CASE REPORT

Leucocytosis in clozapine-treated patients as predictor of loss of treatment response?

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SUMMARY

Anecdotal evidence tends to suggest clozapine treatment as a cause of leucocytosis in schizophrenic patients, however, no conclusive evidence is available on this topic. We report the clinical cases of two schizophrenic men who were diagnosed with clozapine-related leucocytosis. The clozapine treatment was performed at a dose between 200 and 400 mg/day. When leucocytosis appeared, there was a loss of response to clozapine in both patients. Clozapine-induced leucocytosis in schizophrenic patients could be correlated to occurrence of psychotic symptomatology.

clozapine-induced leucocytosis and its clinical significance are available, to date.

CASE PRESENTATION

We report the clinical cases of two men, respectively, 23 and 34 years old. Their initial body weight was 83 kg (body mass index, BMI: 26.3) and 95 kg (BMI: 28.4), respectively. Men and their caregivers were informed of the study, and gave consent to take part in it. The two patients were chronic cigarette smokers (about 40 cigarette per day). They both suffered from an early onset schizophrenia (paranoid subtype), showing persecutory and reference delusions, auditory hallucinations (commenting voices, with hostile tones) and aggressive behaviour and had been treated for several years with first generation (haloperidol, bromperidol, zuclopentixol) or second generation antipsychotics (olanzapine, amisulpride), at therapeutic doses, reporting only occasional amelioration; such clinical amelioration was usually followed by a worsening of the clinical picture, with a clear tendency to chronic course and significant social, relational and occupational dysfunction. They both underwent many hospitalisations over the years. Given the resistance to other typical and atypical antipsychotics, for both patients, the previous treatment was gradually tapered down and then discontinued; clozapine was gradually introduced, at a dose of 200 mg/day in the first patient, and of 400 mg/day in the second patient. Other medications associated with clozapine were flurazepam (15 mg/day) and ordelozepam (2 mg/day). However, both patients were taking these drugs prior to clozapine introduction and no evidence of leucocytosis was shown. Clinical efficacy was assessed before the initiation of clozapine treatment, and then every week during the first 16 weeks of treatment, by the 18-items Brief Psychiatric Rating Scale (BPRS).¹⁰ Clinical response was defined as a minimum of 20% improvement of the BPRS global score.¹¹ In both cases, there was clinical improvement. After 10 years of clinical compensation for the first and 8 years for the second patient, without any abnormality of blood cell count, leucocytosis appeared. WCC and ANC ranged between 12.56×10^3 and $22.26 \times 10^3/\text{mm}^3$, and between 8.57×10^3 and $17.67 \times 10^3/\text{mm}^3$, respectively. When leucocytosis appeared, a loss of response to clozapine and psychopathological decompensation were observed in both patients. Clinical loss of efficacy was reflected in the thought disorder subtotal score (20) and in the hostility-suspiciousness subtotal score (17). Therefore, clozapine, N-desmethyl-clozapine and

BACKGROUND

Clozapine is an atypical antipsychotic used for the management of treatment-resistant schizophrenia, but it is associated with several side effects.¹ In particular, one of the most serious side effects related to clozapine is agranulocytosis (absolute neutrophil count, ANC: $<500/\text{mm}^3$) and leukopenia (white cell count, WCC: $<3000/\text{mm}^3$).² Leucocytosis, defined as WCC greater than $11 \times 10^3/\text{mm}^3$, appears to be more frequent in men.³ According to the Italian Clozapine Monitoring System (ICLOS), the incidence of leucocytosis is 7.7%.² However, transient and persistent clozapine-related leucocytosis has received little attention in the literature. Anecdotal literature reveals that most cases of leucocytosis in clozapine-treated patients had concurrent conditions, such as cigarette smoking,³ cotreatment with lithium,⁴ esomeprazole,⁵ pretreatment splenectomy⁶ or stress related to rehabilitation training.⁷ Moreover, treatment with the atypical antipsychotic was also reported to be associated with an increased risk of developing acute myeloid leukaemia.⁸ Cotreatment with drugs such as corticosteroids and β -agonists can also cause leucocytosis in clozapine-treated patients.³ Other blood dyscrasias that occurred with leucocytosis in clozapine-treated patients were occasional and with poor clinical relevance,³ except for the elevation of platelets in a case of splenectomy and following treatment with clozapine.⁶ Some authors recently suggested leucocytosis and neutrophilia in clozapine-treated patients to be a dose-dependent effect^{5,9}; however, when the clozapine dose was tapered down, the blood cell counts decreased proportionately: leucocytosis and neutrophilia were resolved, but they returned when clozapine was restarted.⁹ Clozapine-induced leucocytosis was not associated with clinical consequences in all reported cases who continued clozapine treatment. However, no conclusive data concerning

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clozapine-N-oxide plasma levels were obtained for both patients. A daily clozapine dose of 350 mg (clozapine plasma levels: 189.2 ng/mL, N-desmethyl-clozapine: 188.6 ng/mL; clozapine-N-oxide: 85.0 ng/mL) and of 650 mg (clozapine plasma levels: 459.7 ng/mL, N-desmethyl-clozapine: 216.8 ng/mL; clozapine-N-oxide: 201.9 ng/mL), respectively, was reached within 2 weeks. No clinical amelioration was observed, as highlighted by the BPRS global score. However, an increase in the previous WCC was shown; lymphocyte, eosinophil, erythrocytes and platelet count remained at normal values throughout the clozapine-treatment period. Both patients underwent significant weight gain compared to the beginning of the study (87.5 kg and 101.7 kg, respectively).

