A comparative study of detection of myocarditis induced by clozapine: With and without cardiac monitoring

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ABSTRACT

The aim of this study was to investigate and compare the incidence of suspected or definite cases of clozapine induced myocarditis (SDM) and clinical factors which could influence its onset in two different time periods, defined by pre- and post-cardiac monitoring at an inpatient setting, during the initiation phase of clozapine treatment. Hospital records of patients started on clozapine in the inpatient unit between 2011 and 2018 were investigated. Eight in 38 patients (11.3%) were classified as SDM after the initiation of the monitoring protocol, whereas only 1 in 33 patients (1.4%) was classified as SDM, before. Monitored and non-monitored patient groups were similar with regard to demographic and clinical variables. Diagnosis of schizoaffective disorder and use of concominant lithium, valproic acid and atypical antipsychotics were higher in patients with SDM, while clozapine dose titration was similar compared to the rest of the patients. Cardiac monitoring seems to be the main factor leading to the increase in the detection of clozapine induced myocarditis (CIM). If not monitored, the outcome of CIM can be fatal without any warning signs and symptoms. Concominant use of mood stabilizers including valproic acid and lithium, are important risk factors for the development of CIM.

1. Introduction

Clozapine has been found to be superior to other antipsychotic drugs in treatment-resistance and in reducing suicide risk in patients with a diagnosis of schizophrenia (Kane et al., 1988; Meltzer et al., 2003). Despite its superiority, utilization of clozapine is limited due to potentially fatal serious adverse events among which agranulocytosis is the most feared. However, life threatening adverse events are not limited to hematological side effects and include cardiotoxic adverse events, namely early onset myocarditis and late onset cardiomyopathy (Merrill et al., 2005; Curto et al., 2016). Diagnosis of myocarditis related to clozapine treatment is made through a careful evaluation of clinical, biochemical and imaging findings based on clinical suspicion (Savvatis and Mohiddin 2018).

Clozapine-induced myocarditis (CIM) involves myocardium inflammation commonly seen within the first month, particularly in the third week, of the drug's initiation (Ronaldson et al., 2011). Mechanisms suggested include an Ig E- mediated hypersensitivity reaction, an increase in inflammatory cytokines or catecholamines, and imbalance in autonomic functions (i.e. decrease in parasympathetic activity,

increase in adrenergic activity) (Kilian et al., 1999; Wang et al., 2008; Kluge et al., 2009; Ronaldson 2017). The risk factors for cardiac adverse events during clozapine use have been described to include increasing age, rapid dose titration, the presence of weight gain or metabolic adverse effects, the use of illicit substances and concominant use of lithium, phenothiazines, certain antidepressant agents and valproate (Ronaldson et al., 2012; De Berardis et al., 2018).

The first case of CIM accompanying a suspected overdose was reported in 1980 (Vesterby et al., 1980). Since then, over 250 cases of clozapine associated myocarditis have been presented in relevant literature (Curto et al., 2016; Ronaldson, 2017). In 2015, Ronaldson and colleagues reviewed the incidence of CIM calculated from national adverse reaction reporting centers and single psychiatric services from 7 countries, between 1993 and 2013 (Ronaldson et al., 2015). The incidence of myocarditis ranged between 0.15 and 1.19 per 1000 patients in countries other than Australia (UK, Germany& Switzerland, Sweden, United States, Canada) with fatality ranging from 0 to 0.6 per 1000 patients. On the other hand, the incidence of myocarditis was reported much higher in Australia ranging between 1.9 and 85 per 1000 patients, with fatality ranging from 0 to 12 per 1000 patients. This calculation

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indicated nearly 10 times higher incidence of > 1% (up to 3% with systematic follow-up) clozapine-induced myocarditis in Australia compared to other countries (< 0.1%). It was hypothesized that many cases could have been missed worldwide, where non-specific nature of symptoms made a correct diagnosis difficult when routine cardiac monitoring procedures were not followed. Monitoring for CIM has been utilized since 1999 in Australia (Ronaldson et al., 2015). Moreover, mortality in reported cases has been mentioned to involve 10–30 % of all affected patients. This high rate of mortality and a lack of strong indicators for fatal outcome in clozapine-associated myocarditis, makes a strong case for cardiac monitoring (Curto et al., 2016). Routine measures which can be used in early detection and management of myocarditis in the initiation phase of clozapine have been described in detail elsewhere for clinical practice worldwide (Deardorff et al. 2018; Freudenreich 2015; Goldsmith and Cotes 2017; Li et al., 2018; Ronaldson et al., 2010; Ronaldson et al., 2017). Nevertheless, a debate suggesting that "the unusually high Australian incidences raise unfounded clinical concerns for non-Australian patients" receiving clozapine treatment is present, and rapid titration of clozapine has been placed in the center of this argument (de Leon et al., 2015). Other risk factors for the high incidence of CIM observed in Australia have been pointed as genetic factors related with the metabolism of clozapine, and environmental factors such as the high ozone levels in the breathed atmosphere leading to cholinergic dysfunction (Devarajan et al., 2000). On the other hand, inconsistencies in correct diagnosis and reporting (Ronaldson et al., 2015), and nonspecific presentation of the disorder (Curto et al., 2016) have been implicated in the discrepancy observed in the incidence rates of CIM in Australia and the rest of the world.

