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REVIEW

A Review of Clinical Advances and Challenges in Clozapine-Induced Myocarditis

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Abstract: Currently, the treatment of schizophrenia remains primarily pharmacological, with approximately 30% of patients diagnosed with treatment-resistant schizophrenia (TRS). Clozapine continues to be the first choice treatment for this subgroup of patients. As the preferred treatment, clozapine offers clear advantages in efficacy; however, its complex and troublesome adverse effects pose significant challenges for psychiatrists. Common side effects include granulocytopenia, intestinal obstruction, myocarditis, cardiomyopathy, constipation, and seizures. The first two complications are easier to manage due to the availability of laboratory monitoring, and improved management strategies are now in place in clinical practice. In recent years, clozapine-induced myocarditis (CIM) has gained considerable attention because of its potentially severe outcomes. However, the mechanism behind its lethality remains unclear, and there is no widely accepted consensus or treatment guideline, which complicates the implementation of targeted prevention in clinical practice. This review aims to summarize the clinical manifestations of CIM, explore the underlying mechanisms, and discuss recent advances in monitoring, diagnosis, and treatment, with the goal of offering constructive recommendations for future clinical management.

Keywords: clozapine, myocarditis, mechanism, clinical features, monitoring

Introduction

Schizophrenia is a serious mental disorder characterized by a high suicide rate, significant disability, and considerable social risk, affecting approximately 24 million people worldwide. According to the World Health Organization, it accounts for 12.2% of the global disability-adjusted life years attributed to mental disorders, second only to depressive and anxiety disorders.[1] Despite the availability of a wide variety of antipsychotic medications, about one-third of individuals with schizophrenia remain resistant to treatment with two or more antipsychotic agents, a condition known as TRS.[2] Although defining TRS has been a significant challenge in psychiatry, a literature review by the Therapeutic Response and Resistance in Psychiatry (TRRIP) group, which examined 42 studies on TRS, found that only half (n=21) provided a clear definition of treatment resistance. However, the majority of the studies adopted failure of at least two therapeutic trials of antipsychotics at adequate doses and durations as the minimum criterion for diagnosing resistance.[3] The treatment of TRS involves a variety of approaches, including medication, physical therapy, and psychotherapy. In terms of physical therapy, electroconvulsive therapy (ECT) is a non-invasive procedure that requires anesthesia and may result in transient confusion and memory impairment.[4] Repetitive Transcranial Magnetic Stimulation (rTMS) is also non-invasive and has been studied primarily for specific symptoms, with promising early results.[5] Deep brain stimulation

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(DBS) is a newer intracranial intervention that can more precisely target specific brain regions.[6] While it holds the potential to modulate particular neural circuits, being an invasive surgical procedure carries additional risks, including hardware failure. Psychotherapy, although non-invasive, can be effective in alleviating symptom burden but is often time-consuming and requires a high level of patient commitment. Overall, pharmacotherapy remains the cornerstone of TRS treatment today.

Current guidelines recommend clozapine as the first choice of treatment for TRS.[7] Unlike typical antipsychotics, clozapine exhibits weak D2 receptor activity but strong antagonistic effects at D4 dopaminergic, 5-hydroxytryptamine, noradrenergic, histamine, and cholinergic M2 receptors. As a result, it typically causes few or no extrapyramidal symptoms.[8] Meta-analyses have shown that clozapine is significantly more effective than other second-generation antipsychotics in managing both positive and negative symptoms of schizophrenia;[2] it has also been found to reduce patients' risk of suicide and aggression during treatment.[9] However, some adverse effects associated with clozapine limit its widespread clinical use, including granulocyte deficiency, toxic megacolon, and cardiotoxic effects. While the first two adverse reactions have clearer laboratory monitoring indicators and established management strategies, CIM presents with insidious, complex, and sudden symptoms. In severe cases, it can lead to malignant arrhythmias and even sudden cardiac death.[10] It is significant to state that common early symptoms of CIM include mild fever, tachycardia, and fatigue.[11] These nonspecific symptoms closely resemble the typical response to the initial titration of clozapine dosage. As a result, physicians may misinterpret these signs as flu-like manifestations, potentially overlooking the need to test for CIM-related laboratory markers or mistakenly attributing them to other signs of infection. This may complicate early detection of myocarditis. Given the variety of clinical manifestations, most signs and symptoms of CIM are nonspecific. Therefore, medical personnel should maintain a high level of clinical suspicion for any unexpected or sudden onset of signs and symptoms during clozapine therapy and promptly assess the patient for potential myocardial injury.

