Revisiting the Discussion: Termination of Clozapine Treatment Due to Renal Failure

To the Editor: In 2013, Nielsen et al[1] published an article, "Termination of Clozapine Treatment Due to Medical Reasons," with the objectives of identifying clozapine side effects leading to clozapine discontinuation and determining if some of these side effects could be managed without discontinuation or with a rechallenge. The article and accompanying charts, explicating discontinuation rules and management strategies, remain extremely useful in the clinical setting. The findings of their review were recently condensed into a summary table, Clozapine's Dangerous Side Effects and How to Manage Them, in *Current Psychiatry*[2] for use by psychiatry residents and other clinicians. Renal failure is not included as a possible dangerous side effect in either commonly studied article. We believe this oversight needs to be corrected.

Various nonspecific signs can develop in the first month of treatment with clozapine. Røge et al[3] state that up to 50% of patients have fever in the first month, possibly due to increased cytokines, and within that same period there is an increased risk of side effects with an immunologic basis. They conclude that, while fever "in most cases is a harmless phenomenon,"[3(p210)] when fever occurs, efforts should be made to seek out "possible new inflammatory symptoms that may be related to clozapine treatment."[3(p210)] In 2011, Roberts et al[4] completed a thorough review of another nonspecific sign, clozapine-induced eosinophilia. They noted that not all eosinophilia is associated with end-organ damage, but when combined with evidence of "organ-specific inflammation," clozapine is normally discontinued to prevent further organ dysfunction. They recommended close monitoring of renal and pancreatic function in patients with idiopathic eosinophilia even though there are "no standard recommendations in the literature"[4(p1149)] for doing this. We agree with Roberts et al and with the principles expressed by Røge et al. When eosinophilia or fever is noted in a patient treated with clozapine, renal function should be monitored.

In 2011, our group[5] reviewed 8 cases of clozapine-induced acute renal failure (CIARF), 7 cases from the literature and 1 reported by us. Mild eosinophilia preceded and later frank eosinophilia coincided with acute renal failure in our patient and at least 3 others. Fever was the most commonly mentioned hypersensitivity reaction, occurring in at least 6 of the 8 cases, including all 4 with eosinophilia. White blood cells or protein in the urine of patients taking clozapine were also strong indicators of renal involvement.

Since our review, at least 4 additional case reports of CIARF have been published.[6–9] Fever and/or eosinophilia were mentioned in all 4 case histories. We commented on the need for caution when using antibiotics in such cases.[6,10]

In all 12 of these case reports, clozapine was discontinued, resulting in improved or normal renal function in every case. Two of the 12 patients were rechallenged: one was 4 days after experiencing fever[11] and one was 4 years after developing CIARF.[12] Both rechallenges resulted in the reoccurrence of CIARF.

In summary, we recommend modifying the clozapine-monitoring protocol of Nielsen et al to include the monitoring of renal function when eosinophilia or fever present during clozapine treatment.

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Dr Nielsen and Colleagues Reply

To the Editor: We thank Drs Woesner and Kanofsky for commenting on our article, "Termination of Clozapine Treatment Due to Medical Reasons."[1] We fully acknowledge that nephritis/renal failure is a rare adverse effect of clozapine that warrants further attention. It seems that nephritis adds to a growing number of presumably dose-independent adverse drug reactions (ADRs) of clozapine with a possible immunologic origin, including, for example, colitis, pancreatitis, pericarditis, myocarditis, and polyserositis.[2]

These ADRs have in common an emergence within the first month of clozapine treatment and often with the presence of fever and flu-like symptoms. Some of these features overlap with or represent clozapine-induced fever, which is usually benign and transient, but which may also indicate marked immunologic activation.[3]

Several risk factors for these ADRs have been suggested. The presence of eosinophilia is considered an indication that these ADRs reflect an immunoglobulin E hypersensitivity reaction.[4] However, eosinophilia can also occur as a benign and often transient phenomenon during clozapine treatment. For myocarditis, rapid initial titration rate of clozapine and cotreatment with sodium valproate have been suggested as relevant risk factors.[5] Interestingly, 5 of 8 cases of clozapine-induced nephritis/renal failure were cotreated with sodium valproate.[6] Common for these possible risk

factors is that they are based on low numbers of patients and have not been replicated.

We do not believe that the available data justify routine laboratory testing, such as troponins for myocarditis or serum creatinine for renal failure in the absence of suggestive clinical changes, as abnormal results will not confirm an etiologic relationship with the clozapine treatment. In addition, an even more complicated monitoring routine may prohibit some psychiatrists from prescribing clozapine. However, psychiatrists should pay extra attention in case of fever, flu-like symptoms, or eosinophilia during the first month of clozapine treatment and bear in mind that this phenomenon may affect any organs.

We agree that signs of these inflammatory adverse effects should lead to termination of clozapine. However, as clozapine is an effective antipsychotic drug, the highly clinically relevant question emerges: is clozapine rechallenge safe and meaningful?

Currently, the number of rechallenged patients is far too low to draw any firm conclusions. As Woesner and Kanofsky state, 2 of 2 rechallenged patients reexperienced clozapine-induced nephritis. However, a review by Manu et al[7] found that clozapine rechallenge was successful in 3 of 4 cases of myocarditis. As these low numbers illustrate, it is highly important that any patient who experienced a serious/potentially life threatening ADR with clozapine who is later rechallenged is reflected in the literature, so that we can learn more about under which circumstances clozapine rechallenge is or is not safe.

Finally, we would like to emphasize that clozapine is highly underutilized and that further underutilization because of these very rare adverse effects should not occur.[8] Clozapine is, under the right circumstances, a safe and frequently live-saving antipsychotic.[9]

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