

Agranulocytosis monitoring with Clozapine: to follow guidelines or to attempt therapeutic controversies?

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ABSTRACT

Clozapine is an atypical antipsychotic with superior efficacy in the treatment of refractory schizophrenia. But it can cause agranulocytosis, which occurs in one to two percent of patients. This paper was prepared to discuss the condoned and controversial issues of therapy with this drug, but only within a haematological context. The feasibility of attempting therapeutically controversial blood monitoring regimes, as opposed to following standardised Western guidelines, given the differences in terms of accessibility, convenience and financial considerations between the public and private sector medical care will also be discussed. The proposal of adopting a structured pro forma, with a risk-benefit assessment, in the event of unavoidable veering from the guidelines may allay medicolegal implications, especially in countries where blood monitoring is not mandatory. It is hoped that this article will stimulate further research in our region, bearing in mind the increasing awareness and focus on genetic polymorphism, and the possibility of drawing up our own monitoring guidelines in the near future.

Keywords: agranulocytosis, antipsychotic drugs, Clozapine, refractory schizophrenia, schizophrenia

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INTRODUCTION

Clozapine is a unique atypical antipsychotic agent which has superior efficacy, for positive and negative symptoms, over conventional antipsychotics. Its reputation lies mainly with its repeated proven efficacy in the treatment of refractory schizophrenia. For some patients, it remains the best alternative among currently available antipsychotics, either in terms of efficacy or tolerability. It has also been shown to reduce substance abuse, violence, persistent

aggression and suicide tendencies in schizophrenic patients. This drug has affinity for many receptors (including dopamine, serotonin, muscarinic and histamine receptors). The Cochrane review, which included 29 studies involving 2,490 participants, confirmed the favourable clinical impressions of patients taking Clozapine having fewer relapses, a greater reduction in symptoms, fewer drop-outs and greater satisfaction.⁽¹⁾ However, it has a well-known side effect—agranulocytosis—which can occur in 1%–2% of patients on Clozapine. Other haematological effects include leucopenia, neutropenia and eosinophilia. Anaemia, leucocytosis and increased platelet counts have also been reported in less than one percent of patients on Clozapine.⁽²⁾

We will be discussing the current standardised western guidelines adopted in Malaysia and several ASEAN countries, as well as the feasibility of attempting therapeutically controversial blood monitoring regimes. Concerns in the light of differences in terms of accessibility, convenience and financial considerations between public and private sector medical care will be highlighted. It is hoped that this discourse would not only promote more regional research, bearing in mind issues pertaining to genetic polymorphism, and also possibly spur the institution of regionally-sanctioned guidelines soon to allay unavoidable medicolegal implications of such measures. A suggestion to use a simple structured pro forma, entailing a risk-benefit assessment, may be the answer to patients on Clozapine, with good clinical control of symptoms, refusing to comply with the currently-prescribed blood monitoring guidelines. However, it should be reserved for the worst-case scenario and not be considered as an alternative option.

DISCUSSION

The signs and symptoms of agranulocytosis are high fever, lethargy, sore throat and mucosal necroses in the throat, perianal and genital areas. The normal range of total white blood cell (WBC) count is 4.0–11.0 × 10⁹/L and absolute neutrophil granulocyte count (ANC) is 2.5–7.5 × 10⁹/L. Clozapine is contraindicated in patients with:

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Table I. Summary of international monitoring guidelines.

| | |
|----|---|
| A. | First 18 weeks – Weekly WBC counts |
| | Post-18 weeks – Monthly WBC counts |
| B. | If: |
| | <ul style="list-style-type: none"> • total WBC count falls below $3.5 \times 10^9/L$, and/or • ANC falls below $1.5 \times 10^9/L$ <ul style="list-style-type: none"> – Bi-weekly blood counts |
| C. | If, while still on treatment or after stopping treatment, and: |
| | <ul style="list-style-type: none"> • total WBC count does not fall below $3.0 \times 10^9/L$, and • ANC does not fall below $1.5 \times 10^9/L$ <ul style="list-style-type: none"> – May resume Clozapine treatment – Re-start schedule applicable for new patient |
| D. | If : |
| | <ul style="list-style-type: none"> • total WBC count falls below $3.0 \times 10^9/L$, and/or • ANC falls below $1.5 \times 10^9/L$ <ul style="list-style-type: none"> – Withdraw Clozapine immediately – Never resume Clozapine |
| E. | If, after stopping treatment: |
| | <ul style="list-style-type: none"> • total WBC count falls below $2.0 \times 10^9/L$, and/or • ANC falls below $1.0 \times 10^9/L$ <ul style="list-style-type: none"> – Continuous haematological supervision |

- (1) An abnormally low WBC count, i.e. less than $3.5 \times 10^9/L$,
- (2) A history of drug-induced agranulocytosis, i.e. ANC of less than $0.5 \times 10^9/L$,
- (3) Bone marrow disorders,
- (4) Alcoholic and other toxic psychoses,
- (5) Drug intoxication,
- (6) Comatose conditions, and
- (7) Severe hepatic, renal or cardiac diseases.