Since 1980, when Vesterby et al first reported the cardiotoxicity associated with clozapine, this side effect has raised significant concern globally.[12] Various studies have reported differences in the prevalence of CIM, with rates as high as 3% in Australia compared to less than 0.1% in the United States.[13,14] Studies have examined the regional variations in the incidence of CIM and have attempted to identify the underlying factors contributing to these differences. Several factors may account for these regional disparities: first, the susceptibility of different populations to CIM may vary due to genetic differences and individual variations in clozapine metabolism;[15] second, differences in clozapine administration practices, such as titration rates, across countries could also influence the observed incidence rates;[16] and the lack of standardized diagnostic criteria and inconsistent diagnostic and reporting practices across regions may further contribute to discrepancies in CIM incidence statistics.[17] Although the exact pathogenesis of CIM remains unclear, its early onset during clozapine treatment for schizophrenia and the presence of eosinophilic infiltration in myocardial tissue suggest possible mechanisms. Several hypotheses have been proposed, including that clozapine may trigger myocardial inflammation by activating the immune response, as well as having direct toxic effects on the myocardium.[18,19] Discontinuation of clozapine is the primary treatment for CIM; however, for some patients, stopping the medication can lead to persistent hallucinations, thought disorders, and a significantly increased risk of suicide and death.[20] Therefore, discontinuation should be approached with caution after ruling out other potential causes of cardiomyopathic inflammation, while also considering the likelihood and necessity of reintroducing clozapine.

In recent years, CIM has garnered increasing attention from psychiatric clinicians and researchers. While the cardiovascular adverse events associated with clozapine have been extensively documented and studied, significant gaps remain in the literature regarding geographic variations in CIM prevalence, its pathogenic mechanisms, and consensus on monitoring and treatment strategies. Current guidelines for monitoring clozapine treatment are provided by organizations such as NICE,[21] TRRIP,[22] and the Royal Australian and New Zealand College of Psychiatrists.[23] However, these guidelines have limitations in terms of international applicability and harmonization. Specifically, they are hindered by the singular nature and lack of representativeness in the consensus methodology, leading to a lack of globally harmonized protocols. Consequently, there is an urgent need for more widely agreed-upon expert guidelines to improve the management of patients with CIM and to facilitate future research advancements. This review aims to summarize recent advances in the clinical features and pathogenesis of CIM and briefly address the controversies surrounding management protocols, with the goal of providing recommendations for the monitoring and treatment of CIM.

Current Epidemiology of CIM

The true incidence of CIM may be underestimated. More than 250 cases of CIM have been reported, predominantly among relatively young male patients aged 27 to 46 years.[24] Determining the actual incidence of CIM is challenging due to the variability in clinical presentations and the insidious nature of the episodes. Additionally, nonfatal cases of CIM may go undetected and resolve without the need to discontinue clozapine therapy.[13]

Additionally, there are significant regional differences in the prevalence of CIM. In the absence of standardized surveillance guidelines, reported prevalence rates vary: 0.015% in the United States,[14] 0.05% in Sweden,[25] 0.03% in Germany and Switzerland,[26] and a notably higher rate of 3% in Australia.[27] Factors contributing to these discrepancies may include varying population susceptibilities to CIM, differences in clozapine usage across regions, and inconsistencies in diagnostic accuracy and reporting practices.[13]

Although clozapine has been widely used in China in the past, a study analyzing the World Health Organization's pharmacovigilance database found that more than half of CIM cases were reported from Australia, with only 41 cases documented in Asian countries and none in China.[28] There are currently no large-scale retrospective studies indicating the prevalence of CIM in China. The scarcity of both retrospective and prospective studies with large sample sizes underscores the need for extensive exploration in this research area within the country.

Risk Factors for CIM

CIM Is Associated with Rapid Titration of Clozapine

Myocarditis typically occurs during the first six months of clozapine therapy, with 85% to 90% of cases arising within the first eight weeks, particularly peaking during the third week of treatment.[29] Guidelines from the UK's National Institute for Health and Clinical Excellence (NICE) recommend a gradual escalation of the clozapine dose to the minimum effective level, generally between 250 to 400 mg per day. One study indicated that the median dose of clozapine at the time of diagnosis for patients with myocarditis was 250 mg/day,[30] while another reported cases in patients taking doses as low as 12.5 mg/day.[31] The evidence regarding a dose-dependent relationship between clozapine and myocarditis remains inconclusive. However, rapid titration—defined as increasing the dose by more than 25 to 50 mg per day—may elevate the risk of developing CIM.[32] Ronaldson et al found in a case-control study that rapid titration was significantly associated with myocarditis, showing a 25% increase in risk for every 250 mg of clozapine accumulated within the first nine days of treatment.[33] A recent study by De Leon et al summarized data on the incidence of CIM across Australia, the US, Canada, Japan, Korea, Denmark, and the Netherlands, suggesting that faster titration rates may explain the higher incidence of CIM in Australia. Based on this hypothesis, the authors recommend adopting slower, personalized titration regimens and enhanced monitoring of C-reactive protein (CRP) levels to improve the global safety of clozapine use.[17]

