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Clozapine rechallenge after clozapine-induced myocarditis: A case report to validate a previously published protocol

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Abstract

Introduction: Clozapine is an effective antipsychotic indicated for treatment-resistant schizophrenia (TRS). Its use is limited by its extensive adverse effect profile featuring rare but serious consequences like clozapine-induced myocarditis (CIM). In the event of CIM, clozapine is discontinued; however, there is often no effective alternative for TRS. In this case, a rechallenge of clozapine may be considered. However, there is no standardized protocol to guide clinicians in this process.

Case Report: This report describes the case of a 28-year-old male with a history of CIM who successfully underwent a clozapine rechallenge using a cautious titration protocol described in the literature and reached a daily dose of 150 mg without recurrence of CIM.

Discussion: This case differed from the previously published research protocol in some respects, including the concurrent use of zuclopenthixol for antiaggression and no significant eosinophil-related concerns during monitoring. Despite confounding factors, including concurrent cellulitis affecting inflammatory markers, the patient was successfully rechallenged with clozapine. Limitations of the case include unknown postdischarge outcomes and lack of measurement-based care, such as the use of rating scales, to assess treatment response objectively.

Conclusion: This case report validates the previously published protocol and contributes to the literature on CIM rechallenge, helping clinicians weigh the risks and benefits of rechallenging clozapine in select patients.

Keywords: clozapine, myocarditis, clozapine-induced myocarditis, rechallenge, monitoring

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Introduction

Clozapine, a second-generation antipsychotic indicated for treatment-resistant schizophrenia (TRS), can reduce aggression, suicidality, hospitalization, and mortality.[1-3] Standard initiation involves gradual titration to minimize adverse drug effects, such as sedation, orthostatic hypotension, and constipation.[4,5] Severe neutropenia and clozapine-induced myocarditis (CIM) are 2 notable United States clozapine boxed warnings of both of which require significant monitoring.[1-4] CIM typically occurs within 2 to 8 weeks of clozapine initiation and has been associated with rapid titrations.[1,2,4] CIM may result from direct myotoxicity or a delayed hypersensitivity reaction and is sometimes accompanied by eosinophilia.[1,6,7] CIM is generally diagnosed through a combination of elevated cardiac markers and clinical symptoms.[8] This includes a troponin elevation greater than 2 times the upper limit of normal and a C-reactive protein (CRP) greater than 100 mg/L.[8]

