CASE REPORT

Successful rechallenge with clozapine following 'red alert'

Thelma K Toni-Uebari, John Rees

General Adult Psychiatry, Parklands Hospital, Basingstoke, Hampshire, UK

Correspondence to
Dr Thelma K Toni-Uebari, thelma2@ntlworld.com

SUMMARY

A case is presented of a 23-year-old lady with treatment-resistant schizoaffective disorder who had responded well to treatment with clozapine. Fifteen months after satisfactory use of clozapine she had 'red alerts' from routine haematological monitoring indicating neutropenia. Clozapine was discontinued and she was admitted to the psychiatric hospital to manage the aftermath of discontinuing clozapine and start alternative treatment with other antipsychotics. Her mental health rapidly deteriorated. Adequate trials with amisulpride, haloperidol, olanzapine and flupenthixol decanoate yielded little improvement in her clinical state. After 9 months of non-response to other antipsychotic medications, she was rechallenged with clozapine, followed by improvement in her mental state. She was eventually discharged home after 14 months of hospitalisation in a stable mental state. She remained mentally stable in the community on clozapine for 18 months after rechallenge, with no further red alerts.

BACKGROUND

Clozapine is an atypical antipsychotic medication recommended for Treatment resistant schizophrenia where the illness has not responded satisfactorily to treatment despite sequential use of adequate doses of, at least, two different antipsychotics, prescribed for adequate duration. However, clozapine carries the risk of life-threatening agranulocytosis and is used under strict haematological monitoring guidelines. It is recommended that clozapine be discontinued immediately if a patient develops a 'red alert'—an abnormal white cell count (WCC) of $<3.06\times10^9$/l or neutropenia (neutrophil count $<1.56\times10^9$/l) and further use of clozapine is subsequently contraindicated.[1]

Often trials with other antipsychotics as substitutes tend to be ineffective and the patients remain very unwell, in need of effective intervention. Therefore, the only recourse is to rechallenge patients with clozapine but this is not without additional risks including more severe life-threatening agranulocytosis. In the UK rechallenge with clozapine is an off-label process undertaken following clearance by the Clozapine Patient Monitoring Service (CPMS), at the discretion of the patient's psychiatrist and with the psychiatrist assuming full responsibility for the intervention.[1]

There is limited published evidence for success with rechallenging with clozapine. In our context successful rechallenge refers to the patient not redeveloping neutropenia or agranulocytosis following rechallenge with clozapine. A recently published systematic review involving all reported studies in all languages identified only 30 reports on a total of 138 patients world-wide in who clozapine rechallenge was attempted after a potentially life-threatening adverse event.[2] Many psychiatrists are reluctant to take on the responsibility of going against recommended guidelines regarding 'red alerts' in view of the involved risks, and against a background of paucity of evidence about effectiveness of the rechallenge.

By reporting our experience this report aims to add to existing evidence on the outcome of rechallenging with clozapine after 'red alert'.

CASE PRESENTATION

ST was a 23-year-old Caucasian lady diagnosed with schizoaffective disorder 9 years prior to this presentation. She had previously been treated with haloperidol, quetiapine, amisulpride, risperidone, olanzapine and sodium valproate, all of which were discontinued due to intolerable side effects or lack of effect. She was eventually started on clozapine with good response. She was living independently and required clozapine 137.5 mg daily to keep her mental state stable.

During routine monitoring of her blood tests as required for patients on clozapine she had two consecutive 'red alert' blood results, neutropenia, and immediately discontinued taking clozapine. She had been on clozapine treatment uneventfully for about 65 weeks before having the 'red alerts'. She had no physical health problems at the time.

ST was admitted to the psychiatric hospital to monitor her mental state, provide alternative treatment for her as well as manage the potential fall-out of discontinuing clozapine. Her mental state on admission was stable and she did not present with any signs of psychosis.

Her neutrophil count on first arrival at the hospital was 1.3×10^9/l (normal range $1.5–8.0\times10^9$/l). Over the next few days her neutrophil count was 1.48×10^9/l on day 2; 1.91×10^9/l on day 3 and 1.96×10^9/l on day 4. By the end of day 4 repeat blood tests showed improved neutrophil count of 3.39×10^9/l. Subsequent tests showed normal results. Her WCC remained normal.