Potential Risk Factors for CIM

Several risk factors can increase the likelihood of developing CIM by affecting clozapine metabolism and leading to elevated plasma levels. Clozapine is primarily metabolized in the liver by cytochrome P450 enzymes, with CYP1A2 being the main enzyme involved. Factors that stimulate or inhibit CYP1A2 activity can significantly impact clozapine metabolism.[34] Research by De Leon et al indicated that ethnicity, smoking, and adverse metabolic states—such as co-administration with other medications, obesity, or inflammation—can influence this metabolism.[35] Some studies suggest that co-administering clozapine with certain antipsychotics heightens the risk of myocarditis. For example, Youssef et al examined 129 patients treated with clozapine and found that combining it with a selective serotonin reuptake inhibitor increased the risk of myocarditis by more than sixfold.[27] Similar findings were reported in an analysis of 105 patients with schizophrenia, which demonstrated that concomitant use of clozapine and valproate more than doubled the risk of myocarditis.[33] This increased risk may be attributed to competitive inhibition of cytochrome P450 enzymes between the two drugs.[36]

Mechanism of CIM

The pathogenesis of CIM is not fully understood. However, its early onset during clozapine therapy and the presence of eosinophil infiltration in myocardial tissue support several hypotheses. Current research suggests an immune-mediated mechanism that may lead to myocardial inflammatory responses. Alternatively, clozapine metabolites could be directly and selectively exerting cardiotoxic effects by altering metabolic pathways and triggering oxidative stress. Although the pathological features observed in the autopsy and the timing of onset suggest the possibility of an acute allergic reaction, this hypothesis does not account for the involvement of the heart alone. The immediate cause of death remains disputed, indicating that factors such as metabolic, environmental, or medical conditions—rather than myocarditis and cardiomyopathy alone—may have contributed to the patient's death.[37]

Immunomodulatory and Pro-Inflammatory Mechanisms

IgE-Mediated Immune Pathways

Among the various hypotheses regarding clozapine-induced cardiotoxicity, Killian et al proposed that CIM may result from an IgE-mediated type I hypersensitivity reaction.[18] Previous studies indicate that CIM typically occurs shortly after the initiation of clozapine therapy, with associated cardiac and peripheral blood eosinophilia suggesting a link to acute hypersensitivity.[38] It is hypothesized that clozapine undergoes bioactivation in myocardial tissues, producing chemically reactive nitrate-ammonium ion metabolites that can cause cellular damage, lipid peroxidation, and free radical production.[39] These nitrate-ammonium ions may bind to proteins in the myocardium, forming antigenic complexes that trigger an immune response and promote the migration of eosinophils, neutrophils, and macrophages.[40] This immune response can ultimately lead to myocardial cell injury through the release of free radicals and activation of multiple pro-inflammatory cytokines.[41,42] Although the pathological features observed in the autopsy and the timing of onset suggest the possibility of an acute anaphylactic reaction, this hypothesis does not account for the isolated involvement of the heart. Furthermore, the immediate cause of death has been debated, with some proposing that factors such as metabolic, environmental, or medical conditions, rather than myocarditis or cardiomyopathy alone, may have contributed to the patient's death.[3]

Cytokine-Driven Immune Response

CIM is strongly associated with an increased release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and various interleukins. Research has demonstrated that TNF-α release in the heart exhibits a dose-dependent response to clozapine.[41] TNF released from peripheral inflammatory cells following clozapine exposure triggers the expression of inducible nitric oxide synthase (iNOS) in cardiomyocytes, leading to the production of large amounts of nitric oxide (NO). This effect may be linked to either clozapine itself or its metabolite, N-desmethylclozapine, which acts agonistically on cardiac preganglionic fibers via M1 receptors of the cardiac vagus nerve.[43] NO serves as an immunomodulatory factor and effector molecule that mediates tissue injury; its overproduction inhibits cardiomyocyte contractility, induces negative inotropic effects, and promotes the progression of myocardial damage in myocarditis.[44] Clozapine is subjected to complex metabolism, which may be influenced by various factors. Recent studies have suggested that the formation of highly reactive nitrenium ion metabolites is believed to trigger clozapine toxicity, and that co-administration of valproic acid has a significant impact on the formation of cysteinylated nitrenium ions from clozapine.[45]

Free Radical-Induced Oxidative Stress

Studies have demonstrated that during the development of myocarditis in experimental animals and patients, neutrophil infiltration leads to the production of certain cytokines, such as TNF, which triggers the release of reactive oxygen species (ROS) from mitochondria. This results in elevated ROS levels in cardiomyocytes. Solaini et al found that excessive ROS production in these cells depletes cellular glutathione (GSH) reserves and reduces antioxidants like glutathione peroxidase (GSH-Px), impairing the antioxidant defense mechanisms in cardiomyocytes. Consequently, this oxidative stress causes damage to lipids, proteins, and DNA.[46] In clozapine-treated animals, there was an observed increase in the expression of cysteine-aspartate protease (caspase-3), a key marker of apoptosis, along with elevated levels of 8-hydroxydeoxyguanosine (8-OHdG), a biomarker of DNA damage, both in serum and cardiac tissues.

