



## Early Predictors of Clozapine-Induced Myocarditis

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### Abstract

**Background:** There is minimal data regarding the investigations for early detection of Clozapine induced myocarditis prior to the development of cardiac symptoms. Once the symptoms of myocarditis develop, the injury to the heart has likely, already occurred, requiring a longer recovery period. Therefore, it is important for clinicians to be aware of available markers and investigations that could help detect Clozapine induced myocarditis earlier, which will hopefully result a reduction of the associated morbidity and mortality.

**Aim:** To detect early predictors of Clozapine-induced myocarditis.

**Clinical Details:** This case report describes two patients who initially had raised C-Reactive Protein (CRP) with fever and tachycardia prior to the development of Clozapine induced myocarditis.

**Outcome:** The two cases discussed in this paper illustrate that a patient's CRP can be the first biochemical marker to rise in acute myocarditis in patients on Clozapine.

**Conclusion:** This paper describes the importance of the prompt use of biochemical markers for early detection of clozapine-induced myocarditis. A rise in the levels of CRP could be the earliest evidence to suggest the possible onset of Clozapine induced myocarditis.

**Keywords:** Clozapine, Clozapine induced myocarditis, Treatment resistant Schizophrenia

### Introduction

We are presenting two case reports, who developed myocarditis after initiating Clozapine. Both had raised CRP as an early biomarker prior to development of cardiac symptoms of myocarditis. Patients consent and ethics approval was obtained from Gold Coast Hospital and Health Service, Clinical Case Study and the Human Research Ethics Committee- LNR/2019/QGC/58714.

### Case Report

Patient 1 is a 37-year-old male who was referred into hospital by the Community Mental Health Team (CMHT) for initiation of Clozapine for treatment resistant schizophrenia (TRS). He had an established diagnosis of Schizophrenia and was known to the CMHT since the age of 30. Patient 1 had no significant medical history. He denied any known drug allergies and denied illicit substance use. He smoked 15 cigarettes per day. He developed

a significant deterioration in his mental state despite medication compliance. When unwell, he experienced auditory and visual hallucinations along with persecutory delusions. He was pre-occupied with religious themes and reported seeing evil spirits and devils, which were harassing him. At the time of his admission, he was on Risperidone 8 mg daily and reported no side effects. In the past he had been trialed on oral olanzapine, quetiapine and parenteral paliperidone at optimal doses, and for adequate duration. However, until now, Risperidone was found to be the most effective treatment for his Schizophrenia. The CMHT referred him to hospital for initiation of Clozapine for TRS as despite Risperidone treatment at optimal doses for adequate duration with monitoring for concordance, he was still experiencing ongoing symptoms.

Similarly, patient 2, was a 29-year-old male referred into hospital by the CMHT for inpatient Clozapine initiation. He had an established diagnosis of TRS. He experienced auditory hallucinations, which were causing him significant distress resulting in career burn out. Patient 2 had been on Olanzapine Depot 405mg for 3.5 years after having trialed Risperidone at optimal doses and for an adequate duration. On admission, he was

taking Lurasidone 120mg at night with dinner and Olanzapine 30mg at night, which he had been taking for nearly six months with good concordance. The only significant past medical history was hyperhidrosis. He denied any drug allergies. He had a history of Cannabis use to cope with the auditory hallucinations. He denied any other illicit substance use prior to hospital admission. His last admission was three years earlier, in 2016.

### Treatment

Initial treatment with Clozapine was as per standard protocol, with dosing increasing from 12.5 mg once daily to a total daily dose of 200 mg by Day 14. Patient 1 and Patient 2 were fully compliant with their medications during their admission. Patient 1, on Day 14 of his treatment, developed tachycardia to 130 beats per minute with no associated symptoms. An ECG was performed, which showed that patient 1 was in sinus tachycardia with no signs of myocarditis. Following discussion with the patient and his family, clozapine dosing was continued as per the protocol. Over 48 hours later, he was discovered to be febrile up to 38.5°C but had no other physical symptoms of myocarditis nor cardiac failure. Blood tests revealed troponin levels of 5321 (normal range <20) and a CRP of 150. Cardiology advice was obtained, and an echocardiogram performed which showed a reduced Left Ventricular Ejection Fraction (LVEF) of 45% indicating heart failure. Patient 1 was admitted under the care of a cardiologist; clozapine was ceased, and he was discharged once stable with Risperidone 6mg per day. Appropriate follow up was arranged including an outpatient cardiac MRI scan and three-month cardiology clinic outpatient follow up.