In this study, we aimed to investigate and compare the incidence of suspected cases of CIM and related mortality in two different time periods, defined by pre- and post- cardiac monitoring at an inpatient setting, during the initiation phase of clozapine treatment. In addition, we aimed to evaluate and compare clinical factors which could influence the onset of CIM, such as clozapine dose and concomitant medications.

2. Methods

2.1. Subjects

This study was conducted at Hacettepe University, Faculty of Medicine, Department of Psychiatry Inpatient Unit, in Ankara, Turkey. The inpatient unit was chosen as the study setting since the majority of patients started on clozapine are followed as inpatients until stabilization. After the sudden death of an inpatient diagnosed with schizophrenia in October 2015, due to CIM as suggested by the autopsy report, our clinic has introduced cardiac monitoring as routine practice for all clozapine initiated patients.

From the inpatient records, we retrospectively identified 38 consecutive patients hospitalized between October 2015 and June 2018 who were started on clozapine with cardiac monitoring. Another set of 33 consecutive inpatients who were started on clozapine between January 2011 and September 2015 was identified as the comparison group, representing the patients hospitalized prior to the introduction of routine cardiac monitoring. The beginning of the pre-monitoring period was determined as January 2011 due to a specific technical improvement in the inpatient database and records starting on that date. Thus, all of the clozapine treated inpatients between January 2011 and June 2018 were included and there were no exclusion criteria. The patients with suspected (with clinical evidence suggested by Ronaldson et al. (2011, 2017), and without pathological evidence of biopsy) or definite myocarditis (with biopsy evidence) were categorized as suspected or definite myocarditis (SDM) group. All of the SDM cases described in this study were patients whose clozapine treatment were discontinued due to suspicion of CIM or ended with fatality due to CIM.

The Hacettepe University Faculty of Medicine Research Ethics Committee approved the study protocol.

2.2. Procedures

All hospital records including laboratory results, vital signs documentation and patient files including clinical notes, assessments and treatment records were investigated retrospectively. For each patient a sociodemographic and clinical information form was filled out. Records were specifically screened for information regarding relevant parameters which aid in the diagnosis of myocarditis that have been previously described in detail by Ronaldson and colleagues in 2011 and 2017. The pertinent parameters included signs and symptoms of respiratory, gastrointestinal or urinary tract infection, records of fever, tachycardia, hypotension, chest pain and laboratory findings including erythrocyte sedimentation rate (ESR), eosinophil count, C-reactive protein (CRP) levels, Troponin I or T levels recorded at any time point after initiation of clozapine for non-monitored patients, and at baseline 7, 14, 21 and 28th days for monitored patients. For both non-monitored and monitored patients the first positive finding (if present) was included in the analysis. If there were no positive findings regarding a certain laboratory variable, the final normal value was recorded during the inpatients hospitalization period, and laboratory investigations which were not done were recorded separately. In addition, echocardiography, cardiac magnetic resonance imaging reports and cardiology consultation notes were investigated if they were conducted during the follow-up.

Cardiac monitoring in patients starting on clozapine was conducted according to Ronaldson and colleagues' suggestions (2011). The monitoring included measurements of baseline troponin I/T, C-reactive protein, and monitoring troponin and C-reactive protein on days 7, 14, 21 and 28. If at any point a patient developed signs or symptoms of unidentified illness or heart rate ≥120 beats per minute (bpm) or increased by > 30 bpm or CRP 50–100 mg/l or mild elevation in troponin (≤ 2 upper limit of normal, ULN) clozapine was continued with increased monitoring, checking troponin or CRP daily until the condition resolved. If troponin > 2 ULN or CRP > 100 mg/l or if clinical symptoms and signs suggesting CMI were severe, clozapine was observed to be ceased in the inpatient unit.

