NHS Greater Glasgow & Clyde
Mental Health Services

Protocol for Clozapine Rechallenge Following a Neutropenic Episode (Red result)

Clozapine is the gold standard drug intervention for treatment-resistant schizophrenia. Prescribing of clozapine is strictly controlled by the marketing authorisation (or product licence), requiring regular blood monitoring throughout treatment due to the risk of significant blood dyscrasias. Approximately 2.7 % of patients treated with clozapine develop neutropenia; half of those within the first 18 weeks of treatment and three quarters by the end of the first year.[1]

The marketing authorisation for clozapine states that its use is contraindicated where there is a history of clozapine-induced agranulocytosis. It also states that those individuals in whom clozapine has been discontinued as a result of either decreased white cell count or neutrophil count must not be re-exposed to clozapine. [2]

The use of clozapine after a 'red' result is therefore out with the marketing authorisation (or product licence) (referred to as 'off-label' or 'off-licence')

A 'red' alert is issued by the clozapine monitoring service when;

WBC < 3.0 x 10^9/L and/or neutrophil <1.5 x 10^9/L

Clozapine-induced neutropenia is defined as any episode of neutropenia that occurred whilst a patient was treated with clozapine for which no other possible cause, such as concurrent infection or the concomitant use of medication known to have a substantial potential for causing agranulocytosis, could be given. [3]

The clozapine manufacturers have a process that allows re-exposure to clozapine following an episode of clozapine-induced neutropenia under certain conditions and involves the consultant psychiatrist agreeing to an off-licence disclaimer.

Incidence of recurrence of blood dyscrasia on rechallenge

A review looking at a cohort of 53 patients who had been rechallenged with clozapine following a confirmed blood dyscrasia showed that around 38% of individuals (n= 20) experienced a second blood dyscrasia. In the majority of these patients, the second dyscrasia was more severe, lasted longer and occurred more quickly than the first dyscrasia. 55% of the 53 (n=29) were, however, rechallenged successfully and remained in treatment.[4] The exact cause of clozapine-induced blood dyscrasias is unknown. However, it has been suggested that there are distinct mechanisms that underlie the development of the more severe, potentially lethal agranulocytosis (neutrophils <0.5x 10^9/L) and the development of mild to moderate neutropenia (neutrophils - 0.5-1.5X10^9/L). [5]

The success rate of rechallenge after agranulocytosis is reportedly much lower than after neutropenia. [6] There are significant risks associated with a clozapine rechallenge after a blood dyscrasia and the response to a rechallenge is unpredictable.

NHS Greater Glasgow & Clyde
Mental Health Services

Restarting clozapine following a 'non-confirmed' red result [7,8,9]

Clozapine may be re-started within the conditions of the marketing authorisation if the (initial) red result was not confirmed by another abnormal result and when the following conditions are met for the individual clozapine monitoring services:

Result scenario	CPMS	ZTAS	DMS
Single red followed by one green then one amber	**Restart Clozapine after 2nd result** **Follow amber procedure but confirm next test date with CPMS**	**Amber or red result in the last three months: two consecutive greens before clozapine can restart** **Isolated red: can restart after first green. Daily testing must continue after the amber result until 2 consecutive greens**	**Restart clozapine after 2nd result** **Follow amber protocol following the amber result : twice weekly monitoring & pharmacy can only dispense a maximum of 4 days from the date of the amber blood sample** **Normal monitoring can resume after further green result**
Single red followed by one amber then one green	**Restart clozapine after 2nd result** **Blood tests as normal (unless treatment break) but confirm next date with CPMS**	**Treatment cannot restart** **Daily testing must continue until two consecutive green results**	**Restart clozapine after 2nd result** **Return to normal monitoring frequency**
Single red followed by two ambers	**Restart Clozapine after 2nd amber result** **Follow amber procedure but confirm next test date with CPMS**	**Treatment cannot restart** **Daily testing must continue until two consecutive green results**	**Restart Clozapine after 2nd amber result** **Follow amber protocol: twice weekly monitored until a green result then resume normal monitoring & pharmacy can only dispense a maximum of 4 days from the date of the**

			amber blood sample

Confirmed red result

After a red result, daily blood testing should commence. Confirmation of the red result is recommended by performing two blood counts on two consecutive days; however, clozapine should be discontinued after the first blood count. The red alert is confirmed if one of the follow-up blood counts is in the red range and the non-rechallengeable procedure is initiated.

Entry into Central Non-Rechallengeable Database

In the event of a confirmed red result, the clozapine monitoring service will submit the patient's details to the Central Non-Rechallengeable Database (CNRD) and the patient should not be re-exposed to clozapine.

Potential explanation for red result

If there is a potential explanation for the red result e.g. a concurrent viral infection or there has been concomitant use of medication known to have a substantial potential for causing neutropenia, this should be communicated to the clozapine monitoring service at the earliest opportunity to allow clozapine to be re-initiated within the terms of the marketing authorisation. In addition, it is also well recognised that there is a diurnal variation in circulating neutrophils resulting in a lower neutrophil count early in the morning compared to later in the day in certain individuals; therefore the timing of samples may have an implication on the perceived result. Close monitoring of the trends of the neutrophils/ white blood counts may demonstrate that timing of samples is implicated in the blood dyscrasia and sample time can be manipulated accordingly.

Clinical case for rechallenge following a confirmed red result

In many situations, clozapine has been the most effective treatment and following a true, confirmed red result the individual may become increasingly unwell. Where it is felt that the benefits of a clozapine rechallenge in terms of the individual's mental state outweighs the potential risks of a further blood dyscrasia, the clozapine monitoring service will consider accepting the individual for a rechallenge under an off-licence (or off-label) agreement.