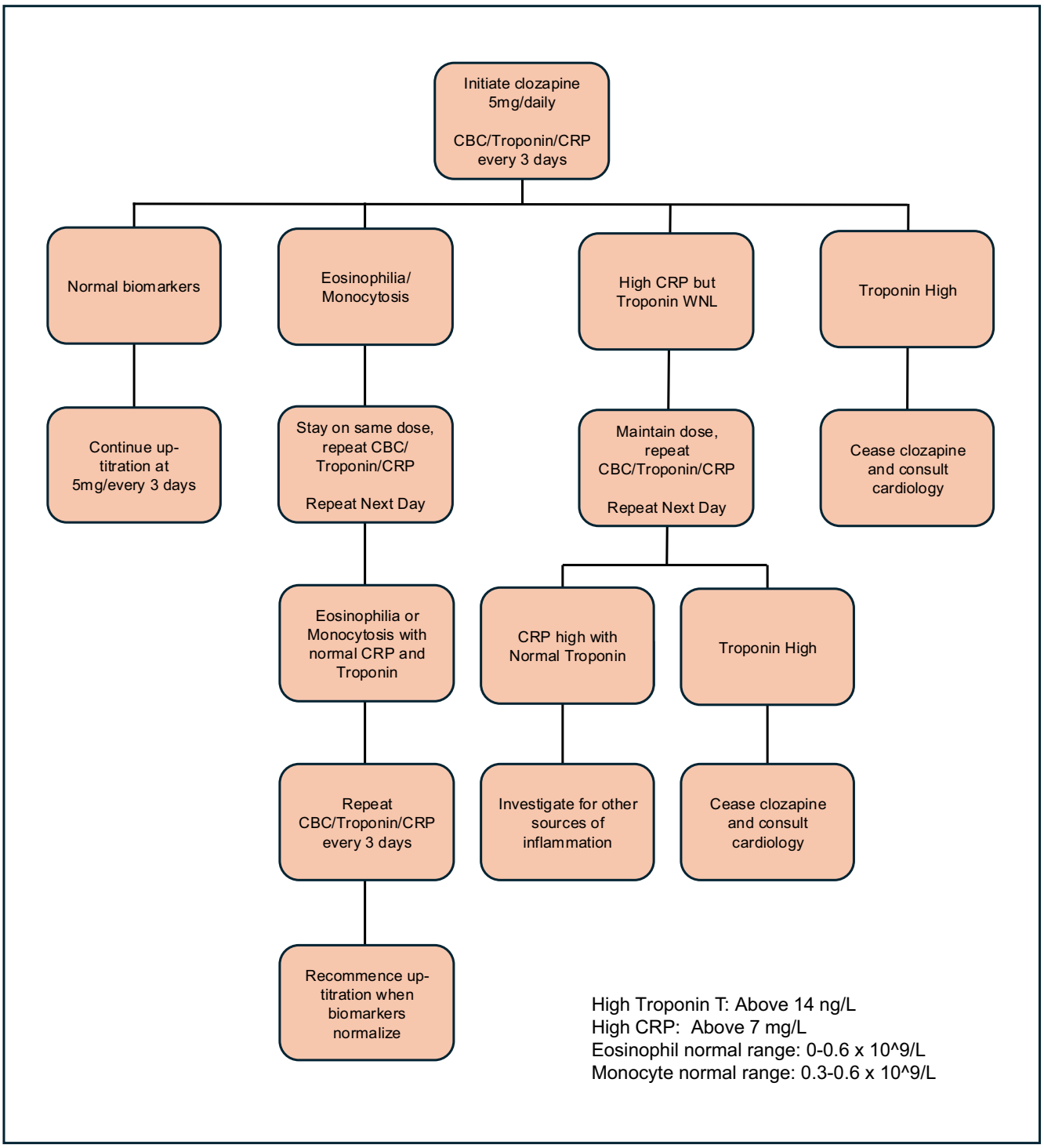

FIGURE 1: Monitoring protocol. Adapted with permission from Shivakumar et al.[7] CBC = complete blood count with differential; CRP = C-reactive protein; troponin = high-sensitivity troponin T; WNL = within normal limits

Concerns about the risk of CIM contribute to prescriber hesitancy in initiating clozapine.[1,2,6] The clozapine product monograph recommends discontinuing clozapine immediately should CIM occur.[4] However, this limits treatment options in TRS. Multiple case studies have reported varied success with clozapine rechallenge after CIM, including a case report by Shivakumar et al.[1,2,5-7,9-12]

The case described below follows the clozapine rechallenge protocol outlined by Shivakumar et al (Figure 1).[7] A MEDLINE and PUBMED search (2019–2024) was conducted to identify any validated clozapine rechallenge protocols published since Shivakumar et al.[7] As of December 2024, no validated protocols were identified. The Shivakumar et al[7] protocol incorporates clozapine desensitization with cautious dose increases and

includes monitoring frequencies for complete blood count (CBC), CRP, and troponin. This paper aimed to describe a case of clozapine rechallenge that followed the Shivakumar et al[7] protocol. Informed consent was obtained for the writing of this case report.

Case Report

Mr. C is a 28-year-old White man with a history of TRS, cannabis use disorder, and tobacco use disorder who was admitted to an inpatient psychiatry unit with increasingly disorganized and aggressive behavior, auditory hallucinations, and delusions. Family history was notable for a brother with Wolff-Parkinson-White syndrome. The patient reported smoking 5 tobacco cigarettes and 1 g of cannabis daily.

Initial Clozapine Trial (2 Years Earlier)