Patient 2 followed a similar titration regime to that of patient 1 and was being monitored as per the CTC. Patient 2 had been persistently tachycardic from Day 3 of his Clozapine titration, but asymptomatic otherwise until Day 11 when he became febrile up to 38.9°C. At this time, he had no other physical symptoms of myocarditis nor cardiac failure. This was associated with a rise in his CRP to 38 from less than 2.0 four days earlier. At this stage, his troponin was at 2 (normal range < 20.0) and his white cell count was found to be elevated at 11.9 (normal range 4-11.0) up from 9.9 four days prior. Once again, the ECG showed sinus tachycardia. A diagnosis of clozapine-induced myocarditis was made on Day 11 when the cardiology team saw him. This was due to recurrent fevers and a CRP of 38. A troponin rise was noted two days later, at a level of 34 (normal range <20). The peak troponin was observed on Day 15, at 201. An echocardiogram was performed on day 11 which showed an LVEF of 48%, indicating heart failure. The cardiology team recommended ceasing Clozapine immediately and to commence bisoprolol and perindopril. He was then reinstated on Risperidone once again with a plan for outpatient cardiology follow up with a repeat echocardiogram.

### Discussion

Schizophrenia is a psychiatric illness involving chronic or recurrent psychosis affecting up to 1% of the world's adult population [1,2]. The indication for initiating clozapine treatment is usually based on treatment resistance to anti-psychotic medications [3]. The definition of TRS has varied throughout literature with no universally agreed upon definition prior to 2017 [4]. At which time, TRS was defined as schizophrenia that was non-responsive to "at least two trials of antipsychotic medications of adequate dose and duration, at which point, the antipsychotic Clozapine is indicated" [5].

There has been limited research conducted into determining the first serially tested biochemical marker in clozapine induced myocarditis. In Australia, the incidence of myocarditis was found to be higher (up to 8.5%) in comparison to the rest of the world (up to 0.7%) [4,6]. The reasons for this difference are unknown, although it may likely be attributed to higher awareness and stricter monitoring guidelines across the continent for patients newly commenced on clozapine [7]. The two cases discussed in this paper illustrate that a patient's CRP can be the first biochemical marker to rise in acute myocarditis. Often greater importance is given to a rise in Troponin, but in the case of patient 2 it demonstrated that a rise in CRP may precede a rise in the troponin.

Both patients have shown tachycardia and pyrexia early in the treatment with Clozapine however, the predictive value of these side effects are limited by their common occurrence (up to 10% incidence and 20% respectively) [8]. To become meaningful predictors of myocarditis, tachycardia and pyrexia need to be accompanied by symptoms of emerging cardiac muscle damage such as tachypnoea, shortness of breath, hypotension or raised jugular venous pressure [8]. It would be therefore preferable to be able to predict the development of cardiac muscle damage before symptoms are present. Although similar cases to the ones presented in this paper have been observed previously, often the CRP is not stated in the results. A case study from 2016 discussed the findings surrounding a male in his twenties with a diagnosis of Clozapine-induced myocarditis [3]. One of the similarities with that study was the finding of 'sinus tachycardia' on an ECG, but importance was not placed on determining how the biochemical markers changed during the illness [3]. There is no estimated financial cost of burden from myocarditis and other clozapine-associated adverse events specific for Australia, although with more than 130 cases per annum, it is a significant cost to the healthcare system [7].

The role of clozapine in TRS should not be underestimated, but our study shows that it is essential to give more weight to a rise in CRP and/or Troponin in an asymptomatic patient who has been started on Clozapine. It is our opinion and recommendation to cease, or at least withhold Clozapine prior to causing cardiotoxicity.

The implications for patient care would be an earlier diagnosis, earlier cessation of clozapine and reduction in the duration of heart failure therapy, thus leaving the door open for a re-challenge. There is some evidence to suggest that a clozapine re-challenge with a slower up-titration regime can improve success rates [9,10]. It was noted in 2012, that there were three main factors that affect the success of a clozapine re-challenge [10]. Namely, the severity of the original acute myocarditis, time between the myocarditis event and re-challenge, and rate of clozapine dose titration during the re-challenge [10].

Clozapine use has increased within the state of Queensland alone by 36.4% over a 10-year period leading up to 2013 [7]. CRP is a widely available test and is regarded as a reliable indicator of inflammation [11]. It has an important role in the early detection of clozapine-induced myocarditis to help reduce its morbidity and mortality in Australia. We recommend baseline testing of these indicators prior to prescribing clozapine. After early initiation of clozapine, regular and closed evaluation of CRP should be considered more than WBC in clinical real world. As myocarditis can be fatal if not diagnosed early, the identification of myocarditis at an early stage could avoid the unfortunate events of sudden death regardless of the use of clozapine.

We recommend future research/studies conducted in this area should explore the specificity and sensitivity of CRP and troponin for making this diagnosis.

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