It should also not be used concurrently with drugs that have the potential to cause agranulocytosis, e.g. Carbamazepine and Mianserin. The concomitant use of long-acting depot antipsychotics should be avoided, because of the need to stop treatment immediately, should agranulocytosis develop. Plasma levels of Clozapine affect clinical response. Patients exhibiting a poor response after six months may have sub-therapeutic drug levels, particularly if they smoke. The minimum plasma level associated with a good response is 350 ng/ml.⁽³⁾ However, it would be prudent here to mention beforehand that Clozapine blood level monitoring cannot be used to prevent agranulocytosis because there is no correlation between agranulocytosis and high blood levels of this compound.⁽⁴⁾ There is also the presence of a diurnal variation in the circadian rhythm of WBCs, which can be described by the term pseudoneutropenia, during its treatment course. When detected during the weekly blood checks, this benign variation does not always

necessitate discontinuation, as proposals have been made that all WBC samplings taken in the morning should be repeated in the afternoon, if the count taken earlier is either falling or below the normal, before the decision to discontinue treatment is made.⁽⁵⁾ In the event of an overdose, provided that the total WBC count has not fallen below $3.0 \times 10^9/L$, or an ANC of below $1.5 \times 10^9/L$, Clozapine can be re-started as soon as the patient has completely recovered from the effects of the overdose.⁽³⁾ The occurrence of both leucopenia and thrombocytopenia (bicytopenia) with its use was also reported and the recovery was prolonged. There has also been a report of three patients who experienced prolonged granulocyte depression, when Olanzapine was initiated while they had decreased granulocyte levels associated with Clozapine use. This stresses that early institution of other medications for patients with Clozapine-induced haematological depression is to be avoided.⁽²⁾

According to the International Monitoring Guidelines, a WBC count and differential WBC count must be performed, before starting Clozapine treatment, to ensure that only patients with normal counts receive the drug. After the start of treatment, WBC counts must be monitored at least weekly for the first 18 weeks, because the risk of agranulocytosis is greatest during this period (75%, and primarily between weeks 4–18). (Table I) Subsequently, a total WBC count must be performed at least monthly, for as long as the patient is on the drug, and it should also be continued for four weeks after stopping treatment. If the total WBC count falls below $3.5 \times 10^9/L$, the ANC falls below $1.5 \times 10^9/L$, or any symptoms or signs of infection occur, a differential WBC count must be performed immediately and blood should be sampled twice weekly. If the total WBC count falls below $3.0 \times 10^9/L$ and the ANC falls below $1.5 \times 10^9/L$, Clozapine must be withdrawn immediately. Following the withdrawal of the drug, the patient must be closely monitored for flu-like symptoms or any other symptoms suggestive of infection. Total WBC and differential WBC counts must then be performed daily following its withdrawal and the patients must never be re-started on Clozapine. If, after removal of the drug, the total WBC count falls below $2.0 \times 10^9/L$ and/or the ANC below $1.0 \times 10^9/L$, the patient should be placed under continuous supervision of a haematologist, and if possible, put in protective isolation. If the treatment is stopped and the total WBC count does not fall below $3.0 \times 10^9/L$, or the ANC below $1.5 \times 10^9/L$, treatment may be resumed and blood monitoring should follow the schedule applicable for new patients to be started on Clozapine.⁽³⁾

Since the regulators of the US Food and Drug Administration (FDA) indicated that roughly 85% of agranulocytosis reports for patients receiving Clozapine treatment occur within the first year, the residual risk to patients after one year of continuous treatment appears to be comparable to other antipsychotic medications. Their schedule is as follows:

- (1) Weekly WBC and differential WBC counts for the first six months,
- (2) For the next six months, if there have been no haematological problems, the frequency goes down to twice weekly, and
- (3) After one year of acceptable blood testing results (both total WBC counts and ANCs), WBC and differential WBC counts may be reduced to every four weeks.⁽⁶⁾

During the US FDA meeting in 1997, three burning questions were put forward. In summary: firstly, should the frequency of WBC monitoring be reduced at some point? Their answer was yes. We would presume this to be the obvious answer for any physician who sees patients being pricked for blood on a weekly to monthly basis. Secondly, what reduced frequency of monitoring would be acceptable? Should it be stopped altogether? The answer to the former was a reduction to bi-weekly tests and to the second part, they were not agreeable at the time, but perhaps that would have to be reevaluated in the future. In our context, that would be barely acceptable in the private setting, not to mention it being cost-ineffective. Finally, should the programme be changed overall? Should it be voluntary? Their recommendation was that it should become voluntary after one year of mandatory testing.⁽⁷⁾

