Zaponex Fact Sheet
Myocarditis and cardiomyopathy

Important Information

The information provided in this fact sheet is intended for healthcare professionals and should not be used as a patient information leaflet.

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on information from scientific literature and previous successful experience. Each case should, of course, be considered individually.

This fact sheet covers the following subjects (click to jump to the corresponding section):

SPC statement

The **black box warning** for myocarditis in the Summary of Product Characteristics (SPC) for Zaponex® (clozapine) states the following:

> "Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely.
>
> Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (*e.g.* unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction.
>
> If myocarditis or cardiomyopathy are suspected, clozapine treatment should be promptly stopped and the patient immediately referred to a cardiologist.
>
> Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine."

In section 4.4 (Special warnings and precautions for use), it further specifies:

> "In patients who are diagnosed with cardiomyopathy while on clozapine treatment, there is potential to develop mitral valve incompetence. Mitral valve incompetence has been reported in cases of cardiomyopathy related to clozapine treatment. These cases of mitral valve incompetence reported either mild or moderate mitral regurgitation."[1]

Lastly, section 4.3 (Contraindications) states that clozapine is contra-indicated in patients with severe cardiac disorders (*e.g.* myocarditis).[1]

Incidence, pathogenesis and risk factors

Incidence of myocarditis

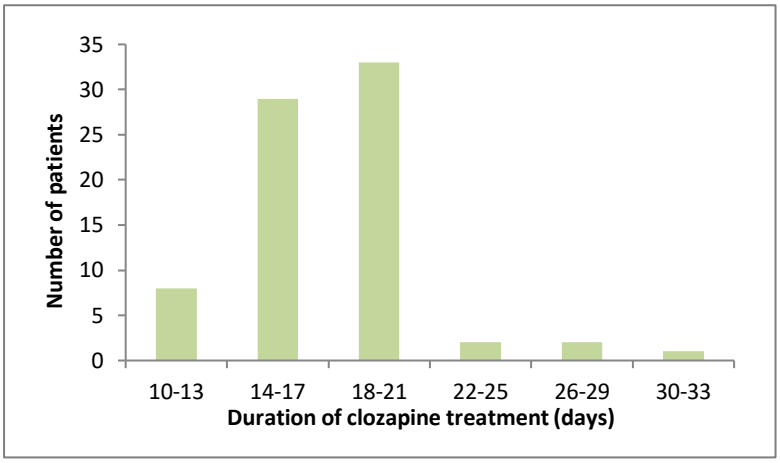
The incidence of clozapine-induced myocarditis is still a controversial topic. A confounding factor is that Australian studies report a higher incidence of clozapine-induced myocarditis than studies performed in the rest of the world.

Several Australian groups[2,3] and a Canadian group[4] found an incidence of clozapine-induced myocarditis of around 3%, but it is strongly disputed by others that this holds true for the rest of the world.[5–7] In a large data review, Cohen *et al.* estimated the correct incidence outside Australia to be between 0.007 and 0.06%.[6,8] Data for a study by Joy *et al.* were collected from clozapine in-patients referred to a cardiologist. They estimated the incidence of clozapine-induced myocarditis at 0.11%.[9] A Danish nationwide register-based study amongst 3262 out-patients on clozapine recently found an incidence of 0.03%.[10] Other reported incidences of clozapine-induced myocarditis in Western countries range from 0.03% to 1%, with associated mortality rates as high as 25%-50%.[2,10–14]

Possible explanations for these differences include a higher susceptibility due to genetic differences; differences in clozapine titration and other guidelines; or different diagnostic criteria for myocarditis.[2,5,6,15,16] Concerning the first possibility: a study by Lacaze *et al.* investigated possible single nucleotide polymorphisms (SNPs) that are suggestive of increased myocarditis risk. The *HLA-C*07:01* allele was identified as potentially predisposing to clozapine-induced myocarditis.[17] This allele has earlier been described to also correlate with a higher incidence of clozapine-induced agranulocytosis.[18] As for the third potential cause for the observed discrepancy: in a sample of 20 Australian cases of diagnosed clozapine-induced myocarditis, Winckel *et al*. indeed observed that 13 of these (65%) did not meet the generally accepted diagnostic criteria (see also *Preventive monitoring for myocarditis*), which may have led to overreporting.[16]

