Clozapine Rechallenge Following Clozapine-Induced Pericarditis

To the Editor: There are many reports describing the development of myocarditis and cardiomyopathy following treatment with clozapine. Fewer reports exist about the development of pericarditis, and reports of successful rechallenges with clozapine following the development of pericarditis are particularly rare. We report the case of a patient successfully resumed on clozapine treatment following the development of pericarditis and propose an approach to following up such patients.

Case report. A 17-year-old male with treatment-resistant paranoid schizophrenia (*DSM-IV* criteria) and intermittent periods of depression was admitted to the National Psychosis Unit, South London and Maudsley NHS Foundation Trust, London, England, in late 2007. His main symptoms included complex persecutory delusional beliefs, passivity of thought, thought insertion, thought broadcast, and auditory and somatic hallucinations. This presentation was preceded by a 5-year insidious onset of symptoms beginning in 2002.

In June 2006, a trial of clozapine was initiated in which clozapine was titrated up to 350 mg/d in divided doses. The patient started to show early signs of an improvement in his behavioral and psychotic symptoms. Four weeks after commencing clozapine treatment, he developed a sinus tachycardia. His electrocardiogram (ECG) results were otherwise normal. His previous medical history had been unremarkable other than a history of mild asthma. Specifically, he

had no history of cardiovascular disease or hypersensitivities to any medications.

The tachycardia persisted, and 1 week later he developed a low-grade fever and mild gastrointestinal disturbance. He was subsequently transferred to a medical ward, where an echocardiogram revealed a large pericardial effusion. A diagnosis of clozapine-induced pericarditis without ECG changes was made. This diagnosis was in view of the known link between clozapine and such presentations, given the recent initiation of the drug and in the absence of any other suspected causes. Minimal bilateral pleural effusions were observed on x-ray, and blood tests revealed a mild elevation of C-reactive protein. The patient showed, however, no evidence of myocardial disease: there were no ECG abnormalities and no elevation of cardiac troponin.

Given that clozapine was considered the likely cause for the pericarditis, treatment with it was discontinued after the diagnosis was made, and the patient was observed in a pediatric ward over the ensuing days. The pericardial effusion, tachycardia, and inflammatory markers resolved spontaneously, with no need for further treatment.

Clozapine was subsequently substituted with olanzapine in August 2006, up to 20 mg/d. However, the patient's psychotic symptoms returned to the levels seen prior to treatment with clozapine. In February 2007, after a second opinion was obtained from the National Psychosis Unit, the patient was placed on treatment with melperone up to 450 mg/d, an atypical antipsychotic not licensed in the United Kingdom, but occasionally used off license in the management of treatment-refractory schizophrenia in those who have not responded to or are unable to tolerate clozapine. Later that year, in December 2007, the patient was admitted to the National Psychosis Unit inpatient ward after showing no response to melperone.

A second opinion regarding the pericarditis was sought from a cardiologist, who was of the view that, of the many causes of pericarditis, the most likely causes were a viral infection or clozapine-induced pericarditis. The cardiologist advised that, on balance, it could not be concluded with certainty whether the pericarditis was of infective origin or due to clozapine; however, the latter remained strongly suspected given that the pericarditis occurred a few weeks after commencement of clozapine treatment.

After the consultation with a cardiologist, a decision was made by the treating psychiatric team, with the informed consent of the patient's family, to rechallenge with clozapine. It was considered that the psychiatric benefits of a further trial of clozapine outweighed the risk of the development of pericarditis, provided that the patient's cardiac status was closely monitored to allow the early detection of a recurrence of pericarditis, so that the drug could be withdrawn before complications developed.

Clozapine treatment was recommenced with daily measurement of temperature, blood pressure, and pulse rate and monitoring of symptoms of pericarditis including chest pain, cough, and dyspnea. Baseline ECG and echocardiography were performed at initiation and 2 and 4 weeks after the clozapine rechallenge commenced. ECGs were repeated monthly thereafter, with a further echocardiogram at 3 months. During this time, the patient was successfully titrated up to a clozapine dose of 400 mg/d with no adverse effects, and this remains his current dose. A marked improvement in his functioning was observed in the form of increased participation in ward activities, a diminished intensity of persecutory delusions, and an absence of auditory hallucinations. The patient was discharged from the hospital in February 2009 with ECG monitoring every 3 months as recommended by a cardiologist.

Epidemiologic data indicate potentially fatal cardiac adverse effects associated with the use of clozapine.[1] Pericarditis is listed as a rare (≥ 1:1,000, ≤ 1:10,000) and serious side effect of clozapine that has potentially fatal complications, including cardiac tamponade and constrictive pericarditis.[2,3]

We conducted a MEDLINE search of English-language publications from 1966–2009 using the keywords *clozapine* and *pericarditis* and identified 17 publications discussing pericarditis associated with clozapine therapy. Wehmeier et al[4] reviewed the literature in 2005 and reported on 6 such cases. Eleven further cases were identified in our literature search.[5–14] In all cases reported, discontinuation of clozapine therapy resulted in an improvement in physical symptoms.

Our literature search identified only 2 published reports of successful rechallenges or continuation with clozapine in cases of clozapine-induced pericarditis.[9,15]

In 1 of these 2 cases, a 26-year-old man developed pericarditis and polyserositis 9 years after starting clozapine treatment.[9] Having excluded all other causes for the pericarditis, it was suspected that clozapine was the most likely reason, and treatment with the drug was stopped. Although the patient responded reasonably well to other antipsychotics, it was felt that he would improve further with clozapine. After a cardiology consultation, clozapine treatment was successfully restarted with close follow-up. The patient remained well on clozapine treatment for over 2 years after it was resumed. The nature of the follow-up was not detailed in the report.

In the second reported case, a 16-year-old girl developed pericarditis associated with clozapine in which serial ECG changes and rises in troponin I were observed.[15] Following resolution of the cardiac symptoms and ECG changes, clozapine treatment was continued with regular monitoring of troponin I levels, which returned to normal. There was no recurrence of pericarditis, and the authors proposed the measurement of troponin I as a suitable means of monitoring cardiac side effects of clozapine.

In addition to these cases, there is a report detailing a case of polyserositis and pericardial effusion associated with clozapine treatment in a 39-year-old woman who was rechallenged with clozapine.[16] However, the pericardial effusion recurred shortly after clozapine was resumed.

Investigators in Germany carried out a retrospective review of 36 cases of children, adolescents, and young adults treated with clozapine.[17] In two-thirds of the cases, they identified 1 or more markers that could have indicated the presence of pericarditis, myocarditis, or cardiomyopathy. No patients in the report were shown to develop any cardiac side effects from continued clozapine treatment.

There are no evidence-based recommendations for the monitoring of cardiac side effects of clozapine. One consensus view from state hospitals in Victoria, Australia, proposes the use of frequent echocardiography in patients who develop abnormal cardiac symptoms, in addition to regular ECGs and monitoring of cardiac enzymes.[18] These guidelines, however, are nonspecific and are proposed for a range of different cardiac side effects. Guidelines for monitoring of patients rechallenged with clozapine who have a history of pericarditis do not exist.

While it will never be known whether the development of pericarditis in our patient was truly clozapine-induced or viral in origin, we demonstrate that careful monitoring during the first 3 months following a rechallenge with clozapine, using serial echocardiograms and ECGs performed in close collaboration with cardiology colleagues, can be successful. We propose this program of follow-up as a suitable method to monitor for cardiac side effects of clozapine in patients with a previous history of pericarditis who are rechallenged with clozapine and would recommend combining this approach with regular monitoring of troponin I, as suggested by others previously.[15,18]

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