2.3. Statistical analyses

Statistical analyses were performed with the IBM SPSS for Windows Version 22.0. Numerical variables were summarized as mean ± standard deviation. Categorical variables were given as frequencies and percentages. Categorical variables were compared by Pearson chi square or Fisher's exact test. For 2 × 2 contingency tables; Pearson chi square (if all observed cells are more than 25), continuity corrected chi square (if at least one observed cell less than 25) or Fisher's exact test (if at least one expected value is less than 5) was used. For the contingency tables with more than 2 × 2, Pearson chi square (if less than 20% of the cells have an expected value of less than 5) or likelihood ratio (if more than 20% of the cells have an expected value of less than 5) was used. Normality of the continuous variables was evaluated by Kolmogorov–Smirnov test. Differences between the groups for continuous variables were determined by independent samples *t* test or Mann–Whitney U test as appropriate. The analyses were done without adjustment for multiple comparisons as this was planned as an exploratory study. A *p* value less than 0.05 was considered as significant.

3. Results

A total of 38 consecutive inpatients were included in the post-monitoring and 33 consecutive inpatients were included in the pre-monitoring groups within the investigated time period of 6.5 years. There were eight patients (11.3%) with SDM after the initiation of the monitoring protocol, whereas only 1 (1.4%) patient with SDM was

present before the monitoring protocol was initiated as routine practice. Among the SDM group, only 1 (1.4%) patient was diagnosed with definite CIM with autopsy evidence, before the monitoring protocol was initiated. The SDM rate in the monitored patient group was significantly higher compared to the rate in the non-monitored group ($p = 0.031$).

When the SDM cases were investigated separately regarding Ronaldson et al.'s suggestions (2011) for cessation of clozapine, it was observed that 1 case of SDM had clozapine treatment discontinued due to severe clinical signs and symptoms, a CRP level > 50 mg/l and ESR level > 25 mm/h. All other 8 cases of the SDM patients met either item 1 or 2 listed below:

1) Clinical myocarditis signs and symptoms and, Troponin > 2 ULN **or** CRP > 100 mg/l

   or

1) Endocardial biopsy revealing myocarditis.

There was no statistical difference between patients in the monitored and non-monitored patient groups in terms of age, gender, duration of illness, duration of hospitalization, primary psychiatric diagnosis, clinical signs and symptoms with possible relation to myocarditis, clozapine dose titration and clozapine dose at discharge/cessation (Table 1). No significant differences were found in the history of coronary heart disease, heart failure, cerebrovascular and epileptic disorders, endocrinological and metabolic diseases, collagen tissue, autoimmune and hematological diseases, liver and kidney diseases and hypersensitivity reactions, and concominant psychiatric drugs between the two groups. The annual rate of clozapine initiation was calculated,

revealing 7.07 patients/12 months for the pre-monitoring period, for 33 patients between January 2011-September 2015, and 14.25 patients/12 months for the post-monitoring period for 38 patients between October 2015 and June 2018.

When patients with and without SDM were compared, no statistical difference was found in terms of age, gender, duration of illness and duration of hospitalization (Table 2). There was significantly more patients with a diagnosis of schizoaffective disorder in the group of patients with SDM ($n = 8$, 88.9%), whereas schizophrenia was more common in patients without SDM ($n = 48$, 77.4%) (Table 2). No significant differences were found in the above listed history of comorbid medical illnesses between the two groups. Fever and shortness of breath were significantly more common in patients with SDM. Erythrocyte sedimentation rate, C-reactive protein, troponin and BNP serum levels were significantly higher in patients with SDM (Table 2). Some laboratory data, consisting of erythrocyte sedimentation rate, C-reactive protein, troponin and BNP serum levels, were incomplete in the group without SDM, as these were not part of routine laboratory evaluations in the inpatient unit in the pre-monitoring period.

The daily clozapine dose at discharge/cessation was significantly lower in patients with SDM compared to patients without SDM ($p = 0.017$). The titration rate of clozapine in patients with and without SDM did not differ within the first 2 weeks, but showed a difference after the second week (Table 2, Fig. 1). Due to adjustment of the treatment after the emergence of symptoms and signs of myocarditis, patients with SDM had lower doses of clozapine in the 3rd and 4th weeks of treatment. When concominant psychiatric drug use was evaluated, valproic acid, lithium and atypical antipsychotic use were significantly more common in patients with SDM (Table 2).

In a separate analysis the patients with and without SDM were compared within the monitored group. The diagnosis of schizoaffective

Table 1
Comparison of patients receiving clozapine treatment in the pre- and post-monitoring periods.