She was initially started on amisulpride 200 mg twice daily because of some effect on her on a previous trial. Her mental state rapidly deteriorated on the ward. She became paranoid, delusional, distressed, exhibited disinhibited behaviour and was verbally and physically aggressive, posing a risk to herself and other people. Following assessment she was detained under Section 3 of the mental health

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act and transferred to the Psychiatric Intensive Care Unit (PICU) for further treatment.

Her mental state continued to deteriorate despite treatment with other antipsychotic medications. She had bizarre and nihilistic delusions, manifested thought disorder, had auditory hallucinations and was clearly psychotic in her presentation. The CPMS was contacted and they advised against rechallenging with clozapine until at least 4 weeks of consecutive 'green' results with normal neutrophil count were obtained but reiterated that they did not recommend this action. CPMS confirmed that, to restart clozapine, the Consultant Psychiatrist would have to sign an off-label agreement, providing supporting evidence balancing risk with benefit for wanting to restart clozapine, which would have to be considered and approved by CPMS. Antipsychotic medications received while in the PICU included trials of Haloperidol for 10 weeks, flupenthixol decanoate depot injections initially fortnightly and olanzapine. While there was little improvement in her mental state she still suffered from side effects of the medications.

After spending 10 weeks in the PICU she was transferred back to the regular psychiatric ward. She remained mentally unwell, apathetic with blunt affect, experiencing nihilistic and paranoid delusions, distressing auditory hallucinations, agitation and anxiety. The option of rechallenging with clozapine was discussed extensively with the patient and her family, covering results of literature searches, risks, potential benefits and current knowledge base. After serious consideration she and her family were keen to have the treatment especially as other treatments had been ineffective. By this time she had spent about 37 weeks in hospital.

Clearance was obtained from CPMS following signing of the off-label agreement and fulfilment of other conditions. The patient was given clozapine starting with a dose of 12.5 mg at night and following the clozapine dosing regimen for the NHS Trust based on the Maudsley Prescribing Guidelines (table 1). Side effects experienced included tachycardia and hypotension initially. Drowsiness, excessive salivation and weight gain persisted for several months.

Table 1 Suggested starting regimen for clozapine (inpatients)[11]

Day	Morning dose (mg)	Evening dose (mg)
1	–	12.5
2	12.5	12.5
3	25	25
4	25	25
5	25	50
6	25	50
7	50	50
8	50	75
9	75	75
10	75	100
11	100	100
12	100	125
13	125	125[a]
14	125	150
15	150	150
18	150	200[b]
21	200	200
28	200	250[c]

[a]Target dose for female non-smokers (250 mg/day).
[b]Target dose for male non-smokers (350 mg/day).
[c]Target dose for female smokers (450 mg/day).

INVESTIGATIONS

Weekly blood monitoring tests were carried out for the first 18 weeks according to the clozapine monitoring protocol, followed by fortnightly blood tests for up to 1 year and then monthly blood checks. She continued with routine regular blood monitoring after her discharge from the hospital in line with the clozapine protocol. Her most relevant tests were the full blood count, electrolytes and urea, and sometimes serum clozapine levels.

TREATMENT

Antipsychotic medications trialled during this period included amisulpride up to 600 mg daily in divided doses. However, as her mental state rapidly deteriorated necessitating transfer to the PICU, the PICU clinical team took the decision to review her medication and discontinued amisulpride. She had Haloperidol up to 15 mg daily in divided doses for 10 weeks initially. Flupenthixol decanoate depot injections were added and continued for 31 weeks, initially at a dose of 40 mg fortnightly, increasing to weekly injections of 400 mg. Olanzapine was started when haloperidol was discontinued but was stopped after 2 weeks due to side effects. Haloperidol was reintroduced for another 18 weeks, alongside flupenthixol decanoate injections. For some time she was on high-dose antipsychotic therapy. Lithium carbonate was added to her medications for its mood-stabilising effects, initially at a dose of 400 mg daily, gradually increasing up to 800 mg nocte but the patient self-discontinued the lithium after about 9 weeks due to side effects. Medications like quetiapine, risperidone and sodium valproate which had either been ineffective for her in the past or had intolerable side effects, were not repeated. By the time clozapine was started all the other antipsychotic medications had gradually been discontinued.

