Anemia Among Schizophrenic Patients: Influence of Clozapine and C-Reactive Protein

To the Editor: Lee et al[1] studied the impact of clozapine on the erythroid lineage in a sample of schizophrenic patients and found a high incidence of anemia in the first 2 years following clozapine initiation, with smoking and baseline hemoglobin level shown to be significant protective factors. They concluded that there was a need for further studies of the relationships between schizophrenia, clozapine, and anemia. Following their observations and conclusions, we would like to note the following 2 main points:

First, regarding the known dose-related clozapine toxicity, the presence of a mean plasma clozapine level above the upper limit of the therapeutic range (360–690 ng/mL)[2] among anemic patients should be highlighted. In fact, the group of anemic patients[1] presented a mean value of 771.7 ± 287.1 ng/mL (n = 7), which suggests a potentially toxic outcome, compared with a lower mean value of 575.0 ± 262.8 ng/mL (n = 19) in non-anemic patients, although the difference was not significant because of a lack of sufficient statistical power. In this regard, we know that cytochrome P450 reductase (CYP) 1A2 is the most important route of clozapine metabolism,[2] the metabolic activity of which is mediated by smoking, as it is one of most important CYP1A2 inducers. Smoking, which has been shown to have different incidences among anemic and non-anemic patients (22% vs 65%, $Z = 3.6$; 95% CI, 0.1967–0.6653; $P < .001$) according to Lee and colleagues' study,[1] is crucial for the presence of toxicity associated with high plasma clozapine levels; further, there is a proven dose-response relation between plasma concentration and the risk of adverse events.[3,4] Thus, if Lee et al[1] had submitted data on plasma clozapine level and compared smokers with nonsmokers, we would have additional information about the influence of smoking on the plasma levels of clozapine and their toxicity.

Second, regarding clozapine-related anemia that presents following treatment initiation within the first 2 years, the effect of clozapine on high-sensitivity C-reactive protein (hs-CRP), an acute-phase reactant and marker of inflammation, as a possible confounder for the typing of anemia and, therefore, the attribution of its pathogenesis, should be highlighted. For example, anemia of inflammation is most commonly described as normocytic-normochromic, but it can become microcytic-hypochromic (a typical pattern of iron-deficiency anemia) or resolved in accordance with the development of the inflammatory disorder.[5] In fact, we know that clozapine, especially at the beginning, leads to increased hs-CRP unrelated to age, race, or smoking status.[6–8] Moreover, hs-CRP level is inversely related to hemoglobin level, which could result in transient anemia through hs-CRP elevation.[9,10] In this regard, observations based on post hoc comparative data analysis (2010 vs 2013), from our own previous study,[11] showed a decrease in the mean value of hs-CRP ($t = 2.1786$; 95% CI, 0.183–4.217; $P < .05$) and anemia prevalence over time (Table 1). Thus, if Lee et al[1] had submitted data on hs-CRP among anemic compared with non-anemic patients, we would have additional information about the influence of inflammatory cytokines on clozapine-related anemia.

In conclusion, these data, if supplied, would have provided additional insight into the pathogenesis, diagnosis, and treatment of clozapine-related anemia.

Table 1. Anemia Among a Cohort of Clozapine-Treated Patients: Comparative Analysis of the Results From 2 Different Years[a]

Characteristic	Year 2010 (N = 33)	Year 2013 (N = 33)	*P* Value
Anemia, n (%)	5 (15)	2 (6)	.285
Anthropometrics			
Male, n (%)	22 (67)	22 (67)	1.000
Age, mean ± SD, y	39 ± 11	42 ± 11	.272
Body mass index, mean ± SD, kg/m^2	30 ± 6	29 ± 6	.501
Smoking, n (%)	19 (58)	19 (58)	1.000
Clozapine, mean ± SD, mg	235 ± 124	256 ± 129	.503
Period of clozapine treatment, mean ± SD, y	2.7 ± 2.1	6.7 ± 2.2	< .001*
Diagnosis (*DSM-IV*), n (%)			
Schizophrenia	23 (70)	23 (70)	1.000
Schizoaffective disorder	5 (15)	5 (15)	1.000
Bipolar disorder	2 (6)	2 (6)	1.000
Other psychotic disorders	3 (9)	3 (9)	1.000
Psychiatric drug, n (%)			
Antidepressants	8 (24)	9 (27)	.780
Benzodiazepines	12 (36)	11 (33)	.795
Lithium	5 (15)	5 (15)	1.000
Laboratory results			
Hemoglobin, mean ± SD, g/dL	14.7 ± 1.6	14.5 ± 1.4	1.000
C-reactive protein, mean ± SD, mg/L	4.7 ± 4.7	2.5 ± 3.4	.033*

[a]Data from Lozano et al.[11]
*$P < .05$.

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Drs Lee and Remington Reply

To the Editor: Lozano et al[1] raised 2 points related to our recent publication[2] highlighting the association between clozapine and anemia. First, Lozano et al[1] commented that the plasma clozapine levels in the group with anemia (771.7 ± 287.1 ng/mL) were above the therapeutic level and might lead to a toxic outcome and that perhaps smoking acted via cytochrome P450 1A2 (CYP1A2) to reduce plasma clozapine levels in the group without anemia. Our group did consider this possibility and had mentioned it in the discussion; however, the issue of an upper therapeutic limit for plasma clozapine levels remains open to debate.[3] Regarding the relationship between plasma clozapine levels and side effects, there is circumstantial evidence for seizures, though this side effect appears more closely related to increases in the oral dosage.[3] As highlighted by the authors,[1] there is the recent evidence suggesting an association between plasma clozapine levels and metabolic side effects.[4] There has been no consistent evidence linking plasma clozapine levels to agranulocytosis or neutropenia—commonly reported hematologic aberrations linked to clozapine.[3]

The relationship between smoking and plasma clozapine levels has been the subject of numerous reports.[5] As expected, we did find differences in dose-adjusted plasma clozapine levels in our sample, with the group who smoked having significantly lower levels. Unfortunately, we did not have the required data to provide further insight into the relationship between plasma clozapine levels and incidence of anemia.

On the point of smoking as a protective factor for anemia, and as we have discussed, there is evidence to show that even in the non–mentally ill, smoking in itself leads to an up-regulation of hemoglobin.[6] This is a physiological adaptation, and we have no reasons to speculate that the same will not occur in patients with serious mental illnesses. It is also possible that both mechanisms involving smoking acted synergistically, ie, the reduction of plasma clozapine levels, and hence reduced toxicity, and up-regulation of hemoglobin levels.

Second, we agree with Lozano and colleagues' point on the possible link between high-sensitivity C-reactive protein (hs-CRP) and anemia.[1] Anemia of inflammation, as stated in their letter, is sometimes known as anemia of chronic disease, which was discussed as a possibility in our discussion. The pathophysiology of anemia of chronic disease is complex and has been attributed to the direct effect of various cytokines on erythropoiesis.[7] While elevated hs-CRP appears early in the course of clozapine treatment and is reportedly transient,[8] the cases of anemia observed in our study were either recurrent or persistent. Again, since our study was naturalistic in nature and no inflammatory makers of acute phase proteins were measured, we are unable to conclude with certainty.

In summary, the available evidence we have was insufficient for us to attribute the observed anemia to clozapine alone, leaving us to discuss our findings broadly. Importantly, the studied population represents patients with treatment-resistant schizophrenia, and the findings might not be generalizable to all patients with schizophrenia. Nevertheless, we hope that findings from this study will raise awareness among clinicians and perhaps lead to further studies that might clarify the association between clozapine, smoking, and anemia.

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