Additionally, an increase in nuclear factor κB (NF-κB), a marker of inflammation and apoptosis, was noted in cardiac tissues.[47] These findings suggest that clozapine-induced cardiotoxicity can lead to cardiac apoptosis, driven by increased oxidative stress, weakened antioxidant defenses, and subsequent DNA and cellular damage.

Injuries Associated with Hypercatecholaminergic States

Clozapine is associated with elevated levels of norepinephrine and epinephrine, and this hypercatecholaminergic state significantly exacerbates myocarditis in both animals and patients.[41] It is hypothesized that an imbalance in the autonomic nervous system, characterized by decreased parasympathetic tone and increased adrenergic drive, may explain the electrophysiologic effects of clozapine, particularly the presence of tachycardia at rest. Sustained inappropriate tachycardia has been shown to impair left ventricular function in both animal models and humans.[48] Clozapine-induced increases in serum catecholamine levels directly and indirectly elevate myocardial oxygen demand through direct stimulation of the myocardium and increased cardiac workload. Ju-Feng Wang et al found that significant increases in myocardial inflammation in clozapine-treated mice correlated with higher plasma catecholamine levels, and that blockade of β-adrenergic receptors with propranolol significantly mitigated this effect.[41] Additionally, elevated serum catecholamines stimulate the renin-angiotensin-aldosterone system, leading to further increases in cardiac load, which explains the protective effect of angiotensin-converting enzyme inhibitors, such as captopril, against clozapine cardiotoxicity.[49]

The current study lacks data on the detection of myocardial injury markers in humans, which could be further investigated in future research. It has been suggested that individual differences in the incidence of CIM may be related to the underlying genetic backgrounds of individuals, particularly mutations or polymorphisms in genes associated with drug metabolism. However, large-scale studies examining the correlation between antipsychotic drug metabolism and genetic variations are still relatively scarce.[15]

Figure 1 Immunomodulation, oxidative stress, and elevated catecholamine levels are involved in the mechanism of CIM.

Clinical Features of CIM

Clinical Manifestation

The clinical presentation of CIM is highly variable, ranging from asymptomatic disease to fulminant heart failure or sudden cardiac death. Major clinical symptoms include flu-like manifestations (fever, fatigue, sore throat), gastrointestinal disturbances (nausea, vomiting, diarrhea), and cardiovascular symptoms.[50] Among the most common cardiovascular symptoms are tachycardia, chest pain, syncope, arrhythmias, hypertension, and hypotension.[30,51,52] Notably, episodes of CIM may go unrecognized because many signs, symptoms, and clinical indicators are nonspecific in its milder forms.[53] For monitoring and diagnosing CIM, key auxiliary tests include cardiac biomarkers, electrocardiograms, echocardiograms, cardiovascular magnetic resonance (CMR) imaging, and endomyocardial biopsy (EMB).

Cardiac Biomarker

There is no clear expert consensus on laboratory screening for CIM.[22] Studies suggest that appropriate laboratory screening parameters for CIM include CRP, troponin, eosinophil counts, markers of heart failure, and inflammatory markers such as interleukin-6 and TNF-α.[54–56] These tests should be performed at baseline and then weekly for the first eight weeks after initiating clozapine therapy.[7]

Elevated troponin and CRP are both strong diagnostic indicators of myocarditis. In most cases of CIM, fever or elevated CRP levels typically precede elevated troponin levels by a few days, with CRP levels often exceeding 50 mg/L.[57] Aviv Segev et al found that elevated troponin has a high specificity of 89.1%, and that troponin levels more than twice the upper limit of normal, or CRP levels greater than 100 mg/L, significantly enhance diagnostic specificity in the clinical monitoring of CIM.[58] Additionally, it is recommended to assess brain natriuretic peptide (BNP) or N-terminal pro b-type natriuretic peptide (NT-proBNP) at baseline and in suspected cases of CIM.[59]