The incidence of clozapine-induced myocarditis thus varies wildly from 0.06% to up to >3% depending on literature, and this highlights the diagnostic challenge in this group, where underreporting and missed detection likely plays a role.[19,20] Myocarditis tends to manifest early on following clozapine initiation and can occur as early as week 1 and up to week 3, and very occasionally later in treatment.[1,19–23] A recent systematic review showed that at time of diagnosis of clozapine-induced myocarditis, the mean age of patients is 33.5 years with a mean clozapine dose of 360 mg.[24]

Figure 1. *Bar graph indicating the distribution in time to onset of myocarditis for cases, as measured by the duration of clozapine.*[19]



Incidence of cardiomyopathy

In comparison to clozapine-induced myocarditis, there is far less literature available on clozapine-induced cardiomyopathy. This is a very rare but nonetheless dangerous side-effect, with an incidence of 0.01-0.1%, depending on the literature, and mortality rates of up to 17.9%.[25–27] Cardiomyopathy usually occurs later in treatment (median 9 months) but may occur at any time[1,22], ranging from three weeks to four years, and most often in the first month.[27]. Because of this, it is difficult to determine the causality with clozapine treatment, also because the condition is more frequently associated with abuse of alcohol and cocaine.[27] Estimating the exact contribution of clozapine to the occurrence of cardiomyopathy is further complicated by the fact that the prevalence of several cardiovascular risk factors is increased in patients with schizophrenia as compared to the general population, which could theoretically lead to an increased risk of cardiomyopathy independent of clozapine use.[28,29] Rechallenge of a patient with clozapine who has previously experienced a clozapine-induced myocarditis or cardiomyopathy is strongly discouraged.[30]

Pathogenesis

Specific data regarding the pathophysiology of clozapine-induced myocarditis is scarce. However, there are a few proposed mechanisms. One hypothesis states that clozapine-induced myocarditis likely results from a type I IgE-mediated acute hypersensitivity reaction. The time of onset of clozapine-induced myocarditis and peripheral eosinophilia along with eosinophilic myocardial infiltrates frequently observed in the course of the disease all support this hypothesis.[25,31] However, a recent study by Shivakumar *et al.* suggests the possibility of a delayed hypersensitivity reaction, which would be type II or IV-cell mediated. The authors hypothesise that clozapine forms an antigen with cardiac myocytes to which monocytes attach. This results in an inflammatory reaction, damaging the myocardium and leading to myocarditis.[20] Other possible mechanisms of clozapine-induced myocarditis involve clozapine-induced cytokine release and hypercatecholaminaemia.[32] A recent study by Nikolic-Kokic *et al.* investigated the effect of clozapine treatment on the morphology of the rat heart. After 4 weeks of clozapine treatment, histopathological analysis of the heart was performed. The authors concluded that treatment with clozapine induced pathophysiological alterations in rat heart, which appeared to be associated with disturbances in antioxidant capacity.[33]

It has been suggested that cardiomyopathy can occur as sequelae of an underlying myocarditis, which might explain why it usually occurs later in treatment, and why eosinic infiltrates in myocytes are often

found in cardiac biopsies as well. An IgE-mediated acute hypersensitivity reaction to clozapine is therefore thought to be a cause of cardiomyopathy as well, although direct toxic effects to the heart are also suspected.[27]

Left ventricular dysfunction

There have been a couple of studies indicating that subclinical cardiac dysfunction (associated with either myocarditis or cardiomyopathy) may be quite frequent in clozapine-treated patients. The frequency of grade I diastolic dysfunction was found to be 12.8% after 3 months of treatment with clozapine in a cross-sectional study, although this study lacked a baseline assessment of cardiac function.[34] In a (preliminary) prospective study, 60-80% of the participants showed subclinical but substantial decreases in left ventricular (LV) functioning after 4 weeks on clozapine.[35] Although a more recent medium-term study by Joy *et al*.[9] found that decreases in LV ejection fraction (LVEF) may be associated with clozapine use (mean LVEF was 52% after 4 months of clozapine in 27 patients referred for cardiac review, interquartile range 44-55%), they ultimately found no significant correlation between clozapine treatment duration and LV ejection fraction, suggesting that clozapine did not seem to cause a cumulative detrimental effect on cardiac function.[9] In another recent study by Andreou *et al*, a correlation was found between the use of clozapine or a non-clozapine antipsychotic and a reduced LVEF in males as compared to healthy controls. Among female participants, no difference in mean LVEF between patients and controls was found.[36] At this time, the clinical relevance of these findings is uncertain and long-term studies are needed to clarify whether the observed abnormalities pose a clinical risk.

