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Blood dyscrasias in clozapine-treated patients in Italy

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ABSTRACT

Background and Objectives. **Clozapine is a dibenzodiazepine derivative that is more effective than standard neuroleptic drugs in refractory schizophrenic patients, but its introduction in some countries was delayed by its propensity to cause blood dyscrasias. However, over the last ten years, different reports have clearly demonstrated that agranulocytosis and neutropenia can be easily prevented by means of strict hematologic surveillance. This article reviews the results of the first five years of the *Italian Clozapine Monitoring System* (ICLOS).**

Design and Methods. **The hematologic parameters of 2,404 patients registered between 1995 and 1999 were collected in a central database, before the patients began clozapine-treatment, weekly for the first 18 weeks, and then monthly throughout the duration of therapy. On the basis of conventional criteria, different risk levels have been identified with total leukocyte $<3.0\times10^9$/L and/or an absolute neutrophil count $<1.5\times10^9$/L leading to immediate discontinuation of the drug.**

Results. **The analysis shows that 0.9% of the patients developed neutropenia and 0.7% agranulocytosis, mainly during the first 18 weeks of clozapine treatment. Drug discontinuation led to the normalization of hematologic parameters in all cases, and the use of growth factors reduced the risk of infectious complications. Transient leukocytosis and eosinophilia were also observed but these did not have any serious clinical effects.**

Interpretation and Conclusions. **The ICLOS study confirms that regular hematologic monitoring is highly effective in minimizing the incidence of clozapine-associated blood dyscrasias. The lower than initially expected rates of agranulocytosis and associated deaths are encouraging in view of the benefits of this drug in treatment-resistant schizophrenia and other neurologic disorders.**

Key words: clozapine, agranulocytosis, neutropenia

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Blood dyscrasias and liver toxicity were the main reasons for withdrawing some drugs from the market in the past, but a number of these drugs were subsequently reintroduced after it was realized that the risk had been initially over-estimated and/or was easily prevented. The history of clozapine provides a classic example: this dibenzodiazepine derivative was discovered 30 years ago, but its use was restricted in the mid-1970s because it induced agranulocytosis.[1,2] In the USA[3] and UK,[4] it was licensed in the early 1990s for two main reasons: a) it is highly effective in treating patients with schizophrenia who do not respond to conventional neuroleptics; and b) the induced neutropenia and agranulocytosis appear to develop slowly and are easily detected by means of regular hematologic monitoring, which means that the cytopenias are reversible if the treatment is promptly discontinued.

Over the last ten years, a large number of epidemiologic studies have been undertaken in order to obtain an accurate estimate of the incidence of clozapine-induced blood dyscrasias. Surveillance reports from different countries have shown that the risk of agranulocytosis and neutropenia is respectively 0.38% and 1.5-2.9%; as a result of hematologic monitoring, these rates decrease significantly after the first year of treatment, as does the risk of death due to secondary complications.[3-10]

The aim of this paper is to describe the results of the *Italian Clozapine Monitoring System* (ICLOS) in relation to the risk of agranulocytosis and neutropenia in 2,404 clozapine-treated patients registered between 1995 and 1999, and to discuss related aspects such as the role of predisposing risk factors and the occurrence of other blood alterations, particularly leukocytosis and eosinophilia.

Design and Methods

Clozapine (Leponex – Novartis) came onto the Italian market in 1995, when the ICLOS monitoring service was independently set up by the *Institute of Advanced Biomedical Technologies of the Italian National Research Council* (CNR). The main purpose of this service is to support psychiatrists in the management of cases of clozapine-induced neutropenia and agranulocytosis, and to avoid drug re-exposure in schizophrenic patients who have previously had to discontinue treatment because of the occurrence of such hematologic side-effects. This is done by collecting demographic, case history and hematologic data. The hematologic parameters are evaluated before

the beginning of treatment, weekly for the first 18 weeks, and then monthly throughout the duration of therapy. The data are promptly sent to the CNR by the physician responsible for the psychiatric center via modem, on a floppy disk or on paper (in the case of any delays in sending blood parameters, the physician is contacted by telephone), and are subsequently entered in a central database in which the patients are identified by means of a code that respects their anonymity.

