

Observations From 8 Cases of Clozapine Rechallenge After Development of Myocarditis

To the Editor: Clozapine is an exceptionally effective drug for the treatment of schizophrenia,¹ but it may occasionally cause myocarditis, typically within 3 weeks of clozapine initiation.² The effectiveness of clozapine in the individual patient may be manifest before the onset of myocarditis despite its early occurrence, and clozapine withdrawal may lead to rapid deterioration in psychiatric state.^{3,4} Hence, clozapine rechallenge has considerable appeal. In the course of data collection for a case-control study of clozapine-induced myocarditis, we have documented 8 cases of rechallenge that occurred between 2002 and 2006 and describe them here in an attempt to explore what factors may enhance the likelihood of successful rechallenge.

Case series. The patients were 7 men and 1 woman aged 22–51 years who had previously had an episode of myocarditis meeting a case definition⁵ (Table 1). In 4 patients, clozapine treatment was continued after rechallenge with no apparent cardiac consequence (cases 1–4), and in 4 patients, clozapine was withdrawn early (cases 5–8). Only 1 of the 4 who discontinued clozapine after rechallenge had diagnostic evidence of myocarditis (case 5). This patient self-medicated with a single 400 mg clozapine dose and had a troponin I concentration of 78.5 µg/L 3 days later. The other 3 patients developed nonspecific illness within 2–7 days of rechallenge, and clozapine was discontinued (cases 6–8). After recommencing clozapine treatment, cases 1 and 3 also had symptoms of a mild illness, but without a rise in troponin, and were able to continue taking clozapine without lasting ill effect.

Three factors that may influence the success of clozapine rechallenge after myocarditis are severity of the original acute myocarditis, time between the myocarditis event and rechallenge, and rate of clozapine dose titration during rechallenge.

There is no established measure for assessing the severity of nonfatal myocarditis. The 2 cases with the very high C-reactive protein and eosinophil counts (cases 6 and 8) may have been severe, as may those with measured left ventricular impairment (cases 4–8). The 1 patient with severe myocarditis by these measures who was successfully rechallenged (case 4) had exceptionally slow dose titration at reinitiation, and subsequent echocardiography showed normal left ventricular function.

With regard to the possible benefit of a delay after the development of the initial episode of myocarditis, cases 7 and 8 indicate no such benefit, and a successful rechallenge commenced 9 days after the onset of myocarditis and involved more rapid introduction of clozapine than in the first instance (case 1).

In only 1 case of successful rechallenge was the rate of dose titration exceptionally slow (case 4). None of the unsuccessful instances of rechallenge involved slow dose titration.

Of 5 published reports of rechallenge after clozapine-induced myocarditis,^{3,4,6–8} rechallenge was successful in 4 instances.^{3,4,6,8} In the unsuccessful case,⁷ clozapine treatment was initiated about 6 weeks after the first episode, and the dose was increased by 12.5 mg every third day. Clozapine treatment was ceased after mild illness and electrocardiographic changes, though without an elevation in troponin. Details of the dose titration regimen for the successful cases are sketchy or nonexistent.

Across the total of 13 cases now described, there are not sufficient instances of rechallenge, successful and unsuccessful, to identify factors that may improve the outcome. Some authors have recommended slow initiation of clozapine during rechallenge.^{6,8} There is no added harm in introducing clozapine very slowly. If a repeat of myocarditis can be avoided by this strategy, clozapine may yield a long-term benefit for the patient.

