Research Paper

COVID-19 infection causes a reduction in neutrophil counts in patients taking clozapine

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Background: Monitoring of white cell counts during clozapine treatment leads to cessation of therapy if levels fall below predetermined values. Reductions in white cell counts, driven by lower levels of lymphocytes, have been observed with coronavirus disease 2019 (COVID-19). Neutropenia during COVID-19 has not been reported. We present data for 56 patients who were taking clozapine and had COVID-19. **Methods:** We included patients who were taking clozapine at the time they tested positive for COVID-19. We compared absolute neutrophil counts, lymphocyte counts and white cell counts between baseline and the first week of infection, and baseline and the second week of infection. **Results:** We observed reductions in absolute neutrophil counts ($p = 0.005$), lymphocyte counts ($p = 0.003$) and white cell counts ($p < 0.001$) between baseline and the first 7 days of COVID-19. All cell counts had returned to baseline levels by days 8 to 14. Six patients experienced neutropenia (absolute neutrophil counts $< 2.0 \times 10^9$/L) and of those, 4 underwent mandatory cessation of clozapine. For 3 patients, clozapine treatment had been established for more than 6 months with no previous neutropenia, neutrophil levels returned to baseline within 2 weeks and no further neutropenia was observed on restarting treatment. **Limitations:** This was a retrospective chart review; larger cohorts are required. Clozapine plasma levels were largely not measured by clinicians. **Conclusion:** These data strongly suggest that mild neutropenia in the acute phase of COVID-19 in patients who are well established on clozapine is more likely to be a consequence of the virus than of clozapine treatment.

Introduction

Clozapine has unique efficacy in treatment-resistant psychosis, and for many people is the only effective treatment for their chronic psychiatric illness.[1] The coronavirus disease 2019 (COVID-19) pandemic has raised particular concerns for those taking clozapine, and it has presented challenges to safe and uninterrupted treatment for various reasons. First, clozapine is associated with an increased risk of pneumonia,[2] resulting in excess mortality. The reasons for this association are not fully understood, but higher rates of smoking[3] and frequent presentation of comorbidities such as cardiovascular disease, respiratory disease, diabetes and chronic renal failure[4] are likely to be contributory. The propensity of clozapine to cause adverse effects such as weight gain may also increase the risk of infection, and there is emerging evidence of a direct effect of clozapine on immunoglobulins.[5] These factors, including the reduction in immunoglobulins, has led to fears that patients taking clozapine might be particularly vulnerable to coronavirus infection. Data have recently been published that confirm these concerns, demonstrating that patients taking clozapine are indeed at increased risk for COVID-19.[6]

The potential for clozapine to cause neutropenia in a small number of patients (usually in the first 18 weeks of treatment), with progression to life-threatening agranulocytosis in a minority, is well known. Frequent blood monitoring mitigates the risk of undetected blood dyscrasias, but the pandemic has prompted efforts to minimize contact between patients and health care professionals and facilities, reducing the frequency of blood testing.[7] Early in the pandemic, changes in leukocytes were reported in Chinese populations.[8–13] Most authors reported reductions in total white cell counts largely driven by lymphopenia, although some also saw increases in white cell counts.[14] However, none of the patients in these studies was reported to be taking clozapine, so the potential effect of COVID-19 on the monitoring of neutrophils and other white blood cells for patients taking clozapine is unknown.

We have published some data on changes in neutrophil levels during COVID-19 illness in patients taking clozapine.[15] Here, we present a retrospective chart review of a larger cohort of these patients.

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Methods

Patients who were taking clozapine at the time of a positive nasopharyngeal swab for the viral RNA of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from March to May 2020 were included in this review. All patients were under the care of 1 of 5 London mental health trusts. Patients were identified from individual trust-held lists of patients who had recorded positive tests for the virus. Demographic data (age, sex, ethnicity, diagnosis and medical comorbidities) were collected by clinical staff from electronic patient records and categorized to maintain anonymity where necessary. We used the absolute neutrophil count (ANC), lymphocyte count and total white cell count (WCC) taken at least 14 days before a positive SARS-CoV-2 swab as a "baseline" level. We designated the day of the positive swab as day 0. We reported mean ANC, lymphocyte count and WCC for days 0 to 7 and 8 to 14. When no blood test was taken on days 8 to 14, we used the next available counts as representative of the post-infection results. We compared baseline blood results with the mean levels for days 0 to 7, and with the mean for days 8 to 14, using paired-samples *t* tests. We compared data for patients with available paired samples; we excluded patients for whom no paired outcome was available. We analyzed data using SPSS Statistics 26 (IBM Corp.).

Approval for data collection and pooling of anonymized data was granted by information governance committees or drug and therapeutics committees at individual trusts.

Results

We obtained data for 56 patients. Demographic parameters are presented in Table 1, and patient comorbidities are described in Table 2.

