Leukocytosis Associated with Clozapine Treatment

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Clozapine is the only antipsychotic approved for treatment-resistant schizophrenia. Despite its superior efficacy profile as compared with other antipsychotics, clozapine remains underutilized. Clozapine monitoring systems clearly describe the proposed management of clozapine-induced neutropenia; however, no specific mention is made of how to interpret neutrophilic leukocytosis, despite that being a relatively frequent finding.

Keywords: clozapine ; atypical antipsychotics ; neutrophilia ; leukocytosis

1. Introduction

Schizophrenia (SCZ) is a severe psychiatric disorder affecting approximately 1% of the general population [1]. Although the past twenty years have seen the development of antipsychotics with innovative mechanisms of action, namely partial agonism at D_2 and 5-HT_1 receptors, there is a large proportion of patients affected by SCZ who present suboptimal response or treatment resistance. For this population of patients, clozapine remains the most effective therapeutic option. Indeed, currently, clozapine is the only approved drug for treatment-resistant SCZ [2]. In SCZ clozapine has also shown a superior profile of efficacy for the treatment of suicidality [3], co-morbid substance use disorder [4], hostility[5][6][7], psychosis in Parkinson disease[8], and treatment-refractory mania[9]. Despite its known impact on metabolism[10], several lines of evidence suggest a positive effect on overall survival as compared to no treatment or to other antipsychotics [11][12][13][14]. Despite the mounting evidence suggesting its value in the management of the most severe cases of SCZ, clozapine remains significantly underutilized[15]. One possible explanation is the perception from prescribing physicians as a drug that needs too extensive clinical monitoring and that presents an unfavorable safety profile. Thus, experts have tried to increase the knowledge and confidence in the management of common side effects as well as in the interpretation of possible blood markers derangements of clozapine [16]. Thirty years have passed since the reintroduction of clozapine in the market following the influential paper authored by Kane [17] with mandatory blood monitoring required in numerous countries. Arguably, this factor may have further reduced the likelihood of using clozapine in certain settings but helped to determine with a reasonable level of confidence the real incidence of severe hematological side effects, up to the point of questioning the usefulness of these protocols [18]. However, considering the complex history surrounding this drug, determining the clinical significance of either a leukopenia or a leukocytosis represents a particularly critical step. In most laboratories, the reference range for circulating leukocytes is included between 4500 and 11,000 units per mm^3 (units/mm^3). Under physiological conditions, neutrophils represent their vast majority, ranging from 1800 up to 7700 units/mm^3 [19]. When considering the possible underlying causes for these anomalies, clinicians should always evaluate the absolute count of each leukocyte subpopulation: the total leukocyte counts by themselves can be misleading as an absolute leukocyte count falling within the normal range may instead be harboring an abnormal composition in one or more of its subpopulations. Clozapine monitoring systems clearly describe the proposed management of clozapine-induced neutropenia. However, no specific mention is made of how to interpret neutrophilic leukocytosis, despite it being a relatively frequent finding. Prescribers unfamiliar with this molecule may misjudge its clinical significance, potentially leading to untimely treatment interruption.

2. Leukocytosis Associated with Clozapine Treatment

Notwithstanding the significant efficacy of clozapine, in the years following its re-introduction in clinical use numerous side-effects have been described, some relatively minor and others potentially life-threatening. Its use is associated with an increased risk of weight gain, metabolic syndrome, sialorrhea, constipation, sedation, enuresis and seizures. Despite the great attention devoted to the possible development of agranulocytosis (or severe neutropenia as it is currently described, i.e., < 500 neutrophils per microliter), this is a rare event: it is estimated that the risk of observing a fatal agranulocytosis case during regular monitoring is 1 in 8000 and with a negligible risk after the first 12 months of treatment. This is a much lower risk as compared with the risk of fatal myocarditis or fatal pulmonary embolism associated with its use, estimated as 1 in 4500 and 1 in 1000, respectively [20]. Prescribers and service users alike need to be particularly

attentive and proactive in monitoring for the emergence of these major side effects. However, despite these findings, clozapine remains one of the most efficacious pharmacological treatments, and the one associated with the lowest risk of overall-cause death and treatment discontinuation as compared with the absence of treatment and with the other available treatments [14][21]. This is a particularly striking finding, especially considering how a long-acting injectable version of this medication is not available, and how its use is limited to the most severe, treatment-resistant cases.