The 3 clozapine manufacturers have different procedures for rechallenge so the clozapine monitoring service that the patient will be registered with should be contacted to confirm what process and documentation is required.

If the first dyscrasia had the following characteristics, it is thought that the chances of a successful rechallenge are low (i.e. the likelihood of a further neutropenia is high): [10]

- The drop in neutrophils was inconsistent with previous counts and was not merely a slight drop in a patient with a pattern of repeated low WBC counts
- The neutropenia/agranulocytosis occurred in the first 18 weeks of treatment

- The drop in neutrophils was severe and fell below $0.5x10^9/L$
- The blood dyscrasia was prolonged (>10 days)
- There were no alternative explanations apart from clozapine for the first neutropenia/agranulocytosis, such as other medication or an infection

Developing a treatment plan for clozapine rechallenge

The following is recommended when considering a patient for a clozapine rechallenge following a blood dyscrasia;

- A second opinion from another consultant psychiatrist supporting the rechallenge.
- Advice from haematology regarding the dyscrasia and the likely relationship with clozapine and/or any other potential causes or relevant factors.
- Advice from a specialist mental health clinical pharmacist which may include a medication history and review supporting a rechallenge.
- Clear documentation of a discussion with the patient and/or carer regarding risks and benefits of a rechallenge and documentation of consent from the patient.
- For patients receiving treatment under the terms of the Mental Health (Care & Treatment) (Scotland) Act 2003, ensure that the statutory treatment plan includes the off-label prescribing of clozapine.
- Consider convening a case conference with relevant parties (including clozapine clinic staff) to discuss practical issues relating to increased monitoring and to ensure clear lines of responsibility.

A **patient-specific treatment** plan should be developed (which may involve input from haematology). This should include;

1. Increased monitoring
   - First 12 weeks: twice weekly (in the event of 3 sequential falls in WBC and/or neutrophils, monitoring should be increased to three times weekly)*
   - Weeks 12-18: weekly
   - Weeks 18-52 fortnightly
   - Thereafter: fortnightly* or monthly monitoring proposed in the 2nd year, according to further evaluation of risk. [3]

   * Note: Clozapine monitoring systems are unable to manually change the monitoring frequency from their 'standard' monitoring frequency for a rechallenge in order to flag when a blood is overdue i.e. they cannot set the frequency of bloods as twice weekly and highlight when this is late. Therefore, it is imperative that the team involved in the patient's care check when bloods are due according to the treatment plan and not solely rely on the clozapine monitoring system and agree on a system of

inputting any local FBC results on to the clozapine monitoring system. It is vital to liaise with Leverndale pharmacy closely with regards any increased monitoring frequency.

2. Avoiding the use of other medications which may have an impact on FBC results. Input from a specialist mental health clinical pharmacist is advisable in this respect.

3. Consider the timing of the sample. The potential diurnal variation in circulating neutrophils seen in certain individuals can result in a lower neutrophil count early in the morning compared to later in the day. Consider taking blood samples in late morning/ early afternoon to avoid this potential.

4. A clear action plan in the event of a further blood dyscrasia, including;

   - Emergency contacts for key personnel (patient, carer, consultant psychiatrist, haematology, pharmacy)
   - Actions to be taken in the event of an amber or red result.
   - Altered monitoring parameters for WCC/ neutrophils (if these are to differ from standard clozapine monitoring parameters)
   - If the management of the neutropenic episode is to include the use of prophylactic antibiotics and/or G-CSF (granulocyte-colony stimulating factor), the treatment plan should clearly state the thresholds for initiating this.
   - Management options for treating the patient's mental state during the neutropenic episode. (NB all antipsychotics have the potential for causing/ delaying recovery from neutropenia and should ideally be avoided until 2 green results have been obtained. Antipsychotics with the lowest potential for blood dyscrasias include amisulpride, aripiprazole and haloperidol).
   - The patient must be given education about the relevance of any physical changes, particularly fever, sore throat or other signs of symptoms of infection, and to whom these must be reported.

5. A copy of the treatment plan should also be shared with Leverndale pharmacy.

References:

1. Munro J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R. Active monitoring of 12, 760 clozapine recipients in the UK and Ireland. Beyond pharmacovigilance. *Br J Psych* 1999; 175:576-580
2. Zaponex Summary of Product Characteristics last updated 9/12/16. www.ztas.co.uk Accessed online 5/1/18
3. Recommendations for rechallenge with Zaponex (clozapine) after clozapine-induced neutropenia. Leyden Delta. Mar 2017. www.ztas.co.uk. Accessed online 5/1/18
4. Dunk LR, Annan LJ, Andrews CD. Rechallenge with clozapine following leucopenia or neutropenia during previous therapy. *B J Psych* 2006; 188:255-263
5. Whiskey E, Taylor D. Restarting clozapine after neutropenia. *CNS Drugs* 2007; 21(1): 25-35

6. Manu P, Sarpal D, Muir O, Kane J M, Correll C U When can patients with potentially life threatening adverse effects be rechallenged with clozapine? A systematic review of the published literature. *Schizophr. Res* 2012; 134:180–186
7. Zaponex Treatment Access System (ZTAS) Manual. Leyden Delta April 2015. www.ztas.co.uk Accessed online 24/1/20
8. Clozapine, neutropenia and agranulocytosis, red alert management. Clozaril Connect May 2018. https://www.hcpinfo.clozaril.co.uk/en-gb/downloads Accessed online 24/1/20
9. Denzapine red protocol. Britannia Pharmaceuticals November 2017.
10. Zaponex Fact Sheet- Agranulocytosis and neutropenia. www.ztas.co.uk May 2017 Accessed online 5/1/18
11. Norfolk and Waveney Mental Health Partnership NHS Trust. Protocol for re-exposure to clozapine after a blood dyscrasia requiring discontinuation. July 2007.