Eight patients had cardiac troponins measured in the 2 weeks following their COVID-19 diagnosis; the mean level was 13 ng/L (range 5–19 ng/L). More patients had C-reactive protein measurements taken (n = 33); mean levels were 50 mg/L (range 1–315 mg/L). Nineteen (34%) patients were admitted to hospital for inpatient treatment within 14 days of the SARS-CoV-2 test; of these admissions, 13 were for complications related to COVID-19, 3 were for other reasons and data were unavailable for the remaining 3. Four patients died within 2 weeks of testing positive for SARS-CoV-2; 3 of them have been described previously,[15,16] and the fourth patient died from COVID-19 pneumonia on day 10 of infection.

The mean length of patients' current clozapine treatment episode was 4.6 years (range 12 days to 28 years). The mean clozapine dose at the time of the COVID-19 diagnosis was 342 mg/d (range 50–800 mg/d). When we excluded patients who were no longer taking clozapine, the mean increased to 348 mg/d (range 100–800 mg/d) after the 14-day designated COVID-19 infection period, but this difference was not statistically significant (p = 0.11). Most patients (n = 36; 64%) had no change in their clozapine dose during the infection period. Six (11%) patients had their clozapine dose reduced, 1 (2%) had their dose increased and 13 (23%) had their treatment stopped (4 patients for less than 14 days, 9 patients for more than 14 days). Of the 13 who had their treatment stopped, 4 stopped because of neutropenia (described in detail below). The remaining patients stopped because of concerns about continuing treatment during a concurrent infection (n = 7), nonadherence with clozapine monitoring (n = 1) or a preplanned switch to a different antipsychotic (n = 1).

Table 1: Demographic characteristics (n = 56)

Characteristic	*n* (%)
Age, yr	
< 20	1 (2)
21–30	4 (7)
31–40	12 (21)
41–50	11 (20)
51–60	16 (29)
61–70	7 (13)
71–80	4 (7)
> 80	1 (2)
Sex	
Male	36 (64)
Female	20 (36)
Ethnicity	
Black	24 (43)
White	20 (36)
Asian	8 (14)
Other	4 (7)
Diagnosis	
Schizophrenia	36 (64)
Schizoaffective disorder	16 (29)
Other	4 (7)
Benign ethnic neutropenia	
Yes	5 (9)
No	51 (91)
Inpatient at time of positive swab	
Yes	48 (86)
No	8 (14)

Blood parameters are presented in Table 3. Of the 56 patients, 6 (11%) experienced neutropenia (ANC < 2.0×10^9/L). None of these 6 patients had a diagnosis of benign ethnic neutropenia. Four had neutropenia severe enough to reach the threshold for mandatory cessation of clozapine; their cases are described more fully below.

Patient A

Patient A was a non-White female in the 21–30 age group. She had been taking clozapine for 231 days; up to the day before her COVID-19 diagnosis, she had never had a recorded neutrophil count below 2.5×10^9/L. Her first recorded episode of neutropenia was an ANC of 1.8×10^9/L the day before her COVID-19 illness was detected. Her ANC rose on day 1 of infection to 4.2×10^9/L. The next recorded ANCs were 1.2×10^9/L on day 8 and 1.4×10^9/L on day 9. These consecutive episode of neutropenia resulted in the cessation of clozapine treatment for 24 hours. The

Table 2: Comorbidities (n = 56)

Comorbidity*	n (%)
Chronic lung disease	
Emphysema	1 (2)
Chronic bronchitis	4 (7)
Asthma	3 (5)
None	47 (84)
Missing data	1 (2)
Cardiovascular disease or hypertension	
Yes	25 (45)
No	31 (55)
Diabetes	
Type 1	2 (4)
Type 2	19 (34)
None	35 (63)
Estimated glomerular filtration rate < 60 mL/min	
Yes	12 (21)
No	38 (68)
Missing data	6 (11)
Body mass index, kg/m^2	
< 18.5	3 (5)
18.5–24.9	5 (9)
25–29.9	21 (38)
30–39.9	16 (29)
> 40	7 (13)
Missing data	4 (7)
Smoker	
Yes	27 (48)
No	29 (52)
Alcohol use disorder	
Yes	5 (9)
No	49 (88)
Missing data	2 (4)
Substance use disorder	
Yes	4 (7)
No	50 (89)
Missing data	2 (4)

*Where data were unavailable, this has been recorded as "missing data."