Some patients want to stop this monitoring, especially when receiving long-term treatment. They do not object to the medication itself, but to the blood tests. The prescribing physician may be faced with a choice between stopping Clozapine treatment or continuing it without WBC monitoring. If WBC monitoring were omitted, there is a lower chance of identifying imminent or frank agranulocytosis at an early stage, as leucopenia is not clinically obvious at this stage. Symptomatic infections usually occur only when the granulocyte count is very low. Not all prescribing physicians in our region follow the WBC monitoring guidelines used by the public and university hospitals. This is especially so if the guidelines are not made mandatory in the practising country. Although the doses of Clozapine prescribed by these doctors may be considerably lower, this does not lead to a corresponding lower risk of a patient developing agranulocytosis while receiving treatment. Physicians

also may face the dilemma of weighing significant improvement in a patient undergoing Clozapine therapy against patient refusal to blood sampling tests.

Considering the risk of mortality resulting from agranulocytosis, associated with drugs other than Clozapine, is 4.2% if they are treated with a granulocyte colony-stimulating factor, Schulte, in his controversial article, proposed that after at least six months of treatment with Clozapine, the mortality involved in stopping WBC monitoring is about the same as the mortality associated with other medications (e.g. Mianserin and Phenylbutazone) and with life in general (e.g. traffic and occupational accidents). He based his conviction on the consideration that the risk of Clozapine-induced agranulocytosis decreases exponentially over time, monthly WBC monitoring does not offer absolute protection because agranulocytosis can develop in less than one week. And since this drug reduces mortality through prevention of suicide, he suggested that the monthly WBC monitoring may be stopped after at least six months of treatment. However, before discontinuing the blood sampling, the patient should have:

- (1) asked for the monitoring to be stopped,
- (2) been informed about the risks involved,
- (3) stated in writing that he/she is prepared to take those risks, and
- (4) been counselled again that in the event of any symptoms of agranulocytosis, the WBCs should be investigated immediately.

It would be advisable to ensure that, upon the onset of suspicious symptoms, the patient should be able to obtain a WBC count outside of office hours. If WBC monitoring is stopped, occasional checks, e.g. every three months, should be recommended because slow, progressive decreases in WBC counts could be traced that way.⁽⁸⁾

Given the data on the risk of Clozapine-induced agranulocytosis, implementing blood monitoring while a patient is on the drug would be the safest path. On the other hand, if the risk in the decision to stop this monitoring outweighs the loss of clinical control of symptoms if the drug is withdrawn, then very stringent steps have to be taken to avoid any possible repercussion of malpractice. Medicolegally, several issues have to be considered when making a decision to agree to a patient's request for WBC monitoring to be stopped. They are:

- (1) Legal aspects of liability and competency may differ from country to country.
- (2) The patient must be capable of making a treatment decision, or a representative guardian will have to decide in the best interest of the patient. The presence of a mental disorder does not imply

Table II. Proposed risk-benefit pro forma.

| | Yes | No |
|--|-----|----|
| Patient | | |
| Did you ask for the blood monitoring to be stopped? | | |
| Have you been informed of the risks involved? | | |
| Have you been counselled again after your decision, and agreed, that that in the event of any symptoms of agranulocytosis, blood investigations will be carried out immediately? | | |
| Prescribing physician | | |
| Is the patient/representative guardian capable of making a treatment decision? | | |
| Is the patient/family member(s) well prepared to recognise the signs of agranulocytosis? | | |

incapacity to make decisions. There is literature, and an assessment tool, which can be used to gauge the ability of schizophrenic patients to make decisions regarding their treatment.

- (3) Some patients may be well prepared to recognise signs of agranulocytosis or may be supervised by family members, whereas other patients may live in isolation and may not pay much attention to their somatic condition.
- (4) Some patients may stop Clozapine if they are not allowed to put an end to the WBC monitoring and this may result in a reduction in their quality of life and conversely, an increased risk of suicide.
- (5) The concept of quality-adjusted life years may help to weigh dissimilar entities like longevity and quality of life.⁽⁸⁾

CONCLUSION

Ideally, following the prescribed WBC monitoring guidelines is widely encouraged. Nevertheless, in the event that a request to stop blood monitoring arises, a proposed risk-benefit assessment with the adoption of a structured pro forma (Table II) entailing the considerations above, may serve to protect one legally. However, it has to be stressed that this is not an alternative option to blood monitoring and should be employed only as a last resort measure. On a final note, prescribing physicians who are constantly faced with the dilemma of whether it is medicolegally justifiable to stop WBC monitoring, while a patient is on Clozapine therapy, will have to make that decision with the patient's best interests in mind.

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