Risk factors for myocarditis

Myocarditis can occur in any patient receiving clozapine treatment, but a large case control study indicated that patients are at increased risk when clozapine is rapidly titrated.[37] This also means that patients with slow clozapine metabolism are at increased risk, since they experience fast increases in clozapine plasma level as a result. Screening of plasma levels halfway through clozapine titration (for instance at a daily dose of 150 mg) may therefore be useful to identify fast or slow metabolisers.[38–40] As mentioned before, several genetic variations may predispose to myocarditis.[17] In addition, the concomitant use of lithium[41] and sodium valproate, as well as advancing age are potential risk factors for developing clozapine-induced myocarditis.[37,42] The study by Ronaldson *et al.* revealed that sodium valproate more than doubled the myocarditis risk, and for each successive decade in age of the patient at the start of treatment, this risk increased by 31%.[37] Apart from clozapine, other psychotropic agents such as chlorpromazine, fluphenazine, risperidone, haloperidol and the aforementioned lithium have also been linked to myocarditis and/or cardiomyopathy in a large data mining study.[43] This should be taken into consideration when planning to combine clozapine with these drugs, as co-administration could potentially add to the risk of drug-induced myocarditis.[44]

Diagnosis

Diagnosis of myocarditis

Signs and symptoms of myocarditis include persistent tachycardia at rest, palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (*e.g.* unexplained fatigue, dyspnoea, tachypnoea), or fever, and flu-like symptoms.[1,19] The diagnosis of myocarditis is hindered by the fact that symptoms such as tachycardia and elevated temperatures are non-specific and can also occur as benign transient side effects during the first months of clozapine therapy.[45] Furthermore, clozapine-induced

myocarditis can have a heterogeneous presentation[46,47] and a definitive diagnosis may be difficult to establish. The asymptomatic "silent" presentation is a particularly dangerous one, as it can go unnoticed for too long, and has been suggested to have a higher mortality.[48] Also, other syndromes may be misdiagnosed as clozapine-induced myocarditis (such as viral respiratory infections)[16,49], leading to inappropriate and undesirable discontinuation of clozapine.

A typical case of clozapine-induced myocarditis develops within one to three weeks after clozapine commencement. The first symptoms are non-specific (*e.g.* flu-like or gastrointestinal symptoms), developing 10–19 days after commencement and accompanied by an elevated C-reactive protein (C-RP). A rise in troponin is often delayed another one to five days and is accompanied by classical clinical features of myocarditis (chest pain, ECG and echocardiography changes, signs of heart failure). [19,49–51] Eosinophilia can occur approximately 7 days after troponin elevation.[51,52] A comparative study showed that around 64% of myocarditis cases show eosinophilia, while eosinophilia developed in around 30% of clozapine patients without myocarditis.[19] When myocarditis is suspected, several diagnostic tools can be used to confirm the condition (Table 1), although many of these are non-specific and/or have low sensitivity. To date, cardiac magnetic resonance imaging (MRI) seems to be the most reliable diagnostic tool to confirm suspected myocarditis.[45,53] Endomyocardial biopsies are still often regarded as the gold standard for the diagnosis of myocarditis[53–55], although these are often not performed in clozapine-induced myocarditis.[16] When cardiac MRI is non-diagnostic, additional imaging techniques (coronary angiography, myocardial perfusion imaging, optical coherence tomography) may help to discriminate between other differential diagnoses, such as acute coronary syndrome.[56]

Table 1. *Diagnostic signs and tools for detecting suspected clozapine-induced myocarditis*
Enhanced C-reactive protein (C-RP) levels[19]
Enhanced troponin levels[19,50]
Eosinophilia[51,52]
ECG changes[45,50,53]
Left ventricular dysfunction/wall motion abnormalities on echocardiogram[45,53]
Focal myocardial enhancement on cardiac MRI[45,53,54]
White cell infiltration in endomyocardial biopsies[53]