	Pre- monitoring patients (N = 33) Mean ± SD	Post- monitoring patients (N = 38)	Statistics	p
Age	39.6 ± 12.2	38.4 ± 14.2	$t = 0.364$, df = 69[a]	0.717
Duration of illness (years)	15.9 ± 9.4	14.3 ± 11.4	$Z = -1.079$[b]	0.281
Duration of hospitalization (days)	61.5 ± 36.0	65.8 ± 33.5	$Z = -0.755$[b]	0.450
Dose of clozapine at discharge/cessation (mg)	334.9 ± 125.5	242.2 ± 183.5	$Z = -2.741$[b]	0.006*
Dose of clozapine at the				
7th day	72.9 ± 37.4	79.4 ± 25.9	$Z = -1.213$[b]	0.225
14th day	172.9 ± 59.8	175.0 ± 73.3	$Z = -0.007$[b]	0.995
21st day	275.4 ± 139.9	230.9 ± 108.2	$Z = -0.801$[b]	0.423
28th day	289.9 ± 86.4	250.7 ± 108.8	$Z = -1.738$[b]	0.082
	n (%)			
Gender (F/M)	20/13	15/23	$\chi^2 = 2.367$, df = 1[c]	0.124
Primary psychiatric diagnosis				
Schizophrenia	26 (78.8)	22 (57.9)		
Schizoaffective disorder	5 (15.2)	11 (28.9)	LR = 6.9, df = 1[d]	0.137
Bipolar disorder	1(3)	4 (10.5)		
Other	1 (3)	1 (2.6)		
Clinical signs and symptoms with possible relation to myocarditis				
Signs and symptoms of respiratory, gastrointestinal or urinary tract infection	2 (6.7)	6 (16.7)	[e]	0.275
Tachycardia	11 (36.7)	22 (61,1)	$\chi^2 = 5.333$, df = 2[f]	0.069
Hypotension	3 (10.0)	6 (16.7)	e	0.494
Chest pain	3 (10.0)	7 (19.4)	e	0.327
Shortness of breath	2 (6.7)	5 (13.9)	e	0.442
Palpitation	5 (16.7)	4 (11.1)	e	0.721
Fever	3 (10.0)	12 (33.3)	$\chi^2 = 3.831$, df = 1[c]	0.050

* $p < 0.05$, 2-tailed.
[a] = Independent samples *t* test.
[b] = Mann–Whitney *U* test.
[c] Pearson chi-square continuity corrected.
[d] Pearson chi-square likelihood ratio (LR).
[e] Fisher's exact test.
[f] Pearson chi square.

Table 2

Comparison of patients receiving clozapine treatment with and without a diagnosis of suspected or definite myocarditis.

	Patients with SDM ($N = 9$) Mean ± SD	Patients without SDM ($N = 62$)	Statistics	p
Age	36.7 ± 15.9	39.3 ± 12.9	$Z = -0.761$[a]	0.447
Duration of illness (years)	13.8 ± 9.9	15.2 ± 10.6	$Z = -0.363$[a]	0.716
Duration of hospitalization (days)	64.0 ± 36.5	63.7 ± 34.5	$Z = -0.078$[a]	0.938
Dose of clozapine at discharge/cessation (mg)	221.9 ± 74.9	326.7 ± 131.9	$Z = -2.389$[a]	0.017*
Dose of clozapine at the				
7th day	80.6 ± 32.5	75.6 ± 32.1	$Z = -0.340$[a]	0.734
14th day	180.6 ± 68.2	172.9 ± 66.9	$Z = -0.057$[a]	0.954
21st day	158.3 ± 143.6	267.2 ± 116.7	$Z = -2.220$[a]	0.026*
28th day	158.3 ± 143.6	287.3 ± 79.3	$Z = -2.837$[a]	0.005*
	n (%)			
Gender (F/M)	4/5	31/31	b	1.000
Erythrocyte sedimentation rate mm/h				0.001*
< 25 mm/h	34 (55.7)	3 (33.3)	LR = 13.768, df = 2[c]	
> 25 mm/h	8 (13.1)	6 (66.7)		
C-reactive protein (mg/l)				0.001*
< 50 mg/l	1 (11.1)	29 (47.5)	LR = 17.134, df = 3[c]	
50–100 mg/l	5 (55.6)	9 (14.8)		
> 100 mg/l	3 (33.3)	4 (6.6)		
Troponin				0.002*
< 1ULN	2 (22.2)	34 (55.7)	LR = 14.332, df = 3[c]	
1–2ULN	1 (11.1)	5 (8.2)		
> 2ULN	5 (55.6)	3 (4.9)		
Eosinophilia (> 6%)	5 (55.6)	10 (16.4)	LR = 6.432, df = 2[c]	0.040*
BNP (pg/ml)				0.031*
< 100 pg/ml	0 (0.0)	8 (13.1)	LR = 6.916, df = 2[c]	
> 100 pg/ml	2 (22.2)	1 (1.6)		
Echocardiographic abnormalities	1 (11.1)	1 (1.6)	LR = 18.061, df = 2[c]	0.000*
Primary psychiatric diagnosis				0.000*
Schizophrenia	0 (0.0)	48 (77.4)		
Schizoaffective disorder	8 (88.9)	8 (12.9)	LR = 26.801, df = 4[c]	
Bipolar disorder	1 (11.1)	4 (6.5)		
Other	0 (0)	2 (3.2)		
Clinical signs and symptoms with possible relation to myocarditis				
Signs and symptoms of respiratory, gastrointestinal or urinary tract infection	1 (12.5)	7 (12.1)	b	0.167
Tachycardia	6 (75.0)	27 (46.6)	LR = 4.118, df = 2[c]	0.128
Hypotension	1 (12.5)	8 (13.8)	b	1.000
Chest pain	2 (25.0)	8 (13.8)	b	0.596
Shortness of breath	3 (37.5)	4 (6.9)	b	0.033*
Palpitation	1 (12.5)	8 (13.8)	b	1.000
Fever	6 (75.0)	9 (15.5)	b	0.001*
Coadministered Drugs				
Antidepressants	1 (11.1)	18 (29.0)	b	0.428
First generation antipsychotics	1 (11.1)	4 (6.5)	b	0.503
Second generation antipsychotics	6 (66.7)	12 (19.4)	b	0.006*
Valproic acid	5 (55.6)	7 (11.3)	b	0.005*
Lithium	4 (44.4)	1 (1.6)	b	0.001*
Benzodiazepines	0 (0.0)	6 (9.7)	b	1.000