Table 3: Mean blood parameters by time period

Parameter	n	Cell count (range), $\times 10^9$	p value (n)*
Absolute neutrophil count			
Baseline	56	4.72 (2.00–19.50)	
Days 0 to 7	47	3.83 (0.75–10.10)	0.005 (47)
Days 8 to 14	45	4.73 (1.35–20.64)	0.96 (45)
Lymphocyte count			
Baseline	42	2.00 (0.2–5.00)	
Days 0 to 7	41	1.43 (0.56–3.9)	0.003 (36)
Days 8 to 14	40	1.94 (0.6–3.96)	0.54 (39)
White cell count			
Baseline	54	7.43 (3.50–22.2)	
Days 0 to 7	47	5.79 (2.25–12.42)	< 0.001 (46)
Days 8 to 14	45	7.42 (3.40–25.71)	0.96 (45)

*Compared to baseline.

neutropenia resolved by day 14 (no blood results were recorded for days 10 to 13) and was not repeated in the subsequent 6 months.

Patient B

Patient B was a Black male in the 51–60 age group. He had been taking clozapine for 520 days before he tested positive for SARS-CoV-2, but he had also had a previous treatment episode of 5 years. This previous episode ended because of 1 unexplained episode of neutropenia (recorded nadir 0.7 × 10^9/L) during a critical care admission after a road traffic accident, but the patient had no episodes of neutropenia in the 5 years before that. Patient B's ANC was 0.9 × 10^9/L on day 5 of COVID-19 illness, and it remained between 1.2 × 10^9/L and 2.1 × 10^9/L for days 6 to 8. His ANC recovered (> 2.0 × 10^9/L) by day 9, and his clozapine treatment was restarted. He had no recorded episodes of neutropenia in the subsequent 6 months.

Patient C

Patient C was a White male in the 31–40 age group who had been taking clozapine for 339 days. His ANCs were consistently above 2.5 × 10^9/L until an episode of neutropenia (1.2 × 10^9/L) was recorded on day 6 of COVID-19 illness. His ANC had recovered to 2.7 × 10^9/L by day 8, and clozapine was restarted on day 10. He had no recorded episodes of neutropenia in the subsequent 6 months.

Patient D

Patient D was a non-White male in the 21–30 age group. He had been taking clozapine for 67 days, and up to the day before his COVID-19 diagnosis he had never had a recorded ANC of less than 2.9 × 10^9/L. His first recorded episode of neutropenia was an ANC of 1.3 × 10^9/L the day before COVID-19 was diagnosed. His ANC fell further on day 1 of infection to 0.9 × 10^9/L, and the next recorded ANCs were 0.5 × 10^9/L on day 6 and 0.6 × 10^9/L on day 7. These consecutive results led to cessation of clozapine treatment, and the patient was diagnosed with neutropenic sepsis. No blood tests were recorded between days 8 and 37 of infection, but the neutropenia had resolved by the time of the next test on day 38. Patient D had previously been prescribed a zuclopenthixol decanoate depot injection; the last dose was administered 10 days before he started clozapine. His clozapine treatment was not restarted.

Discussion

This retrospective chart review showed a statistically significant reduction in ANCs, lymphocyte counts and total WCCs in the week after a positive SARS-CoV-2 test result, a finding that was clinically significant for 4 patients (7%), necessitating the cessation of clozapine treatment. This finding strongly suggests that mild neutropenia in the acute phase of COVID-19 illness in patients who are well established on

clozapine is more likely to be a consequence of the infection than related to clozapine treatment. The rapid return to baseline counts supports this conclusion.

Clozapine-associated neutropenia is reported to occur in 2.7% of patients,[17] and can herald life-threatening agranulocytosis (0.4% of patients).[18] Mandatory WCC monitoring (including ANC) has been an effective strategy for mitigating this risk. Agranulocytosis is most common in the first 18 weeks of treatment (80% of cases),[19] and the likelihood of occurrence after the first year is comparable to other antipsychotics.[20] Mild to moderate neutropenia (ANC 0.5–1.5 × 10^9/L) does not increase the risk of infection;[21] agranulocytosis (ANC < 0.5 × 10^9/L) is associated with a mortality rate of 2 to 4%.[22]

Neutrophilia is now considered to be an early indicator of potential COVID-19 infection,[23] predicting a more severe disease course.[24,25] Lymphopenia is commonly reported (83% in a case series of more than 1000 patients in China[11]), but neutropenia is not. A single case report[26] describes neutropenic fever as a possible consequence of COVID-19 in a patient with leukemia and pancytopenia who was taking an immunosuppressant. There is also emerging evidence that clozapine may affect adaptive immune responses;[27] 1 group suggested that immunoglobulins A, M and G may be reduced.[28] The effects of COVID-19 on the innate immune system are certainly present; neutropenia and agranulocytosis occur in a minority of patients.[18] We have identified a correlation between decreased ANCs, lymphocyte counts and total WCCs during COVID-19 in patients taking clozapine. Cranshaw and Harikumar[29] described a case of clozapine toxicity in relation to COVID-19, with concurrent mild and transient neutropenia (ANC 1.6 × 10^9/L). Luykx and colleagues[30] described a patient who was taking clozapine and developed "severe neutropenia" while they had COVID-19. Dotson and colleagues[31] described 3 patients who experienced clozapine toxicity while they had COVID-19, 1 of whom also experienced neutropenia (ANC 1.1 × 10^9/L). This reduction in neutrophils has not been observed in populations who do not take clozapine, although it may be that patients taking clozapine are more closely monitored in this regard. Further data are required to confirm the link and establish any specific interaction effect of clozapine and COVID-19.

