Low-Dose Clozapine-Induced Agranulocytosis in Patients with Movement Disorders—Retrospective Study from India

Clozapine is widely prescribed by both psychiatrists and neurologists in low-middle income countries (LMICs) throughout Asia despite the remote but real possibility of clozapine-induced agranulocytosis and neutropenia (CIA/CIN).\textsuperscript{[1]} Clozapine is comparatively less popular in high-income countries (HICs) where the risks of litigation are high. However, in the last couple of decades the number of lawsuits for medical negligence has increased significantly in LMICs such as India.

Clozapine is licensed for the treatment of resistant schizophrenia.\textsuperscript{[2]} However, its efficacy in treating L-Dopa-induced dyskinesia (LID) and psychosis (LIP) has been increasingly recognized.\textsuperscript{[3–4]} Off-label use of clozapine for LID/LIP has become common among movement disorder neurologists in India, though at lower doses than those used in schizophrenia.

The mechanism of CIA/CIN is largely unknown, but it is thought to result from immunological destruction of leukocyte precursors triggered by the nitrenium metabolite of the drug.\textsuperscript{[5]} The prevalence of CIA, reported in a large cohort of patients in the USA, was 0.5–2% and CIN 3%.\textsuperscript{[1]} CIA and CIN are defined when the absolute leukocyte and neutrophil counts are lower than or equal to 3,500/mm\textsuperscript{3} and 1,500/mm\textsuperscript{3}, respectively, or a significant drop in the absolute counts, even if these remain above the cut-off values.\textsuperscript{[5]} The grading of severity of CIA and CIN is inconsistent in the published literature. In general, the NIH common toxicity criteria might be followed where necessary.\textsuperscript{[16]} If the absolute leukocyte count falls below 3,000/mm\textsuperscript{3} or absolute neutrophil count falls below 1,000/mm\textsuperscript{3}, treatment with clozapine should be interrupted. Close monitoring (ideally daily testing) of blood counts is advised and clozapine can be resumed if the count returns to normal. Treatment should be permanently discontinued if leukocyte or neutrophil counts fall below 2,000/mm\textsuperscript{3} or 1,000/mm\textsuperscript{3}, respectively. Recent evidence suggests, approximately 75% of patients with mild CIN will not progress to moderate–severe CIN.\textsuperscript{[7]} Risk factors for CIA/CIN included increasing age, female sex, and Asian race. CIA/CIN commonly occurs 6–18 weeks after initiation of treatment and recovers spontaneously in the majority of cases after withdrawing clozapine. However, if these conditions are not detected early, or left untreated, severe and life-threatening infections can ensue.

Strict monitoring systems exist in the UK and USA for patients treated with clozapine and require weekly blood testing for the first 18 weeks and fortnightly thereafter.

Unfortunately, there are no published estimates of the prevalence of CIA/CIN in the Indian population, where there is currently no uniform monitoring protocol. Hence, we undertook a retrospective medical record review (digitally archived OPD charts and lab records) of patients treated with low-dose clozapine in a regional movement disorders (MD) clinic. The Institutional Ethics Committee approved the retrospective collection of clinical data, acquired as part of routine patient care, without written consent. We excluded those cases who never returned for a follow-up visit or where the lab reports were either absent or incomplete. Out of 4,224 MD cases (2013–18), we identified 397 patients receiving clozapine. The total duration of follow-up was 367 days (median). Out of 397 patients we excluded 143 cases. The indication for prescribing clozapine was LID (42.51%), LIP (15.74%), LID, and LIP (38.18%), or other (tics and other forms of chorea; 3.54%). The median interval of follow-up was around 3 months (median 94 days). In contrast to the intensive monitoring procedures followed in HICs, the patients prescribed low-dose clozapine in our clinic were requested to undergo hematological monitoring every 3 months. Two patients (0.8%) had CIA but none reported CIN in our cohort [Table 1]. Clozapine was withdrawn in 49 patients (19.29%) due to excessive sedation.

This is the first safety-study of clozapine use in a cohort of movement disorders patients in India. While our data have confirmed CIA in a South Asian population, the risk appears...
Letters to the Editor

Table 1: Clinical details of two cases of clozapine-induced agranulocytosis (CIA)

| Patient 1 | Patient 2 |
|-----------|-----------|
| Indication | LIP       | LID      |
| Age (year) | 77        | 70       |
| Sex        | F         | M        |
| Duration of PD (years) | 7        | 11       |
| Lowest TLC (counts/mm³) | 3200     | 2980     |
| Starting dose of clozapine (mg) | 25       | 25       |
| Dose at which CIA identified | 125      | 50       |
| Duration of clozapine use before onset of CIA (months) | 10       | 11       |
| Whether symptomatic | No       | No       |
| Comorbidities | No       | No       |
| Resolution after stopping clozapine | Yes      | Yes      |

[CIA defined as TLC <3500/mm³; LIP - L-Dopa-induced psychosis; LID - L-Dopa-induced dyskinesia; PD - Parkinson’s disease; TLC - Total Leukocyte Count]

Conflicts of interest

There are no conflicts of interest.

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to be relatively low. Importantly, all cases of CIA were identified without intensive monitoring. Given the economic and geographic barriers to accessing healthcare for large sections of Indian society, our data provide some support for less frequent monitoring of blood counts. Moreover, a recently published meta-analysis reported that the incidence of death from neutropenia following clozapine exposure was rare (0.013%).[7]

Although our study findings require confirmation in large-scale prospective studies, it has provided a firmer foundation for future guideline development in India, where the complications of CIA/CIN can be more devastating than in HICs, and where levels of litigation are on the rise.

Leucocyte Count

LID – L-Dopa-induced dyskinesia; PD – Parkinson’s disease; TLC – Total Leukocyte Count

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