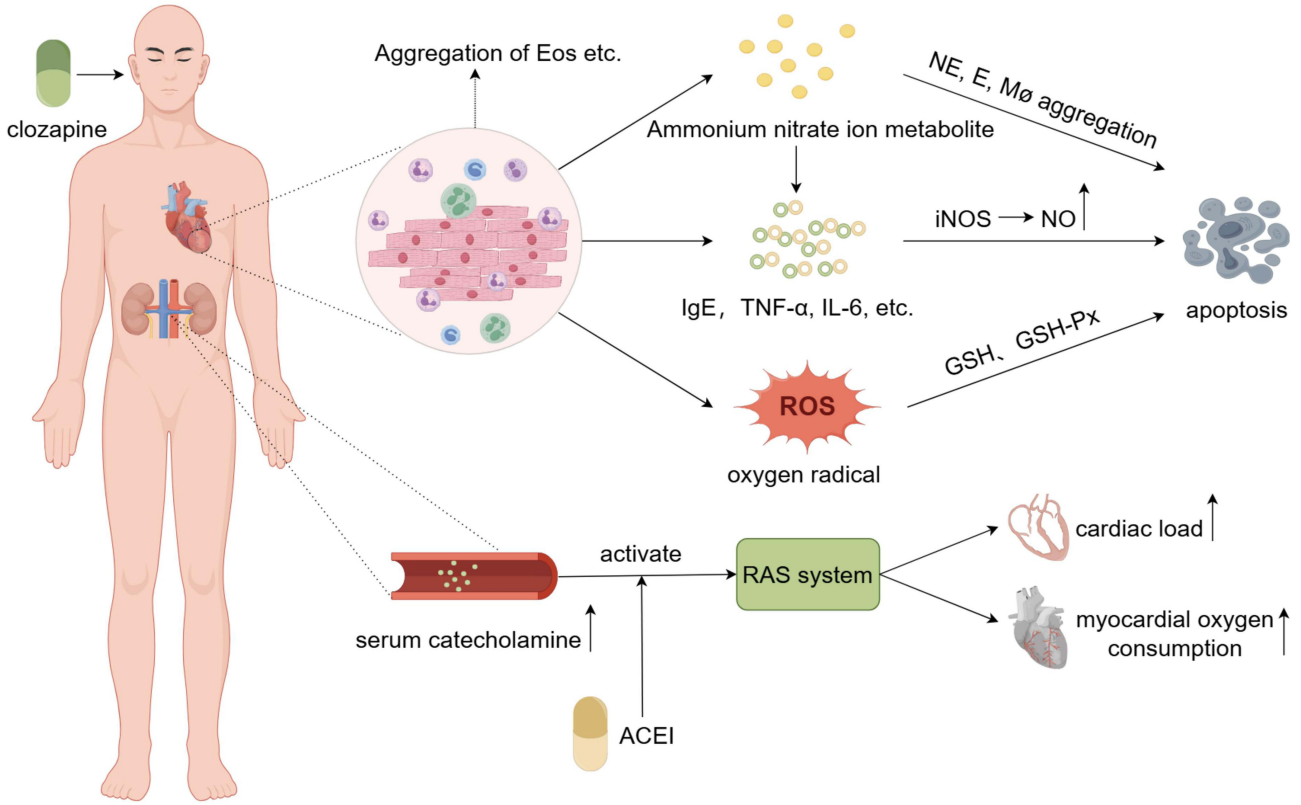

Figure 1 Immunomodulation, oxidative stress, and elevated catecholamine levels are involved in the mechanism of CIM.CIM may be triggered by an IgE-mediated type I hypersensitivity reaction, which induces cardiac and peripheral blood eosinophilia, suggesting a role for IgE in the immune response. Additionally, the metabolism of clozapine in myocardial tissues generates reactive nitrate-ammonium ion metabolites, which could form antigenic complexes that activate the immune response and lead to myocardial cell injury. Clozapine exposure also stimulates the release of pro-inflammatory cytokines, such as TNF-α, which further enhances nitric oxide (NO) synthesis, increases oxidative stress, and impairs cardiomyocyte function. Excessive production of reactive oxygen species (ROS) and compromised antioxidant systems contribute to oxidative cellular damage and promote apoptosis. Finally, elevated levels of catecholamines exacerbate myocardial inflammation, worsening the cardiotoxic response by increasing myocardial oxygen demand and cardiac load. In summary, the pathogenesis of CIM involves the interplay of immune response, oxidative stress, and catecholamine-induced injury.

Electrocardiography (ECG)

In cases of suspected CIM, ECG monitoring is essential. While no specific ECG changes have been identified for the diagnosis of CIM, some common alterations include sinus tachycardia, arrhythmias, prolonged QT interval, T-wave inversion, and ST-segment elevation.[60] Due to the low sensitivity of the ECG in diagnosing myocarditis, Ronaldson et al do not recommend using the ECG to detect the progression of the condition. However, clinicians may still monitor heart rate and evaluate the QT interval via ECG, which can provide additional insights into evolving cardiac changes.[61]

Imaging Examination

Echocardiography

The most common method for diagnosing CIM is echocardiography,[62] which typically reveals left ventricular or biventricular dysfunction, including reduced left ventricular ejection fraction (LVEF) and apical hypokinesis.[63] While echocardiography can effectively assess localized left ventricular function, these changes are often subtle and may be indistinguishable from preexisting dysfunction without baseline measurements. Therefore, Ronaldson et al recommend incorporating routine echocardiography prior to clozapine initiation as part of monitoring for potential side effects. Furthermore, once CIM is diagnosed, echocardiography should serve as the primary monitoring tool during follow-up, as improvements in left ventricular function post-clozapine discontinuation are strongly associated with favorable clinical outcomes.[64]

CMR

When blood tests or echocardiography do not establish a diagnosis of CIM, CMR presents a safe and noninvasive method with high diagnostic accuracy for acute myocarditis.[65] CMR evaluates functional and morphological abnormalities associated with myocarditis through late gadolinium enhancement, detecting intracellular and interstitial edema, necrosis, and fibrosis.[66] However, in mild cases of myocarditis, these changes may be subtle and not easily observed. It has been noted that CMR may not reveal any abnormalities when ECG and echocardiographic findings are minimal, and creatine kinase levels are within the normal range.[67] Despite CMR's high accuracy in diagnosing acute myocarditis, it may fail to capture abnormalities in some mild cases, underscoring the need for a combination of imaging and clinical indices for a comprehensive diagnosis.