The hematologic toxicity of clozapine is determined on the basis of criteria indicated in the international literature, which define leukopenia as a total leukocyte (WBC) count of less than 3.5×10^9/L, neutropenia as an absolute neutrophil count (ANC) of 1.5-0.5×10^9/L, and agranulocytosis as a reduction in the neutrophil count to less than 0.5×10^9/L. The monitoring is therefore structured in such a way as to identify three risk levels: 1) a *yellow* alarm when the WBC count is 3.0-3.5×10^9/L and/or the ANC is 1.5-2.0×10^9/L, which requires a hematologic evaluation to be made every three days; 2) a *pink* alarm when the WBC count is < 3.0×10^9/L and/or the ANC is 1.0-1.5×10^9/L, which implies the immediate discontinuation of the drug; and 3) a *red* alarm when the ANC is < 1.0×10^9/L.

In addition to leukocyte counts, the monitoring includes collection of data relating to other hematologic parameters such as absolute eosinophil (AEC) and platelet (Plt) counts, as well as data concerning any non-hematologic effects attributable to clozapine and the psychopathologic status of the patient. As of March 1999, the monitoring system involved 542 psychiatric centers which had transmitted data relating to 2,404 schizophrenic patients: 30% of the centers used a modem, the others used floppy disks or paper. Table 1 summarizes the clinical characteristics of the ICLOS-registered patients. The majority were patients with refractory disease in whom clozapine was used because of a lack of response to conventional treatments, or the onset of extrapyramidal side effects caused by classic neuroleptics. The prevalent mean drug dose was 200-350 mg/day, which was reached over a time interval of 3-6 weeks and subsequently maintained.

Table 1. Baseline characteristics of 2,404 ICLOS-registered schizophrenic patients treated with clozapine.

	Males	*Females*
No. of patients	1,515 (63%)	889 (37%)
Age at onset of schizophrenia (yrs)	21.8±6.7	23.3±8.4
Duration of schizophrenia (yrs)	13.5±9.3	15.4±10
Diagnosis (DSM IV)		
Paranoid schizophrenia	47.3%	42.1%
Disorganized schizophrenia	25.1%	26.1%
Catatonic schizophrenia	2.9%	2.1%
Undifferentiated schizophrenia	11.7%	15.5%
Residual schizophrenia	8.5%	8.2%
Unknown	4.5%	6%
Reasons for stopping previous neuroleptic therapies*		
Lack of efficacy	85.7%	83.1%
Hypersedation	5.1%	6.6%
Extrapyramidal side effects	34.4%	33.4%

**The total is > 100% because of the possible concomitance of more reasons.*

Results

Since the ICLOS marketing surveillance system was started in 1995, 689 patients (29.8%) have had to discontinue clozapine after a median of ten weeks (range: 1-836 days): 6% because of poor clinical efficacy, 6.3% because of non-compliance, 12.5% for reasons unrelated to the drug, and 3.3% because of various side effects (mainly excessive sedation, sialorrhea, tachycardia, weight gain, arterial hypotension, and nausea and vomiting).

As far as hematologic dyscrasias are concerned, 40 patients (19 males and 21 females with a mean age of 40.7±13.4 years, representing 1.7% of the treated population) discontinued clozapine because of the appearance of neutropenia or agranulocytosis within the first 18 weeks of beginning the therapy (89% of the cases) or between 18 and 78 weeks after initiating treatment (11%). Two of these patients were withdrawn from the analysis: one because the appearance of undifferentiated blastic cells in bone marrow and peripheral blood during neutrophil recovery led to a diagnosis of acute myeloid leukemia; the other because the peripheral differential count revealed a non-neutropenic leukopenia

Table 2 shows the incidence of the individual events, with 22 cases of neutropenia (0.9%) and 16 of agranulocytosis (0.7%). In four patients (two with neutropenia and two with agranulocytosis), clozapine was administered together with other potentially myelotoxic drugs (carbamazepine, lamotrigine, methimazole).

All of the cases of neutropenia spontaneously resolved after the discontinuation of clozapine: after 2-6 days in the patients with moderate neutropenia (ANC 1.0-1.5×10^9/L), and after an average of ten days in those with severe neutropenia (ANC 0.5-1.0 $\times10^9$/L). Among the latter, two received growth factor (G-CSF 300 µg/day subcutaneously), which significantly reduced the mean time to 3.7 days.