Apart from the trials with the antipsychotic agents described she also received PRN medications including haloperidol, lorazepam 1–2 mg doses, clonazepam 1–2 mg doses for agitation, procyclidine tablets for extrapyramidal side effects of the antipsychotics agents and propranolol for sinus tarchycardia.

She was rechallenged with clozapine starting with an initial dose of 12.5 mg daily, gradually titrating upwards to higher doses twice daily according to the dosing regime. She eventually stabilised at 400 mg daily, taking 100 mg in the morning and 300 mg at night. The side effects were managed symptomatically, including the use of oral hyoscine hydrobromide for hypersalivation.

OUTCOME AND FOLLOW-UP

Within a few weeks of the start of clozapine her mental state began to show improvement. She gradually became brighter in mood and more alert, more reactive and more motivated to self-care. She would respond appropriately during conversations and the auditory hallucinations stopped. She began to engage in other activities including occupational therapy sessions and had successful leave periods away from the hospital. She continued to improve gradually until she was assessed to be mentally stable and well enough to cope with living independently in the community and fit for discharge.

She was discharged home on clozapine, with on-going support from the community mental health team and follow-up at the out-patients clinic. She was seen regularly by the team while she continued with her medications and regular blood

monitoring tests. Her WCC and neutrophil count have been within normal ranges. She had been on clozapine continuously for 79 weeks since her rechallenge with no further red alerts.

Although clozapine had been effective in keeping her mentally stable she found the side effects very challenging to cope with, especially excessive drowsiness. She recently decided to discontinue taking clozapine due to persistent side effects. However, following some deterioration in her mental state she has resumed taking clozapine once again.

DISCUSSION

Clozapine, an atypical antipsychotic agent from the dibenzodiazepine group has a broad range of antipsychotic activity. However, due to the risk of life-threatening adverse effects, the therapeutic indication has been restricted to schizophrenic patients resistant or intolerant to other antipsychotics and in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed. Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration. Clozapine is thus accepted as gold standard for treatment-resistant schizophrenia.

However clozapine carries the risk of life-threatening agranulocytosis and is used under strict haematological monitoring guidelines. At least 0.8% of clozapine-treated patients develop agranulocytosis, which is potentially fatal. The risk of death from agranulocytosis in the UK is <1 in 10 000 patients exposed.[3–5]

The mortality risk from agranulocytosis and neutropenia is reduced through regular haematological monitoring of all patients on clozapine and through active involvement of a clozapine monitoring services such as the CPMS and the Zaponex Treatment Access System.[5 6] Patients are only allowed to continue with treatment if the blood results are satisfactory. A red result from haematological monitoring indicates development of the blood dyscrasias and means that the patient must stop taking clozapine immediately. All UK patients who have a red alert are recorded on the Central Non-Rechallenge Database. Patients who develop confirmed neutropenia on clozapine are registered on the database and should never be rechallenged with clozapine again unless there are good clinical grounds to do so.

About 2.7% of patients treated with clozapine develop neutropenia. Of this, half do so within the first 18 weeks of treatment and three-quarters by the end of the first year.[3] In our patient neutropenia occurred after 65 weeks of treatment with clozapine. In a published review of patients successfully rechallenged with clozapine the median duration of clozapine treatment at time of dyscrasia was 44 weeks.[1]

The risk factors for neutropenia include being Afro-Caribbean (77% increased risk), young (17% decrease in risk per decade increase in age) and having a low baseline WCC.[3] The risk is not dose-related. The patient being presented is Caucasian, young but had normal baseline WCC prior to and during the period of initial treatment with clozapine.