Table 1. Cases of Clozapine Rechallenge After the Development of Clozapine-Induced Myocarditis^a

Case No.	Initial Episode		Time to Rechallenge	Rechallenge Strategy	Outcome	Comments
	Clinical Features	Diagnostic Features				
Successful rechallenge						
1	Fever (39°C), bilateral wheeze, tachycardia (140 bpm)	Troponin I = 0.26 (ULN = 0.03) µg/L, CRP = 131 (ULN = 5) mg/L. Echo: normal LV size and function	9 d	Rate of dose titration slightly faster than for first initiation	Developed tachycardia, hypotension, mild diarrhea, but no rise in troponin	Clozapine withdrawn because of neutropenia after 4 mo
2	Fever (38.8°C), nausea, chest pain, hypotension, tachycardia (118 bpm)	Troponin I = 1.2 (ULN = 0.26) µg/L, CRP = 56 (ULN = 5) mg/L	8 mo	Slightly slower titration than standard. Initial daily doses (mg): 12.5, 25, 37.5, 50, 75	Troponin remained normal, CRP = 68 mg/L. No symptoms of illness. Clozapine continued > 14 mo	Echo: LV function normal 8 mo after rechallenge
3	Fever (38.5°C), cough, throat erythema, earache, headache, tachycardia (124 bpm)	Troponin I = 0.7 (ULN = 0.05) µg/L, CRP = 174 (ULN = 5) mg/L. Echo: LV function normal	10 mo	Slow dose titration. Initial daily doses (mg): 25, 50, 50, 50, 50, 75	Rise in CRP to 118 mg/L on day 3, with febrile illness. No rise in troponin. Vital signs normal on day 16. Clozapine continued with ≥ 1 interruption for > 9 y	Echo: LV function normal 3 y after rechallenge
4	Fever (40.5°C), myalgia, hypotension, tachycardia (120 bpm)	Echo: mild global reduction in LV function, hypokinesia	19 mo	Very slow dose titration. Initial daily doses (mg): 12.5, 12.5, 12.5, 18.75, 18.75, 25	No rise in troponin in first 6 wk. Clozapine continued with ≥ 1 interruption for > 8 y	Echo: LV function normal 13 mo after rechallenge
Unsuccessful rechallenge						
5	Fever (39°C), diarrhea, vomiting, hypotension, tachycardia (144 bpm)	ECG changes, CRP = 142 (ULN = 10) mg/L. Echo: mildly impaired LV function	9 mo	Single 400 mg dose	Troponin I = 78.5 (ULN = 0.6) µg/L. Echo: mild-moderate global LV dysfunction	Echo: LV function low normal 7 mo after rechallenge
6	Fever (42.2°C), "flu-like" symptoms, vomiting, diarrhea, tachycardia (136 bpm)	Troponin I = 0.17 (ULN = 0.03) µg/L, CRP = 236 (ULN = 5) mg/L, eosinophils = 3.43 × 10 ⁹ /L. Echo: mild-moderate LV dysfunction	11 d	Took for 2 d only	Became febrile without raised troponin. Clozapine discontinued	
7	Fever (38.8°C), headache, tachycardia (130 bpm)	CRP = 190 (ULN = 8) mg/L. Echo: mild-moderate global LV hypokinesia (EF 40%–59%)	7 mo	Took 7 daily doses: 12.5 mg, 25 mg, then increasing by 25 mg/d	Developed tachycardia, hypotension, chest pain. Clozapine discontinued	Echo: LV function had not fully recovered and did not appear to deteriorate with rechallenge
8	Fever (38.7°C), syncopal episodes, chest pain, tachycardia (130 bpm)	CRP = 277 (ULN = 10) mg/L, eosinophils = 3.1 × 10 ⁹ /L. Gated blood pool scan: EF 46%	8 y	Took 3 daily doses (mg): 12.5, 25, 50	Collapsed with hypotension and tachycardia. Clozapine discontinued	

^aAge and sex have been withheld to obscure identity. Abbreviations: bpm = beats per minute, CRP = C-reactive protein, ECG = electrocardiography, EF = ejection fraction, LV = left ventricular, ULN = upper limit of normal.



In conclusion, the previous occurrence of clozapine-related myocarditis is apparently not always a contraindication to the reintroduction of clozapine treatment. Any decision to rechallenge with clozapine should be made with the consent of the patient and the patient's family after communication of the potential benefits and risks. Rechallenge then is best conducted with considerable caution (very slow dose titration) and an elevated degree of monitoring.²

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