* $p < 0.05$, 2-tailed, SDM: Suspected or definite myocarditis, BNP: brain natriuretic peptide, ULN: upper limit of normal.
a Mann–Whitney U test, b = Fisher's exact test.
c Pearson chi-square likelihood ratio (LR).

disorder, fever, erythrocyte sedimentation rate, C-reactive protein, troponin, BNP serum levels, the use of valproic acid, lithium and atypical antipsychotics were significantly higher in the group with SDM (data not presented).

The demographic and clinical characteristics of the cases with SDM are presented in Table 3. One case had a diagnosis of bipolar disorder, while 8 received a diagnosis of schizoaffective disorder. Most cases with SDM were on mood-stabilizers, with 3 on lithium, 3 on valproic acid, and 2 on both of them in addition to clozapine. In addition, 6 cases were also receiving atypical antipsychotics other than clozapine. Six patients had SDM during the third week of clozapine treatment, while 3 had SDM in the second week. Shortness of breath, tachycardia and fever were the most frequently presented symptoms and signs. Although the 9th case did not show any symptoms or signs of myocarditis, the outcome was sudden death, and the patient received a definite diagnosis of myocarditis by postmortem endomyocardial biopsy. This patient had been hospitalized in the ıntensive care unit after valproic acid and quetiapine intoxication and was transferred to the inpatient psychiatry

unit after clinical stabilization. She had a history of nonspecific cardiac problems and a cardiology consultation was requested before initiation of clozapine. Within this consultation an echocardiography was conducted revealing concentric left ventricular (LV) hypertrophy with normal LV systolic functions, and cross-sectional evaluation of all laboratory assessments including troponin and CRP levels were found to be normal. Clozapine initiation was thus approved by cardiology. All other cases except case 3, fulfills the Ronaldson et al.'s (2011) suggestions for cessation of clozapine due to suspected CIM, having CRP > 100 mg/l and/or troponin > 2 times the upper limit of normal range (ULN). Case 3 had CRP = 78, 1 mg/l with troponin in normal range.

