statistically significant (Table 2). The 6 patients who did develop a second blood dyscrasia had a shorter second event median latency (8 vs 182 weeks, $P = 0.0045$) than the first (Fig. 1).

DISCUSSION

In the present study, almost 70% of patients who were rechallenged with clozapine after a leucopenia or a neutropenia did not develop a new hematological adverse effect, whereas the remaining 30% had a faster but less serious neutropenia.

Clozapine is a second-choice treatment used to treat patients with schizophrenia and other psychotic disorders who are resistant or intolerant to other antipsychotic medications. If a patient receiving clozapine develops a hematological adverse effect, medication should be interrupted. The option to rechallenge these patients with clozapine is indeed a controversial decision. Discontinuation of this antipsychotic may cause a relapse in up to 80% of patients,[12] but the re-exposition may cause other hematological adverse effects, and, in some cases, faster and more severe events may follow.[13] The rechallenge with clozapine should be done only if there is a clear positive benefit that outweighs the risks; therefore, physicians should make a decision considering all factors. In Argentina, the baseline frequency of neutropenia in the clozapine population is 53 cases per year.[3]

The available evidence regarding the effects of rechallenge is limited. The largest study was conducted by Dunk et al,[13] which included 53 rechallenged patients from a United Kingdom database. They found that 62% of patients did not present a new hematological effect after rechallenge. The remaining 38% developed a second blood dyscrasia, and, among 85% of the cases, it was faster and more severe than the first one. Similar to Dunk et al,[13] we observed that the blood dyscrasia with rechallenge developed faster; however, the results did not suggest that second cases had a more severe reaction. Importantly, the sample in the work of Dunk et al[13] included patients with neutropenia and agranulocytosis whereas our sample included only patients with neutropenia.

It has been suggested that patients may develop 2 clinically distinct types of clozapine-induced neutropenia[15]; therefore, rechallenge

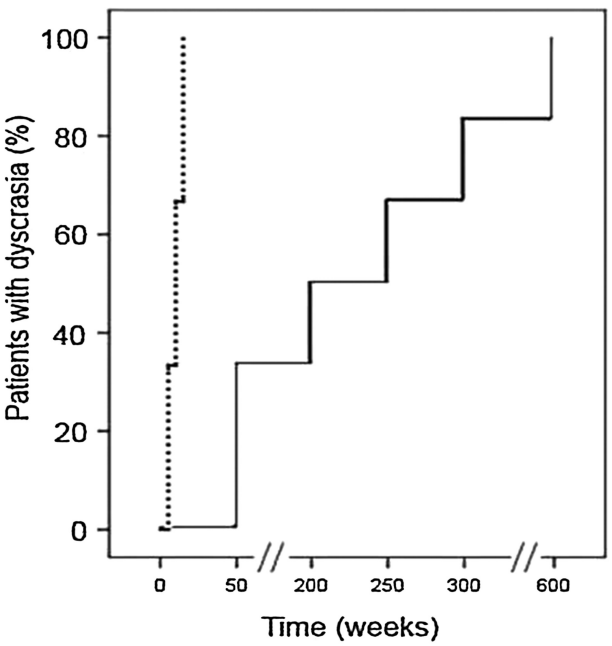

FIGURE 1. Kaplan-Meier plot of time to development of first (——) (median survival = 182 weeks) and second (-------) (median survival = 8 weeks) blood dyscrasias ($P = 0.0045$, n = 6).

may be different between both groups. For example, one type may be a benign form with a neutrophil count from 1500 to 500 cells/μL that occurs in 1.5% to 2% of treated patients, and where the recovery is rapid when the drug is discontinued (2–8 days). A second type may be an incidence of 0.8% that includes a neutrophil count of less than 500 cells/μL (agranulocytosis), does not respond to clozapine discontinuation, and lasts for 14 to 21 days. Specific to agranulocytosis, the cells affected are neutrophil precursors together with mature peripheral neutrophils, whereas the cells affected in neutropenia seem to be only the peripheral neutrophils.[16,17] Therefore, the positive results observed after rechallenge may in part be explained by assuming a benign type of neutropenia. Empirical support is provided by a systematic literature review by Manu et al[18] (2012) specific to rechallenge. In this review, they divided the hematological adverse effects in 2 types: those who developed a neutropenia and those who developed agranulocytosis.[18] The 70% of patients who developed neutropenia with the first clozapine treatment were rechallenged successfully and did not subsequently develop a blood dyscrasia. This proportion is reversed in patients with agranulocytosis, in which only 20% of patients had a favorable outcome with the rechallenge.[18]

Dunk et al[13] observed that the duration of clozapine treatment after the first hematological adverse reaction was not typical for patients who experienced clozapine-induced blood dyscrasia. They reported a median of 44 weeks, whereas in our analysis, the median duration of clozapine treatment at the time of the first dyscrasia was 58 weeks. They also found that the group that did not present a second hematological reaction with rechallenge developed their first reaction faster (a median of 37 and 81.5 weeks, respectively). We observed similar data, but the explanation remains unclear (Table 2).

The European Medicines Agency requires the discontinuation of clozapine and for it to never be prescribed again when the WBC < 3000 cells/μL or the ANC < 1500 cells/μL. However, the Food and Drug Administration recently modified the requirements for monitoring, prescribing, dispensing, and receiving clozapine.[19] These changes determined that WBC is no longer required, and treatment must be interrupted when the ANC is less than 1000 cells/μL for suspected clozapine-induced neutropenia. The restarting treatment may be considered once ANC ≥ 1000/μL. If ANC < 500/μL is detected during treatment, the patient may be rechallenged only if the prescriber determines that the benefits outweigh risks and once ANC > 1500/μL. Understanding the risk and serious complications during close monitoring is limited. An ANC of 1000 to 1500 cells/μL is not accompanied by an increased risk of infection. The risk is only slightly increased when the ANC is 500 to 1000 cells/μL.[20] Taken together, the decision to discontinue clozapine in a patient with a favorable therapeutic response should be delayed for as long as possible.

In conclusion, the present results support the possibility of re-exposing clozapine to patients who developed a neutropenia or leucopenia.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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