Diagnosis of cardiomyopathy

Newly occurring tachycardia in a patient who has been in stable and unchanged treatment for at least a month should raise suspicion of cardiomyopathy[30] and warrants follow-up investigations. The most frequently reported symptoms of cardiomyopathy include shortness of breath, palpitations, and fatigue[24], but chest pain and coughing could also be reported.[27] Sometimes the disease is asymptomatic and cardiomyopathy is detected by routine echocardiography, or via screening of troponin and C-RP levels for myocarditis monitoring.[27]

A diagnosis of cardiomyopathy is usually made primarily on the basis of echocardiographic evidence of reduced LV ejection fraction; this was found to be lowered from around 50% to 20-40% in most cases of clozapine-related cardiomyopathy.[27,57–60] ECGs and blood tests including raised B-type natriuretic peptide and troponin levels can be supportive but are not sufficient for diagnosis.[24,27] Clozapine-induced

cardiomyopathy is often of the dilated type, showing in 39% of cases reviewed by Alawami *et al.*, and it may frequently feature ECG P-wave and T-wave abnormalities[24], as well as QTc prolongation.[27]

As mentioned in the SmPC of Zaponex, in patients who are diagnosed with cardiomyopathy while on clozapine treatment, there is the potential to develop mitral valve incompetence. Mitral valve incompetence (also called mitral valve regurgitation) is a condition in which the mitral valve does not close properly when the heart pumps out blood, resulting in blood flowing back from the left ventricle into the left atrium. This condition can occur due to the dilatation of the left ventricle seen in some forms of cardiomyopathy, which causes the mitral valve to become stretched and not function properly. The ensuing leakage can increase blood volume and pressure in the left atrium, which can increase pressure in the veins leading from the lungs to the heart (pulmonary veins). If regurgitation is severe, increased pressure may result in congestion (or fluid build-up) in the lungs.
Mitral valve incompetence has been reported in cases of cardiomyopathy related to clozapine treatment. These cases of mitral valve incompetence reported either mild or moderate mitral regurgitation on two-dimensional echocardiography.[1] Treatment of mitral valve incompetence depends on symptoms, the severity of the condition, and whether it is stable or deteriorating. For mild leakage, treatment is usually not necessary. However, for more serious cases, heart surgery in order to replace the mitral valve might be necessary. In case mitral valve incompetence is suspected, consultation with a cardiologist is recommended.[61]

Prevention

In cases of pre-existing cardiac problems, family history of cardiac disease or abnormal ECG results, it is highly recommended that the patient is examined by a cardiologist before starting clozapine. If the cardiologist classifies the cardiac condition as severe (e.g. patient is in class III or IV of the New York Heart Association[62] or has severe arrythmia), clozapine use is contraindicated[1] and can only be started off-licence.

Preventive monitoring for myocarditis
Myocarditis usually develops within the first month of clozapine treatment.[19] Consequently, extra care should be taken during this period to consider cardiac abnormalities. It is recommended that the heart rate, temperature, blood pressure and respiratory rate are routinely checked, and the patient should be asked about symptoms indicative of heart problems such as chest pain, cough, shortness of breath and exercise capacity.[63] The patient and his/her carers should be informed and instructed about cardiac risks. As stated above, slow titration and avoiding concomitant sodium valproate may reduce the risk of clozapine-induced myocarditis.[37] Furthermore, Ronaldson *et al.*[19] proposed a monitoring protocol to actively monitor for the possible development of myocarditis. The protocol recommends obtaining baseline troponin, C-RP and echocardiography[64], and monitoring troponin and C-RP on days 7, 14, 21 and 28 (concurrent with the WBC count). Mild elevation in troponin or C-RP, persistent abnormally high heart rate, or signs and symptoms consistent with infective illness should be followed by daily troponin and C-RP investigation until features resolve. A heart rate above 120 bpm or an increase in heart rate greater than 30 bpm are considered risk markers for clozapine-induced myocarditis.[19] Cessation of clozapine is advised if troponin is more than twice the upper limit of normal, or if C-RP is over 100 mg/L. Combining these two parameters has an estimated sensitivity for symptomatic clozapine-induced myocarditis of 100%. The sensitivity for asymptomatic disease is unknown.[19]