The discontinuation of clozapine treatment led to the normalization of the hematologic picture in all of the patients with agranulocytosis, although seven experienced infectious complications that were successfully treated with antibiotics. Thirteen patients received G-CSF and their ANC increased to >1.0×10^9/L after a period of 7-14 days; in the other patients who did not receive growth factor (because it was not available on the Italian market at the time), hematologic recovery occurred a median of 28 days after drug discontinuation.

An investigation was made of the role of predisposing risk factors (age, sex, pre-treatment hemochromocytometric values, and the cumulative drug dose administered before the onset of hematologic complications), but no significant correlations were found.

As shown in Table 2, ICLOS also identifies hematologic alterations other than neutropenia and agranulocytosis. Neutrophil leukocytosis (WBC count of

Table 2. Hematologic side effects in 2,404 ICLOS-registered patients treated with clozapine.

	No. of patients	*Incidence (%)*	*Outcome*
Neutropenia (ANC 0.5-1.5×10⁹/L)	22	0.9%	complete recovery in all patients
Agranulocytosis (ANC < 0.5×10⁹/L)	16	0.7%	complete recovery in all patients
Leukocytosis (WBC 15.0-21.0×10⁹/L)	185	7.7%	spontaneous resolution in all patients
Eosinophilia (AEC > 0.4×10⁹/L)	52	2.2%	spontaneous resolution in all patients
Thrombocytopenia (Plt < 100×10⁹/L)	2	–	spontaneous resolution in both cases

15-21×10⁹/L) was reported in 185 patients (7.7%) after a median of 33.5 days of drug exposure; it was more frequent in males (117 cases = 9%) than females (55 cases = 6.4%). Mild eosinophilia (AEC >0.4×10⁹/L), unrelated to concomitant pathologies and with no difference between the sexes, was observed in 52 patients (2.2%) after a median drug exposure of 27 days. None of the leukocytosis or eosinophilia cases required the interruption of clozapine administration, and all spontaneously resolved 3-4 weeks after onset. Finally, only two patients experienced mild thrombocytopenia (Plt count of 80×10⁹/L), which rapidly normalized after drug discontinuation.

Discussion

The use of psychotropic drugs has long been considered one of the major causes of blood dyscrasias.[11,12] A critical evaluation of the literature reveals that the incidence of agranulocytosis and mild transient neutropenia among phenothiazine users is about 0.08% and 8.9% respectively.[13,14] Furthermore, the propensity of antipsychotic drugs to affect myeloid series was dramatically illustrated by an early Finnish study during which the mortality rate was 50% among the 16 patients who developed agranulocytosis after clozapine treatment.[4,6] After a long period of severely restricted use, compassionate clozapine trials started again in the mid-1980s as a result of pressure from psychiatrists who had no other compounds that were effective in cases of resistant schizophrenia. These studies confirmed the risk of agranulocytosis but also underlined the beneficial effect of hematologic monitoring, which become mandatory when clozapine once again became easily available on the market. In Italy, blood cell counts are made weekly for the first 4-5 months, and then monthly until the end of therapy.

The results from the databases of the national registries of patients monitored in the USA, UK, Ireland, France, Canada and Australia showed that the incidence of clozapine-induced agranulocytosis is about 0.8%,[5] which is in line with the more recent ICLOS data reported in the present paper. However, the 0.9% incidence of clozapine-related neutropenia in Italy is much lower than the 2.9% reported in American[6,7] and British patients;[4] this difference is probably due to the fact that for Italian psychiatrists adhesion to the ICLOS study is optional. Furthermore, an important finding emerging from ICLOS and other epidemiologic studies is that the risk of developing neutropenia and agranulocytosis clearly exists during the first 18 weeks of therapy, but decreases significantly after the first year and is similar to that observed with some phenothiazines whose use is not associated with regular blood testing.[3,4,9] The favorable impact of early detection of dyscrasias in susceptible patients has been recently highlighted by a post-marketing surveillance analysis of 99,502 American patients over a five-year period.[6,7] This study clearly shows that the rate of agranulocytosis has significantly decreased to 0.38%, and the risk of death to 0.012% instead of the higher value initially observed in Finland.[4,6]

The early administration of subcutaneous G-CSF or GM-CSF has further reduced the morbidity and mortality of clozapine-induced agranulocytosis. On the basis of various other reports,[15-17] as well as the ICLOS data, the use of growth factors can be considered warranted in high-risk patients who gradually reach the absolute neutrophil threshold level or those who have rapidly declining leukocyte counts. Further advantages are cost-savings due to the possibility of avoiding hospitalization and the use of broad spectrum antibiotics and antifungal agents for febrile neutropenia.