The symptoms, signs and laboratory results of all of the SDM cases, excluding the fatal case, improved completely after cessation of clozapine, and patients were discharged with new atypical antipsychotic regimes.
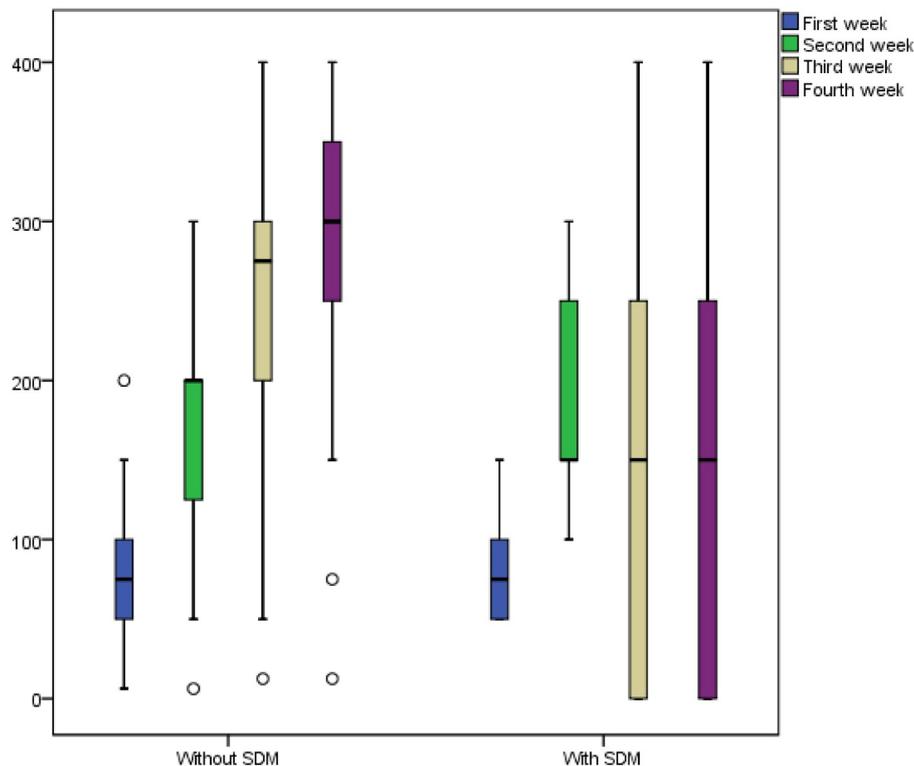
Fig. 1. The rate of clozapine dose titration in patients with and without suspected or definite myocarditis. SDM: suspected or definite myocarditis.

4. Discussion

The main finding of this study is that in a group of schizophrenia inpatients who are started on clozapine upon hospitalization, the number of cases with SDM is significantly higher in the first month of treatment when cardiac monitoring is utilized. Almost all socio-demographic and clinical characteristics of the patients along with clozapine treatment protocol were similar in both monitored and non-monitored patients. Thus, cardiac monitoring seems to be the main factor leading to this increase in the detection of SDM.

In a larger scale, recent national database investigations of annual adverse reaction reports of CIM in both Australia (Dawson et al., 2018; Hollingworth et al., 2018) and Canada (Neufeld and Remington, 2018) show a similar pattern of increase in the number of suspected cases reported. The Australian TGA database showed that a less than 5 annual reports of CIM before the year 2000 rose to more than 130 reports in 2016 (Dawson et al., 2018). Similarly, the number of cases in the Canada Vigilance Program database were less than 5 before the year 2000, and rose to 47 in 2017. This rise has been hypothesized to be related to the use of monitoring protocols for CIM, with guidelines implemented earlier in Australia compared to Canada (Neufeld and Reimington, 2018). Our findings give further support to this view, showing a nearly 8 times increase of SDM cases within a 6.5 years period at an inpatient hospital setting, pre and post-monitoring. It is possible to suggest that higher incidence of SDM in patients receiving cardiac monitoring seems to be mainly derived by the fact that the condition is not being missed.

However, not all recent nationwide register-based studies report such a rise in the rates of CIM. Again, it appears that lack of cardiac monitoring is the leading factor in these conflicting results. In Rohde et al.'s study (2018) from Denmark, the rates of undiagnosed myocarditis was estimated by investigating causes of death after clozapine treatment. Among 3262 outpatients who were initiated on clozapine during a 9 year period (1996–2015), only 1 patient (0.03%) developed myocarditis within the first 2 months after clozapine initiation, but a monitoring protocol was not utilized in these patients. The possibility of overlooked cases of CIM was further examined by assessing causes of mortality, and 26 patients were found to be deceased within the first 2 months after clozapine initiation. The authors estimated a maximum rate of CIM to be 0.28%, much lower than the 3% suggested by Ronaldson et al. in 2015. These results do not dismiss the case that CIM may be overlooked if cardiac monitoring is not conducted. Moreover, some cases of CIM have been reported to resolve and not lead to death. Some reports even suggest that clozapine induced myocarditis may resolve despite continuation of clozapine (Ronaldson et al., 2012; Wang et al., 2008). Successful rechallenge in about 65% of the patients with CIM (Manu et al., 2018), suggests that not all cases of CIM have a fatal outcome, some may resolve before even being noticed.

The annual rate of clozapine initiation doubled from pre-monitoring to post-monitoring periods in the current study. It is possible that, the preference of physicians could have influenced this increase. It has been earlier pointed that the decision to initiate clozapine can vary among physicians (Nielsen et al., 2010; Stahl 2014). Close monitoring could have created a positive influence on the decision to initiate clozapine with less hesitation.

