Short Communication

Clozapine, neutropenia and Covid-19: should clinicians be concerned? 3 months report

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ABSTRACT

Background: Clozapine is among the most effective antipsychotics used for treatment resistant schizophrenia. Adverse reactions to clozapine include neutropenia. In March 2020, at the start of the Coronavirus −19 pandemic, clinicians raised concerns regarding continuation of antipsychotic treatment, and specifically of clozapine, in patients with coronavirus disease. We aimed here at providing a short report focusing on the association between neutropenia and clozapine in a case series of psychiatric inpatients diagnosed with COVID-19.

Patients & methods: We retrospectively inspected data of 10 patients on clozapine, admitted to Highgate Mental Health Centre, Camden & Islington NHS Foundation Trust, between March and July 2020; selection was based on their COVID-19 positive PCR test. We used a linear regression model to estimate whether there was a significant drop in the neutrophil count during SARS-CoV-2 infection.

The analysis was done in R using a linear regression to the origin.

Results: Data were collected on 10 patients, of which 7 were males. During COVID-19 infection, neutrophils' count (ANC) was 4.13×10^9/l (SD = 2.70) which constituted a significant drop from a baseline value of 5.2×10^9/l (SD = 2.24). The mean relative reduction in ANC was −0.2729 (SD = 0.1666). The beta value of 0.8377 obtained with the linear regression showed that ANC values during SARS-CoV-2 infection were 83.77% of the baseline ANC showing that within the two time points there was a decrease of 16.23%. The linear regression had a pvalue = 8.96×10^{-8} and an adjusted R^2 of 95.94% which shows that the variability of the data is very well explained by the model. We also compared baseline ANC with ANC values approximately a month after resolution of the infection and results indicate that ANC values return to a 95% of baseline.

Conclusions: Clinicians should bear in mind that a significant drop in neutrophils' count may occur in patients taking clozapine and affected from a SARS-CoV-2 infectionand that this drop is only transitory.

1. Background

Clozapine is amongst the most effective antipsychotics used for treatment-resistant schizophrenia (Huhn et al., 2019). Clozapine remains significantly underutilized, in part due to frequent blood tests requiring regular absolute neutrophil count (ANC) monitoring (Nichols et al., 2020). Adverse reactions to clozapine include neutropenia (2.7% of patients) which can prefigure an impending life-threatening agranulocytosis, (0.4% of patients) (Atkin et al., 1996; Gee and Taylor, 2020; Pandarakalam, 2020). Clozapine treatment is also associated with diabetes, obesity, pulmonary disease (Gee et al., 2020; Dragoi et al., 2020) and a reported increased risk of COVID-19 infection (Govind et al., 2020). Switching to an alternative antipsychotic in patients clinically stable on clozapine is challenging, both for clinicians and patients, as this strategy is associated with a high risk of relapse due to the high likelihood of patients who have required treatment with clozapine being resistant to

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treatment with other antipsychotics (Butler et al., 2020; Chiappini et al., 2020).

In March 2020, at the start of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, clinicians raised concerns regarding continuation of antipsychotic treatment, and specifically of clozapine, in patients with coronavirus disease (COVID-19) (Boland and Dratcu, 2020). Initially the information emerging from the Chinese experience (Guan et al., 2020) indicated that COVID-19 was linked to lymphopenia but not neutropenia (Gee et al., 2020), and that neutrophils were in the normal range (Huang et al., 2020; Chen et al., 2020; Wang et al., 2020). Case series from around the same period also reported that clozapine-treated patients with COVID-19 symptoms and/or who tested positive to SARS-CoV-2 presented with no documented neutropenia and no statistically significant changes in ANC (Butler et al., 2020; Gee and Taylor, 2020). Furthermore, clinicians were provided with practical recommendations (Gee et al., 2020; Ostuzzi et al., 2020) and advised to continue clozapine treatment in patients with COVID-19 when indicated (Gee et al., 2020; Boland and Dratcu, 2020; Butler et al., 2020).

We aimed here at providing a short report focusing on the association between neutropenia and clozapine in a case series of psychiatric in-patients diagnosed with COVID-19.

2. Patients and methods

We retrospectively inspected data relating to patients admitted to Highgate Mental Health Centre, Camden & Islington NHS Foundation Trust, between March and July 2020. Data were anonymised for the purposes of this evaluation. Patients on clozapine who had COVID-19 symptoms and a positive SARS-CoV-2 PCR test were included. We collected the white cell count (WCC) and the ANC at three different time points: (1) baseline, (2) during SARS-CoV-2 infection and (3) post- SARS-CoV-2 infection. The baseline was an average of thecounts of the previous three years. The second time point was taken during COVID-19 infection with a mean of 3 days (SD = 2.83), a median of 3 and a mode of 2.67 days after onset of symptoms; and the third and final time point was approximately a month after a positive SARS-CoV-2 PCR test (depending on the availability of blood sample) with a mean of 53 days (SD = 50.51), a median of 30 and a mode of 26 days. An ethics' application to the NHS Health Research Authority Tool was made; no further approval was required since this report was felt to be part of a service evaluation.