Preventive monitoring recommendations are an ongoing subject of debate in literature. The protocol by Ronaldson *et al.* has probably set the standard for monitoring development of myocarditis.[19] Others have added the recommendation of weekly ECGs for the first 4 weeks[50], although routine ECGs do not seem effective in detecting myocarditis.[28,65] Several other groups have challenged these recommendations, mainly on the issues of baseline echocardiography and routine ECGs.[5,6,66] In their opinion, the estimated risk in countries other than Australia and New-Zealand does not justify such demanding monitoring[6], as it makes clozapine initiation more problematic in some smaller hospitals and clinics. Our advice based on this debate is that baseline ECG, troponin, and C-RP and weekly monitoring of troponin and C-RP during the first month are recommended, as well as routine monitoring of vital signs and inquiring with the patient for signs of cardiac problems (Table 2). Diligent awareness of cardiac issues during clozapine initiation are also supported by Earnshaw *et al*.[67]; baseline echocardiography and routine ECGs are useful if feasible, but an absence of these should not prevent clozapine-eligible patients from access to clozapine.[5]. Dutch guidelines do not recommend them[39], and other authors are cautious as well, because insisting on too many monitoring criteria may prevent clinicians from selecting clozapine, especially when the low incidence does not justify them.[68] Our recommendations regarding cardiac monitoring are also included in the "Summary table monitoring guidelines" available on the secure area of the ZTAS website.

Table 2. *Monitoring recommendations for cardiac side effects*	Baseline	Daily during titration	Concurrent with blood testing	Weekly during the first month	At least annually
Personal/family history	++				
Blood pressure	++	++	++		
Temperature	++	++	++		
Pulse	++	++	++		
Respiratory rate	++	++	++		
Monitor for side effects		++	++		
ECG*	++				+
Troponin	++			++	
C-reactive protein	++			++	
Echocardiography	+				
*Use the appropriate correction formula for calculating QTc; in case of heart rate above 70 bpm, the Fridericia formula offers more reliable corrections.[69]					

Eosinophilia and myocarditis

Although eosinophilia has been associated with myocarditis, it seems to be a poor prognostic marker as only a limited percentage of myocarditis cases exhibit eosinophilia.[47,51] Eosinophilia does not seem to precede myocarditis either.[47,51] Furthermore, eosinophilia is often also present in patients who do not have myocarditis.[51] Benign asymptomatic eosinophilia occurs quite frequently in the beginning of clozapine treatment, is usually transient, and should therefore be distinguished from pathological eosinophilia.[70] See the fact sheet *Eosinophilia* for more information.

Still, around 66% of patient with clozapine-induced myocarditis experience eosinophilia.[20] Clinical features of clozapine-induced myocarditis include a monocytic/eosinophilic picture of the white cell differential with a predominant role of monocytes.[19,71,72] As mentioned before, these findings suggest a

delayed hypersensitivity reaction (type II or IV-cell mediated) rather than IgE-mediated (*i.e* type I). It is hypothesized that monocytosis may be an early marker of clozapine-induced myocarditis, while eosinophilia may potentially be a late marker of a hypersensitivity reaction.[20]

Brain-type natriuretic peptide (BNP) or NTpro-BNP for cardiac screening
Brain-type natriuretic peptide (BNP) or NTpro-BNP have also been suggested as a potential screening biomarker for cardiac LV dysfunction[73–75], but have not yet been validated in a patient cohort in the context of clozapine-induced myocarditis or cardiomyopathy. BNP seems to be related to subclinical clozapine-induced cardiac (left ventricular) dysfunction in some[75,76] but not all studies.[35] To date, there is too little data to recommend BNP measurement for routine monitoring of cardiomyopathy or myocarditis for all patients. For patients with pre-existing cardiac problems, it may be a consideration.

Management

Managing clozapine-induced myocarditis and cardiomyopathy
The Summary of Product Characteristics for Zaponex® (section 4.4) states that if myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly stopped and the patient immediately referred to a cardiologist. Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.[1,30]

All patients with a suspected myocarditis, even if asymptomatic, must undergo a comprehensive laboratory and cardiologic evaluation. When myocarditis is diagnosed, supportive care must be initiated depending on clinical severity of myocarditis. Most patients with acute myocarditis respond well to standard heart failure therapy including diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists, and the introduction of β-blockers until they are clinically stable.[27,44] Several articles report the use of prednisone to treat acute clozapine-related myocarditis, especially in presence of eosinophilic infiltrates on myocardial biopsy.[77,78] When needed, high-grade atrioventricular block and tachyarrhythmias may be treated with appropriate medications and placement of a temporary pacemaker.[44] The treatment of clozapine-induced cardiomyopathy is similar to that of clozapine-induced myocarditis.