Our results indicate that in cases of SDM, fever (75%), tachycardia (75%), shortness of breath (38%) and chest pain (25%) are the most common presenting signs and symptoms. Evidence of inflammation is noted in 89% of patients with elevated CRP and elevated eosinophil count was present in 55%, troponin levels in 67%. These results are in concordance with a systematic review of Bellisima et al. (2018) where 359 possible cases were reviewed. In this review, the most frequently reported CIM symptoms and signs included fever (67%), tachycardia (58%), shortness of breath (42%) and chest pain (37%). Similarly in the study of Bellisima et al. (2018), 52% of patients presented with elevated CRP, 52% with elevated eosinophil count, 87% and 65% had elevated troponin levels. Interestingly, in the present study, although fever and shortness of breath are significantly higher in patients with SDM, the presence of tachycardia and palpitation were found to be similar between the two groups. It is possible to suggest that tachycardia represents a common and usually benign side effect of clozapine. No significant pattern of association with comorbid medical illnesses was

Table 3
Cases with a diagnosis of suspected or definite myocarditis.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Age	27	32	42	23	19	48	52	23	65
Gender (F/M)	F	M	M	M	F	F	M	M	F
Primary psychiatric diagnosis	SAD	SAD	SAD	SAD	BD	SAD	SAD	SAD	SAD
Duration of illness (years)	4	14	21	7	6	28	10	5	28
Duration of clozapine treatment at onset of SDM (days)	18	18	17	17	14	21	16	13	13
Dose of clozapine at cessation (mg/day)	200	125	250	350	200	300	150	200	125
Comorbid medical illness	–	–	–	–	–	Chronic kidney disease	–	Epilepy	Hypertension
Other medication	Lithium Amisulpride	Lithium Valproic acid Amisulpride	Valproic acid Olanzapine	Lithium Olanzapine Haloperidol	Valproic acid Olanzapine	Lithium	Valproic acid	Lithium Valproic acid Quetiapine	–
Myocarditis signs and symptoms	Signs of GIS infection, Fever, Tachycardia	Palpitation, Shortness of breath, Sharp pain in the chest	Pressure-like pain in the chest, Fever, Tachycardia	Left-upper quadrant abdominal pain, Fever Tachycardia	Palpitation, Sharp pain in the chest, Fever, Tachycardia	Shortness of breath, Tachycardia	Fever, Tachycardia	Shortness of breath, Fever, Tachycardia	Hypertension
Eosinophil (N: 0%, 8–6)	↑ (6,6)	↑ (9,5)	N (4,8)	N (3,9)	↓ (0)	↑ (10,4)	↑ (8,3)	↑ (7,1)	N (4)
ESR (N: 0–25 mm/h)	↑ (87)	N	↑ (45)	↑ (29)	N	N	↑ (61)	↑ (39)	–
CRP (N: 0–8 mg/l)	↑↑↑ (402,0)	↑↑ (86,9)	↑↑ (78,1)	↑↑↑ (118,0)	↑↑ (99,8)	↑↑↑ (120,0)	↑↑↑ (238,0)	↑↑ (73,6)	–
Troponin (N = 8.4–18.3 ng/l)	N	↑↑↑	N	↑↑	↑↑↑	↑↑	↑↑	↑↑↑	N
BNP (N: 0–100 pg/ml)	↑ (102,5)	–	–	–	–	–	↑ (725,9)	N (92,0)	–
CK (N: < 145 U/l)	N	–	–	N	N	↑ (298)	N	N	N
ECG	NSR	NSR	NSR, with early repolariza-tion	NSR	Sinus tachycardia	Sinus tachycardia	NSR	NSR	NSR
Echocardiography	N	N	N	N	N	N	N	N	Concentric LV hypertrophy, normal LV systolic function
Cardiac MRI	–	–	–	–	N	–	–	Myocardial fibrosis	–

SAD: Schizoaffective disorder, BAD: bipolar affective disorder, LV: left ventricular, N: normal, NSR: normal sinus rhythm, GIS: gastrointestinal system.
ESR: erythrocyte sedimentation rate, CK: creatine kinase, CRP: C-reactive protein, BNP: brain natriuretic peptide, ECG: electrocardiogram, MRI: magnetic resonance imaging, , ULN: upper limit of normal.
CRP; ↑: 8–49 mg/l, ↑↑: 50–99 mg/l, ↑↑↑: > 100 mg/l, Troponin; ↑: 1 ULN-2 ULN, ↑↑: 2 ULN-4 ULN, ↑↑↑: > 4 ULN

detected in both studies.