INVESTIGATIONS

Multiple clinical consultations were made to explore the possible causes of leucocytosis. No clinical evidence of infection was present. Vital signs, including temperature, were unremarkable. Urine analysis, hepatitis profile, thyroid/liver/kidney function tests, inflammatory indices (ie, erythrocyte sedimentation rate and high-sensitivity C reactive protein), serum electrolytes, chest X-ray and full abdomen echography were all within normal limits.

DIFFERENTIAL DIAGNOSIS

Medical and haematological consultations found no evidence of any systemic or myeloproliferative illness.

TREATMENT

Clozapine-treatment was gradually tapered down and then discontinued in both patients. When the clozapine dose was tapered down, the blood count decreased proportionately, so that WCC and ANC were within normal range since the discontinuation of clozapine.

OUTCOME AND FOLLOW-UP

Both patients had psychopathological decompensation and an improvement in their psychotic condition was observed after the introduction of another antipsychotic treatment, different from clozapine (paliperidone, at a dose of 6 mg/day in the first patient, and 9 mg/day in the second patient).

DISCUSSION

Both our patients had an early response at 4 weeks. Furthermore, male gender,^{12 13} earlier age of onset,¹⁴ higher levels of positive symptoms^{15–17} and a paranoid subtype of schizophrenia,^{12 15 18} have been reported to predict good response to clozapine, in line with our clinical evidence. On the contrary, Nielsen *et al*,¹³ although considering male gender a positive predictor, did not find an association between clozapine response and schizophrenia subtype. Moreover, our cases suggest the onset of leucocytosis in clozapine-treated patients as a predictor of loss of response to the antipsychotic. The relationship between leucocytosis onset and loss of response to clozapine treatment is not yet clear. The mechanism of clozapine-induced leucocytosis could be related to changes in plasmatic concentrations of granulocyte colony-stimulating factor, tumor necrosis factor- α , interleukin (IL)-2 and IL-6 cytokines, which could be stimulated by clozapine.⁹ In fact, these cytokines are involved in the up-regulation of anti-apoptotic proteins, inducing differentiation and maturation of myeloid cells to granulocytes.⁹ In both cases, we report that the rise of the WCC and ANC was consistent with the increase of clozapine dose, suggesting a dose-dependent effect, in accordance

with the evidence reported by Sopko and Charles⁵ and Liu *et al*.⁹ Furthermore, Lieberman *et al*¹⁹ reported a decreased response to clozapine in chronic schizophrenic patients with an early onset of the illness, especially in those with disease lasting for more than 9 years. Many authors suggest that chronicity plays a crucial role in determining response to drugs. As for other antipsychotics, progression and successive psychotic exacerbations may result in diminished therapeutic responsiveness to clozapine.^{19–21} As mentioned above, some studies have shown significant immunomodulatory effects of clozapine.^{9 22} Clozapine-mediated inflammatory response seems to especially appear during the first month of treatment and it is manifested by increased proinflammatory cytokines. This immunological mechanism could be involved in myocarditis, pericarditis, serositis and hyperthermia, caused by clozapine treatment.²² Otherwise, our cases suggest a delayed clozapine-mediated immunological action, which could present different features, being involved in the therapeutic loss of response to the drug. Furthermore, low doses of clozapine may be sufficient to achieve response in treatment-resistant schizophrenic patients early in their illness.²³ Thus, our report supports the idea that treating patients in an earlier period of their illness, when resistance to treatment is only beginning to develop, may improve the response to clozapine. In accordance to evidence reported by Lieberman *et al*,¹⁹ we suggest that leucocytosis during clozapine treatment may represent a predictor of loss of response to the antipsychotic and therefore of treatment-resistant schizophrenia, due to chronicity. Of course this interpretation remains speculative and further studies, conducted in large populations and controlled environments, are needed to confirm this hypothesis. However, the appearance of leucocytosis during clozapine treatment should not induce clinicians to discontinue the drug, unless a bone marrow biopsy should indicate a toxic involvement of precursor cells in the bone marrow. This could be linked to the toxic effect of clozapine itself, and its major metabolite (N-desmethyl-clozapine), which are reported to have cytotoxic effects on human bone marrow stroma cells.²⁴

Learning points

- ▶ Clozapine-related leucocytosis could be involved in the loss of the antipsychotic response.
- ▶ Clozapine-related leucocytosis seems to be a dose-dependent effect.
- ▶ Early clozapine treatment in treatment-resistant schizophrenia may be critical in preventing a chronic and deteriorating course of the illness.
- ▶ Further research to clarify the real incidence of clozapine-related leucocytosis and its role in the loss of response to the antipsychotic are needed.

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Competing interests None declared.

Patient consent Obtained.

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