NHS
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Clozapine and blood dyscrasias in patients with coronavirus (COVID-19)

Coronavirus infection may depress lymphocyte count but does not reduce neutrophils

Effect of COVID-19 on WCC

Current data suggest that COVID-19 infection results in a lowered white cell count (WCC) for some (9–45% of patients have WCC <4.0 x 10^9/L) (1–5). Lymphocytopenia (lymphocytes < 1.5 x 10^9/L) is reported in 33–83% of patients) (1–6). More severe abnormalities correlate with severity of the disease. Notably however, studies have found neutrophils to be in the normal range (median 3.0 - 5.0 x 10^9/L) (1,6) or raised (>6.3 x 10^9/L, 38% of patients in one study (2)).

Effect of clozapine on WCC

Clozapine is known to cause haematological side effects. The most common (2.7% of patients (7)) is neutropenia, which can be an indicator of increased risk of life-threatening agranulocytosis (seen in 0.8% of patients). For this reason, monitoring of the WCC (including absolute neutrophil count (ANC)) is mandatory. Over 80% of cases of agranulocytosis occur in the first 18 weeks of treatment. By the end of the first year of treatment, the risk of agranulocytosis is comparable to that of other antipsychotics (8).

Current UK monitoring guidelines (9)

Patients without Benign Ethnic Neutropenia (BEN)

Blood counts (x 109/L)	Classification	Action
WBC ≥ 3.5 AND neutrophils ≥ 2.0	**GREEN**	Continue clozapine treatment
WBC ≥ 3.0 and < 3.5 AND/OR neutrophils ≥ 1.5 and < 2.0	**AMBER**	Increase monitoring frequency
WBC < 3.0 AND/OR neutrophils < 1.5	**RED**	STOP clozapine treatment immediately

Patients with BEN

Blood Counts (x 109/L)	Classification	Action
WBC ≥ 3.0 AND neutrophils ≥ 1.5	**GREEN**	Continue clozapine treatment
WBC ≥ 2.5 and < 3.0 AND/OR neutrophils ≥ 1.0 and < 1.5	**AMBER**	Increase monitoring frequency
WBC < 2.5 AND/OR neutrophils < 1.0	**RED**	STOP clozapine treatment immediately

The WCC comprises measures of lymphocytes, neutrophils, monocytes, basophils and eosinophils, among others. However, the adverse effects of clozapine on haematological parameters are related to neutrophils, not other white cells (apart from eosinophilia, which is largely benign). Neutrophil counts of 0.5 – 1.5 x 10^9/L (defined as mild to moderate neutropenia) may not be associated with a significantly increased risk of infection (10), but are important in clozapine patients as they may portend agranulocytosis.

Agranulocytosis is defined as a neutrophil count of <0.5 x 10^9/L, and the case fatality rate is between 2 and 4% (9).

It appears likely that patients with COVID-19 infection will have a low WCC. This seems to be largely due to reduced lymphocytes. As the monitoring parameters for clozapine include total WCC, a reduction may result in patients registering results that, under normal circumstances, require interruption of clozapine treatment. However, the purpose of interrupting clozapine treatment is to protect patients from neutropenia and agranulocytosis. Where a low WCC count occurs in the presence of a normal or non-dangerous neutrophil level in the context of COVID-19 infection, it is reasoned that clozapine can be safely continued.

It is also important to consider the risk of discontinuing an effective antipsychotic treatment such as clozapine at a time when uncontrolled psychotic symptoms (which are unlikely to be treated by other drugs) may present challenges in safely managing an infected patient. So, continuation of clozapine treatment is the imperative unless low neutrophil counts dictate treatment cessation.

Note that serious infection is sometimes associated with an increase in clozapine blood levels, either because of a direct effect on metabolism or because smoking cessation reverses hepatic enzyme induction (or both).

Clozapine and COVID-19

All patients with symptoms of COVID-19

All clozapine patients with symptoms of COVID-19 must have a blood sample taken immediately for WCC and ANC, and for clozapine plasma concentration

The most frequently reported symptoms of COVID-19 infection are fever, cough, myalgia, fatigue and shortness of breath. Symptoms of neutropenic sepsis include a fever, 'flu-like' symptoms, rigor and malaise. The overlap between the symptoms of these two conditions means that rapid differential diagnosis is essential (not covered here).

Suggested actions in COVID-19 infection

1. Clozapine patients with a history or suspicion of clozapine-related blood dyscrasia

ANC (x 10^9/L)	Action	Monitoring
> 2.0 (BEN: > 1.5) AND drop in WCC is temporally consistent with the onset of COVID-19 symptoms	Continue clozapine	Continue to monitor FBC as normal
< 2.0 (BEN: < 1.5)	Stop clozapine	Monitor FBC TWICE WEEKLY. Restart clozapine when two consecutive ANC results are > 2.0 unless there is a clear contra-indication to doing so

Previous blood dyscrasias that fulfil the following criteria are suggestive of being clozapine-related:

- Inconsistent with previous WCC (i.e. not part of a pattern of repeated low WCC)
- Occurred in the first 18 weeks of treatment
- Severe (neutrophils <0.5 10^9/L)
- Prolonged

Subsequent clozapine treatment is more likely to result in more severe and rapid neutropenia/agranulocytosis. Seek specialist advice.

2. Clozapine patients on weekly monitoring

ANC (x 10^9/L)	Action	Monitoring
> 2.0 (BEN: > 1.5) AND drop in WCC is temporally consistent with the onset of COVID-19 symptoms	Continue clozapine	Continue to monitor FBC weekly

1.5 - 2.0 (BEN: 1.0 - 1.5) AND drop in WCC is temporally consistent with the onset of COVID-19 symptoms	Continue clozapine	Monitor FBC TWICE WEEKLY until two consecutive ANC results are > 2.0
<1.5 (BEN: < 1.0)	STOP clozapine	Monitor FBC TWICE WEEKLY. Restart clozapine when two consecutive ANC results are >1.5, but only after consultation with COVID physician

3. Clozapine patients on 2-weekly or monthly monitoring

ANC (x 10^9/L)	**Action**	**Monitoring**
> 2.0 (BEN: < 1.5) AND drop in WCC is temporally consistent with the onset of COVID-19 symptoms	Continue clozapine	Continue to monitor FBC as normal
1.5 - 2.0 (BEN: 1.0 - 1.5) AND drop in WCC is temporally consistent with the onset of COVID-19 symptoms	Continue clozapine	Monitor FBC TWICE WEEKLY until two consecutive ANC results are > 2.0
<1.5 (BEN: < 1.0)	STOP clozapine	Monitor FBC TWICE WEEKLY. Restart clozapine when two consecutive ANC results are >1.5, but only after consultation with COVID physician

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