As in the fatal case of CIM within the SDM group we report here, it has recently been reviewed that in some cases, CIM may develop in an atypical presentation without accompanying symptoms and that the outcome in these patients are often fatal (De Berardis et al., 2018). Bellisima et al (2018) in their recent review reported that all of the fatal cases of CIM had cardiac autopsies revealing predominantly-eosinophilic infiltrates. Our fatal case due to CIM (case 9, Table 3) was followed in the inpatient psychiatry unit during the pre-monitoring period. She had a previous history of non specific cardiac complaints and a positive echocardiography finding of LV hypertrophy with normal LV functions. The normal laboratory values of this patient seen in Table 3 were obtained immediately after admission. If the patient had been monitored for CIM after initiation of clozapine, it is possible to assume that a rise in the troponin and CRP levels and perhaps other biological markers could be detected as early warning signs. Considering the possibility of sudden fatal outcomes without any other warning cardiac signs and symptoms, cardiac monitoring for CIM is of utmost importance for patients with past history of cardiac problems.

In our patient sample, we did not note any differences in the dose titration protocol of clozapine in patients with and without SDM. Although rapid titration of clozapine has been suggested to be a major causative factor in the development of CIM (de Leon et al., 2015), the similar clozapine titration rate in patients with and without SDM observed in the present study indicates that titration rate might not be a substantial contributing factor in every setting. However, the higher rate of schizoaffective patients and the use of lithium and valproate in the SDM cases, point to the necessity of strict evaluation and caution in these patients in such combinations with clozapine. Concomitant use of lithium and valproate have been previously described as risk factors for the development of CIM (De Berardis et al., 2018). Our findings support the view that cardiac monitoring measures should be used for patients with schizoaffective and bipolar disorder, who are also receiving adjunctive mood stabilizers such as valproic acid and lithium.

The serum clozapine, norclozapine levels and clozapine/norclozapine ratios were not found to differ between patients with and without SDM (data not presented), however it is difficult to draw a conclusion from this finding as serum drug levels were measured at different time points of hospitalization for each patient.

In our sample of patients with SDM, the emergence of symptoms and signs with a possible diagnosis is within the first 3 weeks. Findings suggest that CIM, although it is rare, typically occurs within the first month of treatment (Ronaldson et al., 2012). The risk of CIM has been repeatedly found to be greatest within the first 3 weeks (Knoph et al., 2018). A systematic review investigating all articles published from 1988 to 2017 has confirmed that ESR and chest radiography may not be beneficial in routine screening for myocarditis, eosinophilia often occurs after signs and symptoms of myocarditis develop, and that CRP and troponin monitoring is especially beneficial for symptomatic patients (Knoph et al., 2018). The authors conclude that the utility of routine screening in asymptomatic patients is unknown. Our findings also suggest that the rise in serum CRP and troponin levels are especially useful in the detection of cases for SDM. In patients with history of previous cardiac illness clinicians should be especially cautious even when there are no alarming signs and symptoms.

The significantly higher rate of eosinophila and elevated BNP levels in the SDM patient group in the current study, implies that these two laboratory measurements can have additional benefits in detection of some cases.

Among the presented SDM cases, case 3 who had a CRP level of 78 mg/l and troponin level in the normal range, and thus the cessation of clozapine could be debated. This case could have been followed by daily CRP and troponin measurements, without cessation of clozapine, according to Ronaldson et al.'s suggestions (2011). The somewhat early cessation of clozapine in case 3 seems to be due to the clinicians' precautious attitude induced by the severity of patient's complaints of chest pain and tachycardia. Considering the previous reports which suggest that CIM may resolve despite continuation of clozapine (Ronaldson et al., 2012; Wang et al., 2008), clinicians may prefer close monitoring instead of discontinuing clozapine in cases with milder clinical presentation of SDM.

The major limitations of the current study are the retrospective nature of data collection, and the small sample size. Nevertheless, our results indicate that cardiac monitoring is crucial in patients using clozapine in different parts of the world with different genetic and environmental backgrounds. In addition, this study further supports the findings that concomitant use of psychotropics, most notably mood stabilizers including valproic acid and lithium, are important risk factors for the development of CIM. Due to these limitations future dedicated studies are needed to confirm the results.

In the presence of significant cardiac signs and symptoms implying CIM, clinicians are currently in a dilemma of whether to discontinue clozapine to prevent a fatal outcome and cessate a possibly effective treatment in a refractory patient, or to continue treatment with clozapine taking risks. This study emphasizes the fact that without cardiac monitoring missing CIM cases is inevitable. Cardiac monitoring during clozapine use along with careful clinical decision making, seems to be the only safe and sound solution in resolving this dilemma.

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Conflict of interest

Author AEAY has consulted for pharma companies Janssen and Abdi İbrahim Otsuka in the past 3 years. All other authors declare that they have no conflicts of interest.

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