The presence in our study of a patient who had been taking clozapine for 2 months and developed neutropenic sepsis when they had COVID-19 serves as a reminder to clinicians that the well-known adverse effects of clozapine will continue to emerge during the pandemic; diagnostic overshadowing by the virus must be avoided. Without further clinical investigation, we are unable to establish whether the neutropenia for this patient was clozapine-induced or caused by COVID-19. For patients who have been taking clozapine for less than 6 months, we suggest that neutropenia during infection should be assumed to be caused by clozapine, and the usual precautions (including cessation if required) should be followed. When considering a clozapine re-challenge in such patients, the presence of COVID-19 during the neutropenic episode should be included in the evaluation of the risk of recurrence.

The consequences of clozapine cessation can be catastrophic. Relapse of psychosis is highly likely,[32] and other antipsychotics are highly unlikely to provide symptom relief.[1] The safe and effective management of a patient with acute psychosis who has tested positive for SARS-CoV-2 is likely to be challenging. Our data suggest that COVID-19 illness can cause transient mild neutropenia in patients taking clozapine. We propose that this is unlikely to be purely clozapine-induced for patients who have been taking clozapine for more than 6 months, given the late onset in relation to clozapine initiation and the temporal relationship to COVID-19. Given the potential risks of stopping clozapine, we suggest that patients who have been established on clozapine for more than 6 months and who have had no previous episodes of neutropenia should continue taking clozapine if their ANC drops below 1.5 × 10^9/L during a period of COVID-19 illness. Patients' ANC should be monitored daily and clozapine stopped if their ANC drops below 1.0 × 10^9/L.

We did not find a statistically significant reduction in clozapine doses during COVID-19 illness. At the time of the review, local and national advice was to consider a dose reduction,[33] in some cases up to 50%[34] given the risk of escalations in clozapine plasma concentrations during systemic infection and especially if smoking frequency was reduced. Clozapine plasma concentrations were not measured consistently during the infection period in this patient group, so those data have not been presented here. A significant proportion of patients (23%) had their clozapine temporarily stopped in the acute phase of the illness; of those, more than half stopped their treatment out of concerns about continuing therapy during their illness. At the beginning of the pandemic, uncertainty about the potential consequences of COVID-19 for patients taking clozapine was likely to have contributed to anxiety about the continuation of prescribing. With increasing experience,[16] we now suggest that cessation is unnecessary (unless other clinical concerns are present) and should be weighed against the risk of psychotic relapse.

Limitations

Patients were identified for inclusion in this review at a time when testing for SARS-CoV-2 was being carried out largely only for hospital inpatients. Undoubtedly, patients taking clozapine in the community were also contracting the virus but were not being tested. Although this limited our sample size, we do not think it was likely to influence our conclusions; there is no reason for ANCs to be different depending on patients' location or the severity of their psychotic symptoms. Although some patients in this study were transferred to medical settings for severe complications of COVID-19, we have previously described several of these cases in more detail[16] and did not find significant changes in neutrophil levels, suggesting that the severity of infection may not have been a factor influencing neutropenia.

The lack of data for clozapine plasma levels was unfortunate given the suggested risk of this occurrence in other infections. Future work should examine this question more closely with the aim of providing evidence-based guidelines for dose

adjustment. In the absence of clear evidence, it remains our opinion that prescribers should consider cautious dose reduction during severe infection, balancing the risk of relapse with the risk of toxicity. Where possible, dose adjustments should be guided by monitoring of clozapine plasma levels.

Conclusion

Neutropenia may occur in patients who are taking clozapine and contract SARS-CoV-2, but it is likely to be mild and transient. Cessation of clozapine is expected to result in psychiatric relapse, an outcome with difficult practical implications for patients who test positive for the virus. We suggest that stopping clozapine is unnecessary for patients who have been established on treatment for more than 6 months with no previous episodes of neutropenia, and where ANC remains above 1.0×10^9/L.

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Availability of data and materials: The datasets generated during the current study are not publicly available because of restrictions on sharing patient data outside individual NHS trusts. Data are available from the authors upon reasonable request and with permission of the relevant individual NHS trusts.

Ethics approval and consent to participate: Ethics approval and consent was provided by drug and therapeutics committees or information governance committees at individual NHS trusts. Data were collated and analyzed by South London and Maudsley NHS Foundation Trust; drug and therapeutics committee study approval code: DTC/2020/101

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