Other Imaging Examination

Chest radiographs have limited utility in diagnosing CIM and are infrequently used in clinical practice. A meta-analysis of 359 cases revealed that only 27 patients with CIM underwent chest radiography; among these, 17 showed evidence of cardiomegaly and interstitial edema, while nine did not exhibit any abnormalities.[30] Additionally, although the role of positron emission tomography-computed tomography (PET-CT) in diagnosing CIM has not been extensively studied, it is increasingly recognized for its utility in detecting inflammatory heart diseases, including nodular disease and endocarditis. Preliminary evidence suggests that PET-CT may provide valuable insights into disease activity, potentially aiding in the development of therapeutic strategies.[68]

EMB

EMB is a technique that involves obtaining endocardial myocardial tissue using catheterized biopsy forceps, which access the right or left ventricle through peripheral blood vessels. Various methods can be employed to analyze the samples, including hematoxylin and eosin (HE) staining, Masson staining, immunohistochemical staining, Congo red staining, transmission electron microscopy, and qualitative or quantitative PCR, allowing for the diagnosis of different types of cardiomyositis and myocardial diseases.[69] EMB is considered the gold standard for confirming diagnoses of myocarditis, inflammatory cardiomyopathy, infiltrative heart disease, and related conditions.[70] In recent years, advancements in surgical instruments and operator experience have significantly enhanced the safety of EMB, with complication rates—such as perforation and pericardial tamponade—now below 1%.[71] However, due to the uneven distribution of myocardial lesions, there is a risk of sampling error; thus, collaboration with specialists in echocardiography, CMR, and cardiovascular pathology is essential to minimize misdiagnosis. Additionally, because EMB is an invasive procedure, it is not commonly utilized in mental health units due to safety concerns.

Diagnostic

The symptoms, signs, laboratory tests, and imaging findings of CIM lack specificity, making diagnosis challenging. However, studies indicate that early detection of CIM is linked to significantly improved prognosis.[72] Current recommendations emphasize the importance of recognizing new-onset clinical symptoms and monitoring for CIM when there are abnormalities in indicators such as elevated CRP levels between 50 to 100 mg/L or troponin levels that are less than twice the upper limit of normal. Diagnosing CIM requires a comprehensive approach that combines clinical symptoms, laboratory tests, imaging studies, and potentially biopsy, while also excluding other etiologies such as viral infections, autoimmune disorders, drug interactions, and various causes of cardiomyopathy.[73]

Clozapine-Induced Cardiomyopathy (CAC)

CAC is typically defined as a new-onset reduction in LVEF to less than 50%, or a reduction of at least 10% in LVEF compared to baseline measurements, or a decrease in LVEF that correlates with the most recent clozapine therapy. The incidence of clinically induced cardiomyopathy with clozapine is low, occurring in fewer than 1 in 1000 patients. Symptoms typically manifest late, with the onset often occurring between 3 weeks and 4 years after initiating the drug, although the majority of cases are observed 6 to 9 months or even years after therapy begins.[74]

The onset of cardiomyopathy is insidious, with exertional dyspnea and tachycardia emerging as the most common symptoms once the disease progresses to an advanced stage. In most cases, this manifests as shortness of breath during exertion and fatigue.[75] The primary diagnostic criterion is a reduction in ejection fraction as observed through echocardiography. Early echocardiograms may also reveal structural changes, including myocardial hypertrophy, ventricular alterations (such as ventricular attenuation and dilation), and valvular abnormalities.[76] Over time, these structural changes may lead to cardiac insufficiency, ultimately resulting in reduced cardiac output, generalized dyskinesia, and cardiomegaly. Electrocardiograms, along with blood biomarkers such as elevated serum BNP and NT-pro-BNP concentrations, serve as adjuncts in the diagnosis of cardiomyopathy.[51]

The etiology of CAC remains unclear. It has been proposed that cardiac damage resulting from CIM leads to pathological remodeling and reduced cardiac output over time; however, clinical evidence supporting the progression from CIM to cardiomyopathy is limited.[77] Case reports on the re-challenge of clozapine after cardiomyopathy are rare, and the re-challenge of clozapine therapy is generally not recommended.[78]