We compared the baseline ANC ($ANC_{baseline}$) with the ANC during SARS-CoV-2 ($ANC_{SARS-CoV-2}$) to see whether there was a drop between the two and whether this drop was significant. We did so by using a linear regression model where the dependent variable was the $ANC_{SARS-CoV-2}$ and the independent variable was the $ANC_{baseline}$. If there was no difference between the two, the linear model would indicate a slope (β) of 1. Alternatively, the model would indicate a slope less than 1 if $ANC_{SARS-CoV-2}$ was less than $ANC_{baseline}$. Subsequently, we used the same methodology to describe (1) the difference between $ANC_{baseline}$ and the ANC obtained after resolution of the SARS-CoV-2 infection (ANC_{post}) and (2) to describe the difference between $ANC_{SARS-CoV-2}$ and ANC_{post}. The analysis was done in R (R Core Team, 2020), using a simple linear regression to the origin. We have made the data and the code available to the editor and it can be requested by contacting the corresponding author directly.

3. Results

Data were collected on 10 patients, of which 7 were males. Their median age was 45.44 years. Regarding their ethnic origin, 5 subjects were of African descent, 2 were Asian and 3 were Caucasian. The patients had been diagnosed according to the ICD-10 and the most prevalent diagnosis was that of Schizophrenia, which was the diagnosis for 8 patients; 1 patient had Schizoaffective disorder and one patient had Emotionally Unstable Personality Disorder. In terms of comorbidities

documented prior to SARS-CoV-2 infection, 2 subjects had chronic obstructive pulmonary disease, 4 had diabetes mellitus, 4 had dyslipidemia and 2 had hypertension. One patient had an estimated glomerular filtration rate of less than 60 mL/min. One patient had chronic hepatitis B. Three patients were smokers, none had alcohol or substance misuse. One patient had benign ethnic neutropenia (BEN).

All subjects developed COVID-19 symptoms between March and July 2020. All of them tested positive for SARS-CoV-2. Patients were all on clozapine and under the Clozapine Patient Monitoring System (CPMS). The mean duration of clozapine treatment was of 726.1 days prior to the date of sample collection during COVID-19 infection. Patients were receiving doses of clozapine ranging from 200 to 600 mg OD. The dose was decreased in one patient during the infection and for another patient clozapine was stopped. For most patients the course of the SARS-CoV-2 infection was uncomplicated except for one who required an intensive care unit admission and intubation.

During SARS-CoV-2 infection, the mean WCC increased to 6.08×10^9/l (SD = 2.71) from a baseline value of 5.64×10^9/l (SD = 1.73). Concurrently, the ANC dropped significantly to 4.13×10^9/l (SD = 2.70) from a baseline value of 5.2×10^9/l (SD = 2.24) (see Fig. 1). The mean relative reduction in ANC was −0.2729 (SD = 0.1666). The mean WCC after SARS-CoV-2 infection was of 7.49×10^9/l (SD = 2.58) and the ANC was of 5.28×10^9/l (SD = 2.14).

The linear regression with $ANC_{SARS-CoV-2}$ as a dependent variable and $ANC_{baseline}$ as an independent variable can be explained by the following equation:

$$ANC_{SARS-CoV-2} = 0.8377 \cdot ANC_{baseline} + 0$$

The β value of 0.8377 obtained with this linear regression showed that ANC values during SARS-CoV-2 infection were 83.77% of the baseline ANC. This provides a measurement of the drop that occurred between the two timepoints showing a decrease in ANC of 16.23%. This linear regression had a p-value = 8.96×10^{-8} and an adjusted R^2 of 95.94% which shows that the variability of the data is very well explained by the model.

The second linear regression uses ANC_{post} as the dependent variable and $ANC_{SARS-Cov-2}$ as the independent variable. The relationship between the two is explained by the following equation:

$$ANC_{post} = 1.0638 \cdot ANC_{SARS-CoV-2} + 0$$

This β value is higher than 1 and therefore shows an increase in the ANC between the time of infection and after the infection. This increase is of 6.38%. The linear regression has a p-value = 8.32×10^{-5} and an adjusted R^2 of 81.7%.