According to the available data, clozapine use is associated with benign and transient leukocytosis [22][23], the incidence of which ranges from 0.6% to 7.7% [24][25]. A more persistent form has been described mainly in case reports and especially with concomitant lithium use [26]. More recently, Fabrazzo et al. reported leukocytosis in 37.8% of a clozapine-treated cohort of patients, with incidence rates of 11.1% and 26.7% for the transient and persistent types, respectively [27]. Male gender [24][26][28][29][30][31], and lithium co-administration represent the most important risk factors for leukocytosis [32][33]. A retrospective one-year study described a 48.9% cumulative incidence for neutrophilia in a cohort comprising 101 patients treated with clozapine [26].

Smoking is another recognized cause of idiopathic leukocytosis regardless of pharmacotherapy[19], with some studies reporting an association between smoking cessation and leukocyte count reduction [34]. Smoking is also a clinically significant inducer of the CYP450 isoenzyme primarily responsible for clozapine metabolism (i.e., CYP1A2), with smokers needing nearly 1.5 times higher clozapine doses as compared with non-smokers [35]. This effect is independent of nicotine and results from the interactions of hydrocarbons typically found in smoke and cytosolic transcription factors, yielding increased CYP1A2 gene transcription [36][37][38][39]. Similarly, lithium-induced neutrophilia is a well-known hematological effect [19] resulting from a complex interaction with the bone marrow, promoting an increased peripheral neutrophilic count [40]. Although it does not appear to prevent severe neutropenia (i.e., <500 neutrophils/mm^3), lithium augmentation is advised to prevent recurrent clozapine discontinuations in those individuals predisposed to neutropenia with neutrophil counts falling below the danger threshold indicated by the local clozapine monitoring guidelines [41][42].

As with clozapine-induced neutropenia, the precise mechanism underlying neutrophilia is currently unknown; however, a variety of different hypotheses have been proposed to explain the interaction between clozapine and the hematopoietic system's cells. The most popular among them regards this as a dichotomic process, implying both direct and indirect effects with opposing results. According to this theory, clozapine directly induces increased production of reactive oxygen species resulting in a higher expression of pro-apoptotic genes, such as p53, Bax-α and Bik. Increased release of cytokines such as TNF-α, IL-2, IL-6, and G-CSF instead indirectly induces the expression of anti-apoptotic proteins, capable of promoting the differentiation and maturation of myelocytes.

The increase in the absolute neutrophil counts appears directly proportional to higher clozapine doses, suggesting a dose-dependent drug effect. Moreover, a downward dose titration tends to produce a normalization in the neutrophil counts, offering further support to this notion [28][43][44].

A further case series[29] described chronic clozapine-induced leukocytosis in seven individuals. None of them presented medical comorbidities (e.g., traumas, burns) that could contribute to the increased leukocyte count, although all of them were smokers. The highest leukocyte count reported was 19,800 units/mm^3, with durations ranging from two to five years. No adverse consequence was reported, underscoring the benign nature of this phenomenon.

3. Conclusions

Existing evidence indicates that leukocytosis associated with clozapine treatment is an asymptomatic and benign condition. We also reported on eight additional individuals presenting stable and persistent leukocytosis during follow-up ranging from one to ten years, further expanding the available evidence regarding this common laboratory finding during clozapine treatment. Considering these data, no change in clozapine treatment is therefore needed upon its detection. Showing that safe management of asymptomatic clozapine-induced leukocytosis is feasible, particularly when other possible etiologies are ruled out applying accurate clinical monitoring.

It remains unclear whether a particular diagnostic category may be associated with a higher risk of neutrophilia during clozapine treatment. For a variety of selected studies, there was no mention of the set of diagnostic criteria applied. When specified, a clear description of the relative frequency of each nosological condition was not consistently indicated. Similarly, smoking status and age of onset for the primary diagnosis were not consistently reported.

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