Response to CIM

Monitoring of CIM

Pharmaceutical companies in Australia have issued recommendations for monitoring CIM. However, these recommendations tend to prioritize the optimization of clinical information management processes to facilitate the development and marketing of commercially available medications. This focus has led to controversy regarding the timing of CIM monitoring, the specific content of the monitoring protocols, and the thresholds for discontinuing clozapine treatment. A widely cited CIM monitoring protocol proposed by Ronaldson et al in 2011 emphasizes that troponin I/T levels, CRP, and echocardiography should be assessed at baseline. Subsequently, CRP and troponin levels should be monitored weekly for the first four weeks of treatment, while vital signs must be recorded at least every other day.[61] If a patient exhibits associated symptoms, an abnormal increase in heart rate, or a CRP elevation exceeding 50 mg/L, daily monitoring of troponin and CRP is recommended. If the troponin elevation is less than twice the upper limit of normal and the CRP remains below 100 mg/L, clozapine may be continued. Conversely, if the troponin level exceeds twice the upper limit of normal or if CRP levels exceed 100 mg/L, it is advised to discontinue clozapine treatment and consult a cardiologist for further evaluation and diagnosis. Additionally, De Leon et al note that worldwide clozapine package inserts insufficiently address the issue of ancestry or titration rates. To address this gap, they have proposed six personalized ancestry-based titration protocols in their recent International Monitoring Recommendations, and recommend monitoring CRP levels along with clozapine blood concentrations during titration. This guideline may offer a inexpensive and straightforward approach to increase clozapine safety.[79] Table 1 presents a comparison of the three monitoring programs discussed above.

Clozapine regulations vary around the world, with regard to both indications and monitoring. The author suggests that clozapine prescribers worldwide should consider in their titrations: (1) the ancestry of the patient; (2) variables that impair clozapine metabolism (obesity, baseline inflammation, or coprescription with relevant comedications such as valproic acid, oral contraceptives, olanzapine or quetiapine); and (3) the use of baseline and weekly CRP monitoring.

Table 1 Comparison of CIM Monitoring Programs

Aspect	Ronaldson et al[61]	Pharmaceutical Companies	De Leon et al[79]
Duration	28 days	14 days	4 weeks (baseline and weekly)
Content	- CRP - Troponin I/T	- Electrocardiography - Troponin I/T or CK-MB	-CRP
Symptoms	Any discomfort and illness symptoms (fever, cough, sore throat, chest pain, etc).	Signs or symptoms associated with heart failure (arrhythmia, fever, chest pain)	No recommendation
Frequency	1 observation every other day	No recommendation	No recommendation

(*Continued*)

Table 1 (Continued).

Aspect	Ronaldson et al[61]	Pharmaceutical Companies	De Leon et al[79]
Enhanced Monitoring Content	- Related disease symptoms - Abnormally elevated heart rate - CRP > 50 mg/L or Troponin I/T > upper limit of normal	No recommendation	TDM (a single TDM in the fourth week which is likely to follow linear kinetics can be used to estimate the minimum therapeutic dose)
Timing (Clozapine Withdrawal)	CRP > 100 mg/L or Troponin I/T > 2× upper limit of normal	No recommendation	Persistent abnormalities of CRP and troponin on daily monitoring
Timing(ECG)	Monitored at baseline and when myocarditis is suspected	Monitored only at month 6 after clozapine administration	No recommendation
Titration protocol	No recommendation	No recommendation	Personalized titration schedules based on ancestry, sex, smoking, co-medication, obesity, inflammation, and PMs

Abbreviations: CRP, C-reactive protein; CK-MB, muscle–brain type CK; ECG, electrocardiogram; TDM, therapeutic drug monitoring; PMs, poor metabolizers.

Treatment of CIM

Discontinuation of clozapine is the primary treatment for CIM, followed by supportive care. Studies indicate that once clozapine is discontinued, myocarditis typically resolves, leading to an improvement in both clinical symptoms and biochemical markers.[80] Discontinuation of clozapine when the left ventricular ejection fraction (LVEF) is greater than 40% is associated with the highest likelihood of complete recovery.[81] Given that the half-life of clozapine is approximately 12 to 18 hours, a resolution of myocarditis symptoms shortly after discontinuation can aid in confirming the diagnosis of CIM. After the onset of related clinical symptoms, it is recommended that patients be placed on bed rest and monitored for electrocardiogram changes, blood pressure, and blood oxygen levels as necessary.

Supportive therapy for CIM typically involves the empirical use of medications aimed at improving cardiac function and minimizing the risk of heart failure. Commonly used agents include:

- Diuretics: These are effective in reducing cardiac fluid load and play a crucial role in managing the progression of heart failure.[51]
- Beta-Blockers: Cardioselective beta-blockers, such as bisoprolol and carvedilol, have a low risk of hallucinogenic side effects, making them suitable for patients with established psychiatric disorders.[82]
- Angiotensin-Converting Enzyme Inhibitors (ACEIs): These medications can help improve cardiac function.
- Glucocorticoids: While routine use of glucocorticoids for CIM is not recommended, they may be considered in severe cases of CIM, such as rare instances of fulminant myocarditis, particularly after ruling out infectious causes through EMB and other diagnostic methods.[83]

Overall, the choice of supportive therapy should be tailored to the individual patient's condition and needs.