Finally, we compared the baseline ANC with the ANC after resolution of the infection. Their relationship is explained by the following equa-
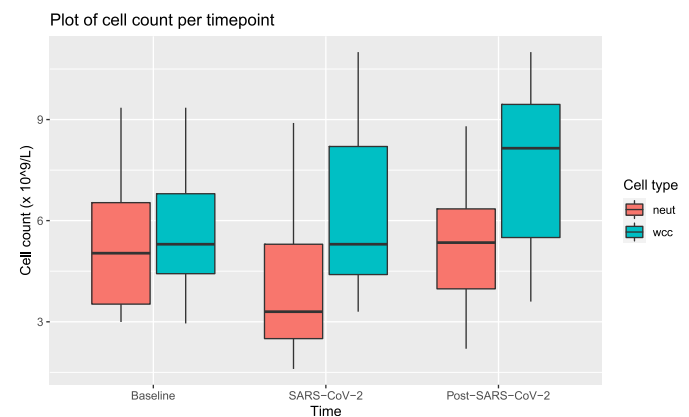

Fig. 1. Absolute Neutrophils Count (ANC) and White Cell Count (WCC) pre-, during, and after SARS-CoV-2 infection in patients taking clozapine. Baseline is an average of ANC and WCC values of previous 3 years.

tion:

$$ANC_{post} = 0.95029 \cdot ANC_{baseline} + 0$$

The equation shows that ANC_{post} is 95.029% of the $ANC_{baseline}$ with a significant drop of 4.97% for the ANC_{post} when compared to $ANC_{baseline}$. The model has a p-value = 4.06×10^{-6} and an adjusted R^2 of 90.57%.

4. Discussion

This is the first report suggesting the occurrence of a significant drop in ANC in patients taking clozapine whilst infected with SARS-CoV-2 infection. In these patients the drop was transitory and was followed by an increase in the ANC that reached values close to baseline after resolution of coronavirus disease. It is noteworthy that, in 3 patients the ANC drop resulted in a change of monitoring status from 'green' to 'amber,' (CPMS thresholds) so that more frequent blood tests were required. However, these 3 patients' amber status changed back to green, with an ANC normalization, when SARS-CoV-2 infection resolved.

In essence, these results show that, in patients with COVID-19 taking clozapine, ANC values initially decline by 17% from baseline; but subsequently increase again to around 95% of the pre-infection values following resolution of the infection. Furthermore, all patients, including the 3 who had 'amber' results whilst infected with COVID-19 achieved 'green' results approximately three months after the resolution of the infection.

These results are of considerable clinical importance for clinicians and patients as they give reassurance about continuing clozapine treatment during COVID-19 illness – when this is clinically indicated. We are aware of limitations of current report and in particular the fact that our case series included only 10 patients. We therefore advocate for studies with a larger sample size and a control group.

We also offer below a potential explanation of the role of clozapine during SARS-CoV-2 infection that looks at its potential immune-modulatory role.

An association has been suggested between severe COVID-19 and lymphopenia (lymphocytes values $< 1.5 \times 10^9$/l; 33–83%) (Fan et al., 2020), with a higher neutrophil to lymphocyte ratio (NLR) (Liu et al., 2020), predicting disease progression and likely poorer outcomes in COVID-19 pneumonia (Henry et al., 2020; Gee and Taylor, 2020). Admission lymphopenia and neutrophilia have also been reported as predictors of COVID-19 severity and mortality (Henry et al., 2020). On the contrary, in our sample a significant decrease in the ANC between the baseline and the time of SARS-CoV-2 infection was observed. It may be too speculative to claim that clozapine might act as a modulating factor against severe outcome of COVID-19, by reducing the ratio neutrophils/lymphocytes at the time of the SARS-Cov-2 infection. However, there is evidence that clozapine has immunosuppressant and pro-inflammatory effects at high doses (Clark et al., 2018) and there are suggestions that clozapine may also work on immunomodulation rather than neuromodulation only (Pandarakalam, 2020; Røge et al., 2012). Notably, fluvoxamine (Lenze et al., 2020), chlorpromazine (Plaze et al., 2020), valproic acid (Bhargava et al., 2020; Singh and Singh, 2020) and lithium (Murru et al., 2020) have recently been repurposed as potential immunomodulators in COVID-19 treatment. Conversely, inflammation has the potential to precipitate clozapine toxicity (Cranshaw and Harikumar, 2020), due to cytokines which cause CYP1A2 enzymes' inhibition and increase levels of clozapine plasma concentration (Pfuhlmann et al., 2009).

At this stage, the correlation between clozapine, SARS-CoV-2 and immunomodulation remains largely unclear. Although current data will need to be replicated in larger samples, this report may still help clinicians in focusing on a range of relevant issues, including: 1) there may be a significant drop in ANC during infection with COVID-19 for patients taking clozapine; 2) the drop may, in some cases, be so significant as to change the monitoring status from 'green' to 'amber', giving rise to

queries and concerns amongst clinicians about whether to continue clozapine treatment; 3) closely monitoring the outcome of COVID -19 infection is of paramount importance, as it is likely that once this is resolved the ANC will return to normal range.

Declaration of competing interest

Prof Schifano is member of European Medicines Agency (EMA) Psychiatry Advisory Board.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2021.100212.

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