The mechanism of clozapine-induced neutropenia and agranulocytosis is not known but immune-mediated and direct cytotoxic effects may be implicated.[7]

The disorder is reversible in the vast majority of cases if clozapine is withdrawn promptly.[1] In our patient the neutrophil count returned to normal within 4 days of discontinuing clozapine. In a published case report there was recovery of granulocytes within a few days.[8] In another review of patients on clozapine who developed neutropenia, leucopenia or agranulocytosis, the duration of blood dyscrasia ranged from 1 to 16 days with a median duration of 3 days.[1] Two clinically distinct types of neutropenia have been postulated, the first type is a mild-to-moderate neutropenia with neutrophil count below 1.5×10^9/l but not lower than 0.5×10^9/l, occurring in 1.8% of treated patients. Rapid recovery follows discontinuation of clozapine (2–8 days). The second more severe type of neutropenia with neutrophil count of below 0.5×10^9/l has an incidence of 0.78% and agranulocytosis develops in some patients irrespective of discontinuing clozapine and generally lasts 14–21 days.[1]

Discontinuation of clozapine in patients due to neutropenia or agranulocytosis is frequently followed by worsening of psychotic symptoms, functional status and quality of life.[2 9] Unfortunately, trials with other antipsychotics often tend not to be effective in managing the symptoms in these patients, leaving clinicians with the difficult decision about whether to rechallenge with clozapine. Over a period of 10 months our patient was tried with various combinations of antipsychotics with little improvement in her mental state. Rechallenging with clozapine is an off-label process requiring the patient's psychiatrist undertaking full responsibility for the process.[1] Some psychiatrists are reluctant to take on this responsibility in view of the risks of neutropenia and agranulocytosis and the paucity of evidence available. The decision to rechallenge with clozapine should not be taken lightly.

Of the 53 patients rechallenged with clozapine in a published review 33 patients did not develop a blood dyscrasia on rechallenge. Twenty patients representing 38% of the patients rechallenged with clozapine drawn from a cohort of patients registered with the CPMS, developed neutropenia or agranulocytosis on rechallenge with clozapine.[1] In another recent systematic review 78 of the 112 patients were successfully rechallenged with clozapine after initial red alert for neutropenia and did not subsequently develop a blood dyscrasia.[2] In those with unsuccessful rechallenge, neutropenia reoccurred within a mean period of 4.3 weeks and 15 of the patients went on to develop a more severe dyscrasia. This finding is consistent with the earlier published report that in patients who experienced further dyscrasia at rechallenge, the second dyscrasia was more severe, lasted longer and occurred more quickly on rechallenge with clozapine.

During clozapine rechallenge many patients are given treatments that have been shown to elevate neutrophil counts such as lithium and granulocyte colony-stimulating factor (G-CSF).[2 6 10] Lithium might be useful in keeping the WCC higher in patients with benign ethnic neutropenia who could potentially be discontinued from using clozapine due to confusion with clozapine-induced blood dyscrasia.[2] However, the use of lithium to elevate WCC in patients with clear prior clozapine-induced neutropenia is not recommended.[4] Lithium should only be used to elevate WCC where it is strongly felt that prior neutropenic episodes were unrelated to clozapine.[4]

Clinicians need to be aware that concomitant treatment with other drugs that cause leucopenia may also increase the risk of agranulocytosis.[1 10]

In conclusion, rechallenge with clozapine remains a viable option for patients with previous red alert who have not responded to trials with other antipsychotic medications but the patients have to be very carefully selected, weighing the risks and benefits. More research is needed to help clinicians determine the patients least likely to develop further blood dyscrasia following rechallenge with clozapine.

Learning points

- Rechallenge with clozapine is a viable option for patients with previous red alerts who do not respond to alternative antipsychotic medication.
- The risks and benefits of rechallenge with clozapine have to be weighed very carefully and patients carefully selected.
- Rechallenge patients have a higher risk of agranulocytosis and neutropenia compared to clozapine-naïve patients.
- Co-prescription of other drugs that cause leucopenia could increase the risk of neutropenia or agranulocytosis with clozapine.

Competing interests None.

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