Re-Challenge of Clozapine After CIM

There is ongoing controversy regarding the re-challenge of clozapine for TRS following the onset of CIM. Some clinicians argue that if clozapine is suspected to have caused CIM, patients should avoid returning to this medication due to the elevated risk of recurrence.[84] However, clozapine offers distinct advantages that are not matched by other antipsychotics, particularly in enhancing treatment adherence,[85] reducing suicide risk,[20] and minimizing extrapyramidal side effects.[85] Therefore, after meticulously evaluating the risks associated with discontinuation and subsequent

reintroduction, it may be prudent to consider the re-challenge of clozapine under stringent monitoring. Current evidence indicates that the average success rate for re-challenge clozapine after CIM is approximately 60%.[86–88]

The authors concluded that the severity of myocarditis episodes is a crucial predictor of the success of clozapine re-challenge. Both CRP levels and LVEF have been identified as potential predictors of this outcome. One study found that the mean peak CRP in patients who successfully underwent re-initiation was 120 mg/L, compared to 211 mg/L in those who failed re-challenge. With regard to echocardiographic findings, 75% of patients with successful re-challenge demonstrated normal left ventricular function during the myocarditis episode, whereas all patients who failed re-challenge exhibited left ventricular dysfunction.[89] Furthermore, Ronaldson et al analyzed 10 fatal cases and compared them to 66 survivors, finding no significant differences in age, gender, smoking status, drug dosage at the time of onset, or the concurrent use of sodium valproate between the two groups.[90] The re-challenge of clozapine must be approached with utmost caution. Retesting should be contemplated only after clinical symptoms of myocarditis have fully resolved, with no evidence of cardiac damage, and should occur in a controlled environment with hospitalization and strict monitoring. When the benefits outweigh the risks—such as the failure of alternative medications and the worsening of the patient's psychiatric symptoms—decisions should be made collaboratively with psychiatrists, cardiologists, patients, and their families.[91]

Given that the titration rate of clozapine is most strongly associated with the risk of CIM, the principle of "close monitoring, low starting dose, and slow titration" should be adhered to during its reintroduction. Qubad et al recommend initiating clozapine reintroduction with an initial titration rate of 6.25 mg every four days, gradually increasing to therapeutic doses. Close monitoring should include markers such as ECG, echocardiography, CRP, troponin T, and NT-proBNP. Furthermore, all screening measures should be conducted at least as frequently as during the initial phase of routine clozapine therapy, ideally once or even twice weekly.[92]

Conclusion

To summarize, CIM presents a significant barrier to the clinical use of clozapine as a therapeutic agent for treating TRS. Given the unclear pathogenesis of CIM and the absence of specific clinical manifestations, both monitoring and diagnosis pose significant challenges for clinicians, hindering accurate identification and prevention of the condition. A review of previous studies identified at least three key areas for CIM prevention: 1) slow titration from a low starting dose to therapeutic levels of clozapine; 2) close monitoring of electrocardiographic, echocardiographic, and troponin levels, among other markers; and 3) minimizing the concomitant use of multiple medications, particularly those known to increase the risk of cardiotoxicity. Before initiating clozapine therapy, patients should undergo a comprehensive medical evaluation, including a detailed history and physical examination. Rapid titration and co-administration of clozapine are significant risk factors for CIM, and a universal titration strategy cannot be applied to all patients. Given this, the current recommendation is to develop individualized titration regimens based on each patient's metabolic characteristics. While this approach increases the management burden on clinicians and raises healthcare costs, a feasible strategy would be to prioritize individualized regimens for patients with more risk factors. This would help balance resource allocation and management efficiency while maintaining therapeutic efficacy. Additionally, for patients taking clozapine, careful evaluation is recommended when co-administering drugs such as VPA and selective serotonin reuptake inhibitors (SSRIs), due to the potential for drug interactions. If co-administration is necessary, close monitoring of symptoms, signs, and relevant physiological indicators is crucial to detect and manage any adverse reactions promptly. Once CIM is diagnosed, clozapine should be promptly discontinued, followed by supportive and symptomatic treatment. Re-administration of clozapine must be approached cautiously, weighing the associated risks and benefits to prevent the possibility of sudden cardiac death.

Future research on CIM should focus on elucidating its pathogenesis, refining monitoring and diagnostic criteria, and discussing the necessity and feasibility of clozapine reintroduction. Clinically, some patients experience sudden cardiac death after long-term clozapine use, despite showing no significant signs of myocarditis during this period. The review of relevant findings revealed that these patients had mild myocardial enzymatic abnormalities at an early stage, which were often

overlooked by clinicians. Based on this, the author suggests that myocarditis may manifest differently in its acute and chronic forms and whether such manifestations are related to factors such as ethnicity and titration rate requires further study.

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Disclosure

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