Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Clozapine-related immunodeficiency: Implications for Parkinson's disease psychosis in the context of the COVID-19 pandemic

Clozapine is a second-generation antipsychotic drug use in psychiatry to treat schizophrenia, affective disorders or some dementia-related symptoms [1]. In neurology, clozapine is frequently use and recommended to manage Parkinson's disease (PD) psychosis or, with less evidence, PD dyskinesia [2,3]. However, average effective daily dose is usually 25–50 mg/day. Thus, doses are significantly lower compared with doses of 300–900 mg/day used in schizophrenia. The risk of neutropenia or agranulocytosis linked to clozapine estimated at 1.3% is well-known to physicians around the world with a peak at one month and a reduction in risk after more than one year [1]. This risk has led to the "no blood, no drug" policy and to the monitoring of blood count weekly for 18 weeks then monthly for the duration of treatment. However, apart from the well-known risk of infection linked to neutropenia, some studies suggest an increased risk of infection linked to immunodeficiency induced by clozapine itself [4–7]. It seems appropriate to shed light on this clozapine-related immunodeficiency in the current context of the coronavirus disease 2019 (COVID-19) pandemic and COVID-19 vaccines [8].

In one study, Lozano et al. [4] were the first to find a statistical association between clozapine use and selective immunoglobulin (Ig) M immunodeficiency (OR = 7.22; 95%CI 1.37–38.06). Later, in one study of 234 schizophrenic patients, Ponsford et al. [5] found significantly reduced Ig serum levels in clozapine-treated patients compared with clozapine-naive patients. Interestingly, a significant association was found between clozapine treatment duration and the degree of reduction in IgG serum levels, with an annual 0.15 g/L decline of serum IgG, thus suggesting a cumulative effect of clozapine on antibody production. Furthermore, clozapine use was associated with an increased proportion of patients using more than five antibiotic courses in a year. More recently in another study of 17 schizophrenic patients treated with clozapine, Ponsford et al. [6] found significant pan-hypogammaglobulinemia, impaired vaccine responses and reduction of class-switched memory B cells (CSMB). Recurrent infections were documented in 10/17 subjects (59%), predominately reflecting sinopulmonary infections. These abnormalities are consistent with those observed in patients with common variable immunodeficiency [9]. Interestingly, clozapine duration was associated with CSMB decline and one patient showed gradual recovery of IgG serum level with clozapine discontinuation [6].

Many studies and reviews of the literature evoke an increased risk of pneumonia in patients treated with antipsychotics and, compared to other antipsychotics, clozapine carries higher risks of pneumonia and lethality during pneumonia [7]. Pathophysiological mechanisms behind understanding the increased risk of pneumonia in patients treated with clozapine are not well established. Some authors mention: decreased immunoglobulin levels, increased interleukin-1 receptor antagonist, decreased swallowing and increased salivation and sedation. Clozapine has a high affinity for muscarinic receptors that may contribute to hypersalivation and its high affinity for histamine-1 receptors that may contribute to sedation [7]. Moreover, clozapine is metabolized by many cytochrome P450 enzymes: 1A2, 2C19, 3A4 and 2D6 [1,7]. Systemic infections release cytokines that inhibit many cytochrome enzymes, leading to an increase of serum clozapine concentration which in turn increases the risk of clozapine side effects [10].

Little data is currently available on clozapine and COVID-19. A few retrospective studies on small cohorts report a transient decrease in neutrophils and lymphocytes in the acute phase of COVID-19 [11,12]. In one study on 6309 participants, of whom 102 were positive for COVID-19, clozapine treatment was linked with an increased risk of COVID-19 infection, more than other antipsychotics [13]. Finally, some reports describe clozapine intoxication by dramatically increasing serum clozapine levels during COVID-19 infection [14,15]. International recommendations have been made regarding treatment with clozapine during the COVID-19 pandemic and propose the following measures [16].

(1) The neutrophil count may be reduced to every three months, with a dispensation up to 90 days for people fulfilling the following criteria: continuous clozapine treatment for more

than one year or never having had a neutrophil count below 2000/mm^3. A recent Japanese study of 19 patients reported no psychiatric or hematological adverse events in patients with extended monitoring interval [17].

(2) Patients on clozapine with any COVID-19 symptoms (cough, fever, chills, sore throat, myalgia, fatigue, and other flu-like symptoms) need an immediate in-person or distance medical evaluation and a complete blood count including neutrophils.

(3) If patients on clozapine become COVID-19 symptomatic, they may be required to decrease by half the dose of clozapine up to three days after the fever has passed, a point at which clozapine can be gradually increased to the pre-fever dose. Where available, clozapine levels could back-up the clinical decision.

These recommendations have been made for patients already on clozapine but no recommendations currently exist for initiating treatment with clozapine during or after COVID-19 infection. However, COVID-19 infection in the elderly and particularly in PD may be associated with confusion, delirium or psychosis that may require clozapine introduction. Furthermore, COVID-19 may even present as a worsening of PD symptoms with confusion or psychosis without respiratory symptoms [18]. In this context and in view of the lack of data, it seems pragmatic to wait for the resolution of the infection before initiating treatment with clozapine and if necessary use other drugs such as benzodiazepines.

All studies currently available concerning clozapine-related infectious risks and immunodeficiency have been carried out on schizophrenic patients. No data are available for PD or PD psychosis, which makes extrapolation of these results difficult in these populations. However, it is well-known that PD patients may be more likely to experience pneumonia compared to the general population and increasing age or presence of dementia are most commonly associated with increased mortality [19,20]. Moreover, even though the doses of clozapine used in PD psychosis are lower than those used in schizophrenia, clozapine-related immunodeficiency appears to be more related to treatment duration [5,6]. In conclusion, it seems urgent to evaluate the unrecognized effects of clozapine on the immunity of patients treated for PD psychosis in order to improve their management and security. This seems even more important in the current COVID-19 pandemic context with possibly a reduced anti-infectious and vaccine response in these patients already weakened by age and disease progression.

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