Two years prior, at the same hospital, Mr. C trialed clozapine after treatment resistance to olanzapine oral up to 15 mg daily for 1 year, risperidone oral (dose and duration unknown), and paliperidone long-acting injectable (LAI) 100 mg intramuscularly every 4 weeks for 1 year. Clozapine was titrated following the facility's standard initiation protocol, starting at 12.5 mg nightly for 2 days, increasing to 25 mg nightly for 3 days, then increasing by 25 mg every 3 days until reaching 200 mg nightly. The initiation protocol includes baseline electrocardiogram (ECG), CBC, CRP, troponin T, liver transaminases, as well as an electrolyte and renal panel. A baseline echocardiogram was not completed. Normal ranges at the facility are CRP (0–7 mg/L), troponin T ($\leq$14 ng/L), WBC (4–11 $\times$ 10^9/L), and eosinophils (0–0.6 $\times$ 10^9/L). Orthostatic vital signs are monitored twice daily, and CBC, troponin T, and CRP are monitored weekly. On day 19 at 150 mg nightly, Mr. C developed chest pain, night sweats, chills, fever (101.12°F), and sinus tachycardia (117 bpm). His blood pressure was 127/75 mm Hg. CBC, CRP, troponin, ECG, and a consult with cardiology were ordered. His troponin T rose from 5.6 ng/L the week before to 136 ng/L. He was diagnosed with CIM. Clozapine was discontinued, despite early clinical improvement. Mr. C was re-initiated on paliperidone LAI at an increased dose of 150 mg IM every 4 weeks with partial response and was discharged on a community treatment order. A community treatment order in XXX is a legal order that allows individuals with mental illness to receive mandatory community psychiatric treatment. Eight months later, he was readmitted with persistent psychosis despite paliperidone and was switched to a combination of aripiprazole 400 mg IM and haloperidol 450 mg IM, both every 4 weeks, administered on the same dates.

Clozapine Rechallenge

Mr. C was readmitted to the same hospital 5 months after starting aripiprazole and haloperidol LAIs. At the time of admission, these were his only medications, the doses were unchanged since his last hospitalization, and he was reported to be adherent to the medication regimen by his outpatient care team. Given Mr. C's psychotic symptoms and history, a retrial of clozapine was considered, with cardiology approval. The titration and monitoring outlined in the study by Shivakumar et al[7] served as a guiding protocol (Figure 1). Owing to the severity of Mr. C's psychotic symptoms and the fact that zuclopenthixol had not been tried, aripiprazole and haloperidol LAIs were discontinued, and zuclopenthixol, a first-generation antipsychotic, was initiated alongside clozapine. Baseline lab work (ie, CBC, CRP, creatine kinase (CK), troponin T, liver transaminases, renal panel, electrolyte panel) was taken, and all values were normal. CBC, CRP, CK, and troponin T were scheduled 3 times weekly during the titration (Figures 2 and 3).

On day 1, Mr. C began titrations of zuclopenthixol (5 mg orally twice daily for 5 days, then 10 mg twice daily for 16 days, then transitioned to zuclopenthixol decanoate 200 mg IM every 2 weeks) and clozapine (5 mg nightly, increasing by 5 mg every 3 days toward a target of 150 mg).

On day 3, clozapine was held for 1 day due to elevated CRP (17.7 mg/L) and white blood cells (WBC; 12.37 $\times$ 10^9/L); troponin T was normal, no ECG was done, and chest X-ray was unremarkable. Vitals showed a heart rate of 137 bpm, blood pressure 142/68 mm Hg, and a temperature of 98.6°F. Between days 3 and 6, WBC and CRP continued to rise, with CRP peaking at 40 mg/L on day 6. Clozapine was resumed and increased, as per the initial titration plan, to 10 mg on day 4, as no concerning signs or symptoms were present.

On day 5, cardiology recommended pausing further titration until labs normalized. Daily monitoring of CBC, CRP, CK, and troponin T began. An echocardiogram on day 6 revealed a mild left ventricular dysfunction (ejection fraction [EF] 43%).

With CRP and troponin trending down by day 7, clozapine titration resumed with a titration to 15 mg. On day 8, Mr. C had a left hip ultrasound for pain and swelling; he used acetaminophen (days 8–12) and ibuprofen (days 8–10). On day 10, he was prescribed cephalexin 500 mg 4 times per day for 7 days for cellulitis, and ramipril 2.5 mg daily was added for low EF (43%).