Retrospective analyses have been performed in an attempt to identify schizophrenic patients who are more susceptible to agranulocytosis. Unconfirmed reports suggest that an older age, female gender, belonging to certain ethnic groups, and HLA haplotype appear to increase the risk, but the clozapine dosage and baseline WBC counts do not.[3,4,8,18,19] The ICLOS analysis does not reveal any significant predisposing factors but, in agreement with occasional reports in the literature, suggests that the concomitant administration of other potentially myelosuppressive drugs may increase the risk of neutropenia and agranulocytosis.

When dealing with potentially drug-associated blood dyscrasias, it is important to acknowledge the existence of transient pancytopenic side-effects that may also be due to external factors or viral infections.[20] Transient neutropenia has been described during phenothiazine therapy[14] and in 22% of clozapine-treated patients.[21] This starts as early as the first week and then generally subsides despite continued drug administration; the main concern is whether the neutropenia is progressive and may lead to agranulocytosis.

Other transient hematologic abnormalities have been described during clozapine treatment. Mild anemia or thrombocytopenia[5,8,22] sometimes occurs but does not usually require the discontinuation of therapy; in such cases, the possibility of pre-existing underlying diseases or external factors causing pseudo-thrombocytopenia should be carefully investigated. Furthermore, a small number of patients develop leukocytosis as a result of TNF-α stimulation which increases endogenous G-CSF production.[19,23] More interesting is the finding of early and transient leukocytosis,[8,23,24] which may predict an increased risk of agranulocytosis; however, it has recently been demonstrated that this also occurs in patients whose neutrophil counts do not fall.[23] Similarly, transient and asymptomatic eosinophilia, which has been encountered in 0.2%-61.7% of clozapine-treated patients, may be an immunologic signal predicting incipient neutropenia or agranulocytosis.[25-27] The ICLOS study does not support this hypothesis but suggests other physiopathologic explanations that take into account the role of the compensatory cytokines released by clozapine treatment.[27]

How clozapine affects hematopoiesis is still unknown,[9] but the existence of a peripheral immunomediated mechanism is supported by the fact that the cytotoxic activity observed in the serum of patients with agranulocytosis is attenuated by antibodies to IgM immunoglobulin.[28] The association with some HLA haplotypes[18,19] suggests a genetic background that may induce the production of autoantibodies, as in the case of patients with idiopathic hydralazine-induced systemic lupus erythematosus.[29] However, a direct toxic effect on hematopoiesis is more likely because patients with clozapine-induced agranulocytosis generally show a slow decline in neutrophil levels and do not have any myeloid precursors in bone marrow.[9,30]

One neutropenic patient was excluded from the ICLOS analysis because acute myeloid leukemia developed after treatment with G-CSF. This case deserves particular mention because clozapine clearly interferes with the maturation and differentiation processes of hematopoiesis *in vitro*,[22,30,31] and isolated cases of various types of leukemia have been reported in the literature.[5] However, a number of factors make it possible to exclude the hypothesis that clozapine is leukemogenic: the reported rate of occurrence lies within the background incidence of leukemia in the general population,[5] no dysplastic morphologic changes have been documented in the bone marrow or peripheral blood of patients with agranulocytosis,[30] and no neoplastic growth pattern has been observed in cells cultured *in vitro* in the presence of clozapine or its metabolites.[22, 30, 31]

In conclusion, the international and ICLOS registries clearly show that regular blood count monitoring is a highly effective means of minimizing the incidence of clozapine-associated blood dyscrasias. Furthermore, the availability of growth factors contributes towards reducing the risk of fatal agranulocytosis complications to a minimum. These results are encouraging when it is borne in mind that, as in the USA population,[6,7] about 30% of Italian schizophrenic patients do not respond adequately to standard antipsychotic agents and are thus potential candidates for clozapine treatment. Furthermore, it has recently been reported that clozapine might offer substantial therapeutic benefits in other neurologic disorders such as Parkinson's disease.[32]

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Potential implications for clinical practice

- The risk of clozapine-associated neutropenia and agranulocytosis is lower than initially expected.
- Regular monitoring and early administration of growth factors significantly reduce the risk of fatal clozapine-induced agranulocytosis.

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