A case report published by Longhi and Heres[79] describes the treatment that their patient received for clozapine-induced cardiomyopathy. The patient was initially treated with heart-failure treatment consisting of an ACE-inhibitor, a β-blocker and a diuretic agent, as well as the immediate discontinuation of clozapine. A near-complete recovery of the cardiac issues took up to 6 months.[79]

A study by Ronaldson *et al.* reviewed five cases of patients with suspected clozapine-induced myocarditis, which resolved despite the continuation of clozapine.[80] This is an indication that there is a subset of patients with myocarditis, possibly due to other causes (such as infectious myocarditis) or related to clozapine but mild, which resolves without treatment discontinuation. This illustrates the clinical predicament regarding clozapine discontinuation in patients exhibiting signs and symptoms of myocarditis. Currently, there is no definitive test that differentiates clozapine-induced myocarditis from any other form of myocarditis. Therefore, clinicians are faced with the dilemma between clozapine discontinuation or termination due to potentially unfavourable consequences of either choice, and should therefore make a thorough assessment for potential causes other than clozapine.[81]

Advice on clozapine re-challenge after clozapine-induced myocarditis or cardiomyopathy
As previously stated, it is not advised to re-initiate clozapine therapy in patients who previously experienced clozapine-induced myocarditis or cardiomyopathy. However, many clinicians feel they run out of options in cases where alternative antipsychotic therapy has been unsuccessful and the mental status of their patient deteriorates. As a last resort, they consider re-challenge with clozapine. Re-challenge after a confirmed clozapine-induced myocarditis/cardiomyopathy is contraindicated and would be considered off-licence treatment, requiring an off-licence agreement signed by the ZTAS registered consultant.

There are several case reports in literature that address re-initiation of clozapine treatment following clozapine-associated myocarditis. Ronaldson *et al*.[71] analysed eight cases of clozapine re-challenge after myocarditis. Four of them were successful, and in four cases the clozapine was withdrawn, but in only one case there was diagnostic evidence of myocarditis. They put forward three factors that may influence the success of the re-challenge: severity of the original acute myocarditis, time between the myocarditis event and re-challenge, and the rate of clozapine dose titration.[71] Another factor suggested to promote the success of rechallenge is discontinuation of concomitant sodium valproate.[82,83] A paper by Cook *et al.* highlights several monitoring recommendations for clozapine rechallenge following clozapine-induced myocarditis; these include the use of echocardiogram, electrocardiogram (ECG), as well as measuring C-RP and troponin-I levels. Further advice highlights the importance of physical observations, for example chest pain, palpitations or flu-like symptoms, as well as monitoring blood pressure, pulse, and temperature during the early rechallenge phase.[40] A case report by Nguyen *et al.* demonstrated a successful rechallenge of clozapine after myocarditis without recurrence of the event. Clozapine rechallenge strategy comprised of a low starting dose, slow titration, and extra monitoring steps including daily ECG, C-RP and troponin-I for four weeks, followed by fortnightly monitoring for three months.[84] Shivakumar *et al.* proposed a model for clozapine rechallenge post-myocarditis in which slow initiation with 5mg daily of clozapine is performed. After initiation of clozapine, several factors including the normal biomarkers, eosinophilia/monocytosis, C-RP and troponin levels will decide the course of treatment.[20] Reinders *et al*. reported on two patients where successful clozapine re-challenge or continuation was undertaken.[85] Several other single cases reported successful re-challenge of clozapine[86–92], one of which concerning an adolescent patient.[90] Rostagno *et al*. reported a case in which co-administration of β-blockers and ACE inhibitors was used to allow successful resumption of clozapine.[93] In contrast, Masopust *et al*.[94] and Jayathilake *et al*.[72] report single cases where re-administration of clozapine caused a recurrence of myocarditis.