Although labs were improving, clozapine was held at 15 mg for 4 days because of a misinterpretation of the treatment plan by the on-call team. On day 14, titration resumed with an increase to 25 mg to keep with the initial titration schedule. Troponin T levels fluctuated slightly during the admission, with the highest troponin T level of 16.8 ng/L occurring on day 19. However, Mr. C remained asymptomatic with stable vitals, so titration continued as planned, which was a deviation from the Shivakumar et al protocol.[7]

On day 20, the clozapine dose was 35 mg daily, and ramipril was discontinued as a repeat echocardiogram showed an

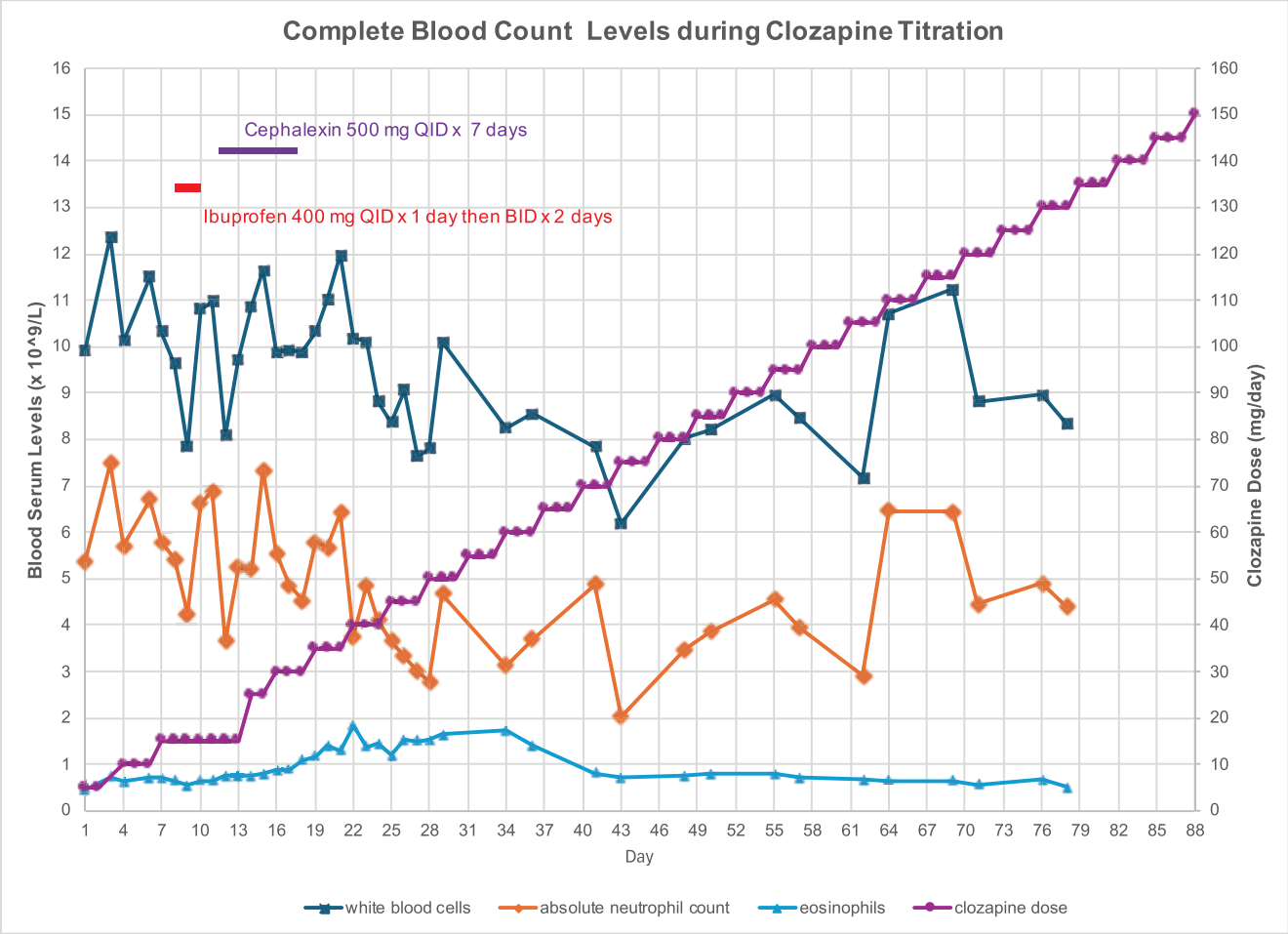

FIGURE 2: Complete blood count levels during clozapine titration. A double-axis line graph depicting complete blood count serum monitoring levels and clozapine dose (mg per day) since clozapine initiation. Blood serum levels are indicated on the left y-axis in units of $\times 10^9$/L. The clozapine dose per day is indicated on the right y-axis in milligrams. The duration of ibuprofen treatment is indicated from days 8 to 10. The duration of cephalexin treatment is indicated from days 11 to 17

EF improvement to 55%. Throughout the admission, the highest eosinophil count occurred on day 22 at 1.84 $\times$ 10^9/L (normal range, 0–0.6 $\times$ 10^9/L). Levels decreased slightly on day 23 but remained between 1.0 and 1.7 $\times$ 10^9/L through day 44. The clozapine dose on day 44 was 75 mg once daily. As the eosinophilia was suspected to be related to cellulitis and/or cephalexin treatment, and as troponin T levels and vital signs remained stable, the clozapine titration was continued. Notably, eosinophilia was attributed to other causes, and given the fact that the patient remained otherwise stable, continuing clozapine despite eosinophilia was another deviation from the Shivakumar et al protocol.[7] On day 29, bloodwork frequency was decreased to twice weekly. By day 88, Mr. C successfully reached the target dose of clozapine 150 mg daily. He was discharged on day 89 to be further titrated up in the community.

During inpatient clozapine titration, Mr. C showed minimal improvement in his auditory hallucinations and delusions. However, by day 44, he was more cooperative with care, and there were fewer reports of agitation and aggression.

Discussion

Mr. C, who previously discontinued clozapine due to CIM, was successfully rechallenged and titrated to the same 150-mg dose that had previously triggered CIM, marking the second reported case to follow the Shivakumar et al protocol.[7]

Excluding clozapine after CIM can severely limit options for patients unresponsive to other antipsychotics, yet rechallenge remains uncertain due to limited guidance and variable success in published case reports.[1,2,5-7,9-12] The diagnostic criteria for CIM outlined by Ronaldson et al[12] were well-cited in these studies, making monitoring relatively similar between them.[1,2,5-11] The protocol by Shivakumar et al[7] was chosen to guide treatment in the presented case for its cautious titration and monitoring approach.

Mr. C's case differed from the patient outlined by Shivakumar et al, Ms. AA, in some notable ways.[7] Mr. C had minimal comorbidities and a family history of Wolff-Parkinson White syndrome, which has not been linked to CIM. Unlike