There are only 5 known published case reports of (re-)starting clozapine after a previous episode of cardiomyopathy. Floreani *et al*. report a successful re-challenge of clozapine after previous cardiomyopathy with the concomitant use of an ACE inhibitor.[58] A report presented by Nederlof *et al.* describes the case of a 63-year-old female who developed dilated cardiomyopathy with an LVEF of 25% after 10 years of clozapine treatment. Its exact cause was never determined, but was probably multifactorial.[60] Clozapine was discontinued and the cardiomyopathy was treated with fluid restriction, low sodium diet, metoprolol, furosemide, spironolactone and lisinopril, as recommended in the guideline of the European Society of Cardiology. Clozapine was re-initiated 100 days later under cardiac monitoring. The patient's heart failure status remained stable for more than a year. Thereafter, a small deterioration in cardiac function was seen. Nevertheless, re-exposure to clozapine was successful during follow-up for at least 2 years.[60] Sanchez *et al.* describe the successful initiation of clozapine in a 36-year-old male patient following a diagnosis of hypertrophic cardiomyopathy. The patient was monitored with regular testing of troponins, inflammatory markers, and ECG. He showed no signs of recurrent

cardiomyopathy and was still on clozapine 3 years later.[95] Lastly, there are two case reports of recurring episodes of cardiomyopathy after clozapine restart.[57,59] In both cases these were typified and identified by the decrease of LV ejection fraction to around 35% after rechallenge.

In summary, the current information on clozapine re-challenge following clozapine-associated myocarditis or cardiomyopathy is limited to case reports and therefore, the risk-benefit ratio remains unclear. It is highly recommended to take extra monitoring precautions when restarting a patient on clozapine after either myocarditis (suggestions for extra monitoring can be found in table 3) or cardiomyopathy.

Table 3. *Summary of extra care used in literature cases of clozapine re-challenge after myocarditis.*
Preceding clozapine re-initiation
Consultation and consent from the patient and his/her carers or family[85–90]
Extensive evaluation of patient's condition by a cardiologist[72,85–90,94–97]
Cessation of sodium valproate[82,83]
Clozapine re-challenge
Extra slow dose titration[20,71,82–85,89,90,98]
Daily physical observations[40,72,89,90]
Every other day or twice weekly troponin[86], C-RP and full blood count.[72,84,89,98] Routine BNP[20,40,90]
Weekly[84,87,90] or twice weekly ECG [89,98]
Weekly[40,72] or monthly[86] echocardiogram; or echocardiogram after one week, then every month[89]
Weekly follow-up by a cardiologist for the first 8 weeks, then monthly for the first half year, and every 3 months thereafter[90]

Bray *et al*. suggest that any patient whose quality of life is very poor as a result of discontinuing clozapine after a cardiac complication should be evaluated for an eventual re-challenge. This should only be done with the consent of all concerned, under adequate monitoring and close supervision by a cardiologist.[86] In this context, it should be noted that patients who previously experienced a mild manifestation of myocarditis symptoms are probably more likely to respond well to re-challenge of clozapine treatment.[71] The extra precautions used in reported cases of clozapine re-challenge after myocarditis as given in Table 3 should be followed in such circumstances. Naturally, rapid titration and the use of sodium valproate should be avoided for these patients[37], as well as co-medication that can strongly inhibit clozapine metabolism and increase its plasma levels (*e.g.* fluvoxamine).

Any decision regarding the patient's re-challenge with clozapine is at the discretion of the treating consultant.

Advice for daily practice:

- Titrate slowly
- Avoid, if possible, sodium valproate (especially during the first 2 months)
- Monitor actively for the development of myocarditis by:
  - routinely checking pulse, temperature, blood pressure and respiratory rate
  - asking the patient about chest pain, cough, shortness of breath, exercise capacity, *etc*.
  - determining weekly troponin and C-RP during the first month
- Cardiomyopathy should be suspected in any patient showing signs of heart failure or newly occurring tachycardia
- Extensive evaluation of a patient's condition by a cardiologist in case of:
  - pre-existing cardiac disorder (clozapine is contra-indicated in patients with severe cardiac disorders)
  - family history of cardiac disease
  - re-challenge after cardiac event (off-licence after clozapine-induced myocarditis or cardiomyopathy)

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