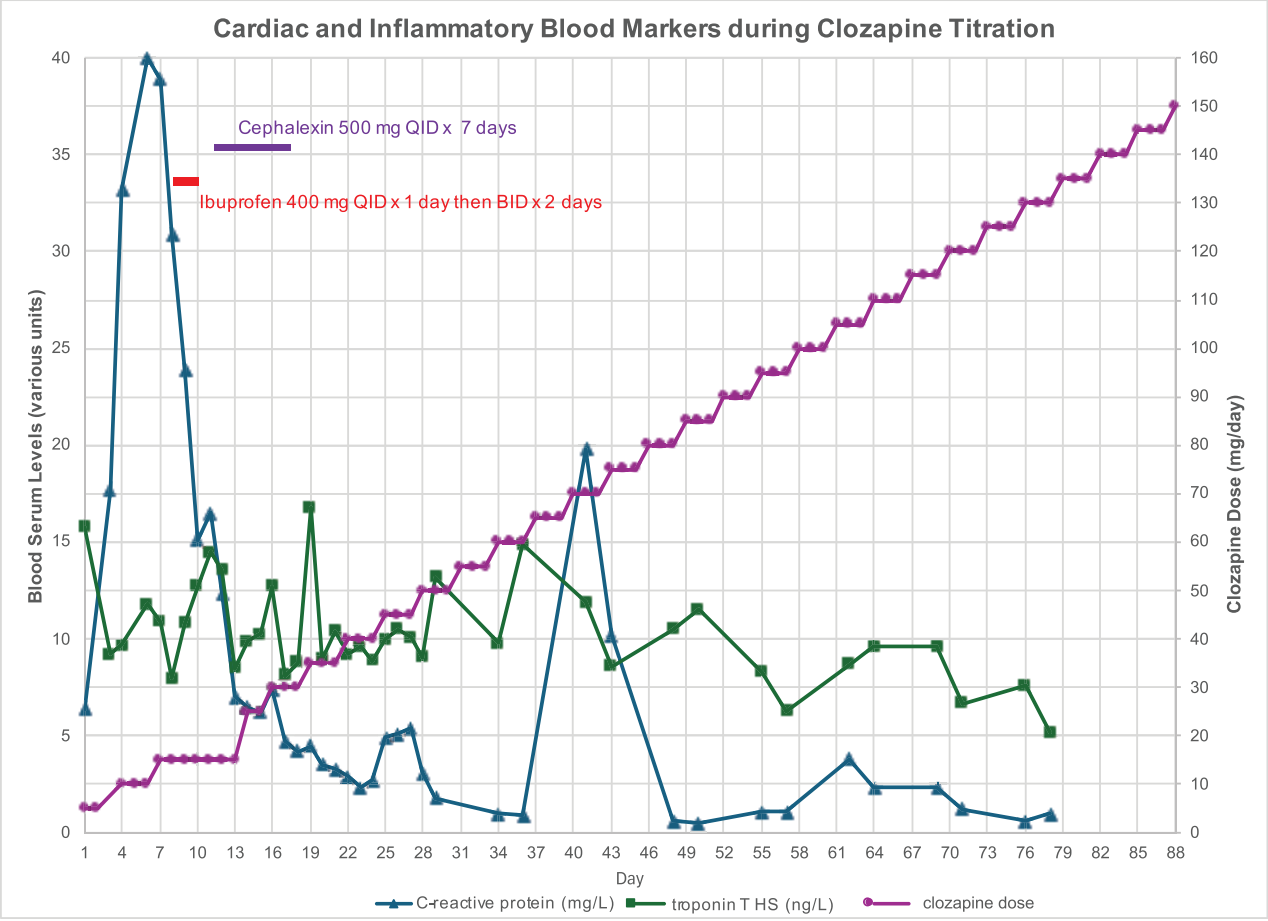

FIGURE 3: Cardiac and inflammatory blood markers during clozapine titration. A double-axis line graph depicting cardiac and inflammatory marker blood monitoring levels and clozapine dose (mg per day) since clozapine initiation. High sensitivity troponin T and C-reactive protein levels are indicated on the left y-axis in units of nanograms per liter and milligrams per liter, respectively. The clozapine dose per day is indicated on the right y-axis in milligrams. The duration of ibuprofen treatment is indicated from days 8 to 10. The duration of cephalexin treatment is indicated from days 11 to 17

Ms. AA, who received chlorpromazine, Mr. C was prescribed zuclopenthixol for its antiaggressive effects and as a backup LAI.[7,13] While Ms. AA's titration was paused multiple times due to eosinophil elevation, Mr. C's eosinophil level remained mildly elevated but never reached a value that matched or exceeded that of Ms. AA.[7] His rechallenge was guided primarily by CRP, troponin T, and physical symptoms (ie, cellulitis).

Mr. C was a good candidate for clozapine rechallenge due to severe refractory psychosis, poor insight, persistent aggression unresponsive to dual antipsychotics, and prior early clozapine response. Confounding factors included residual aripiprazole and haloperidol LAIs, which may remain in the body at decreasing concentrations for up to 235 and 95 days, respectively, and may have contributed to elevated eosinophil levels. Concurrent zuclopenthixol use further complicated the ability to isolate the effect of individual medications.[14] A cellulitis-related CRP increase complicated interpretation of inflammatory markers, and a brief ibuprofen course correlated with CRP decline, though its relevance to CIM is unclear. Brief ramipril treatment had an uncertain impact on CIM risk.

This case has several limitations. Mr. C's progress after hospital discharge is unknown, though no readmissions occurred within 7 months at the city's sole psychiatric hospital. Case-specific confounding factors limit generalizability. Treatment response was not assessed using measurement-based care (eg, rating scales), reducing objectivity. Owing to the lack of a suitable commercial product, a 20 mg/mL of clozapine suspension was compounded by the hospital pharmacy by crushing commercially available clozapine tablets. The troponin T upper limit of normal used in both the Shivakumar et al protocol[7] and the facility where this case occurred was a fixed value of 14 ng/L for both males and females. This may differ from other facilities that use sex-specific reference ranges. Finally, this retrospective report relied on existing chart documentation.

Conclusion

This case describes a successful clozapine rechallenge after CIM using cautious titration, frequent monitoring, and

cardiology input, supporting the Shivakumar et al protocol[7] as a useful guide. Additional cases and prospective studies are needed to further validate this approach.

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