Clozapine re-challenge in patients with history of blood dyscrasia 3 Year follow up
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Abstract: Clozapine re-challenge in an individual with a history of clozapine-induced blood dyscrasia is not often attempted. However it can be considered in patients with history of good response to the drug in the past, and where the risk of re-challenge is considered to be less than the risk of withholding treatment. Increasing the frequency of monitoring of white blood counts and the use of lithium or Granulocyte-Colony Stimulating Factors are the strategies that have been reported to be helpful during re-challenge. A dyscrasia that occurs during rechallenge is reported to be earlier in onset and longer lasting. We report the three year follow up data of two patients who had a blood dyscrasia following which they were re-challenged with clozapine.

Case report 1: Mr. A, a 42-year-old male was diagnosed to have treatment resistant schizophrenia in 2005 after he underwent unsuccessful trials of different antipsychotic agents, including risperidone and olanzapine. He was commenced on clozapine and within a period of 3 weeks he developed neutropenia (total white blood cell count, 2100/cu mm; absolute neutrophil count, 546/cu mm) and a lower respiratory tract infection. Clozapine was discontinued. Following this he received several first and second-generation antipsychotic medication trials with aripiprazole, 30 mg/day; quetiapine, 800 mg/day; amisulpride, 800 mg/day; zotepine, 350 mg/day; haloperidol, 20 mg/day; depot fluphenazine decanoate (100 mg once a fortnight) and sodium valproate (1000 mg/day), each over a 3-6 month period, individually and in combinations. He also received two courses of Electro Convulsive Therapy (ECT). The option of clozapine rechallenge was considered in view of persistent psychotic symptoms and homicidal risk. Treatment plans were made in consultation with a clinical hematologist after written informed consent was obtained. All other psychotropic medications, except for haloperidol, were tapered and stopped. He received thrice-weekly injections of Filgrastim (0.9 mg/week), while clozapine was recommenced. The dose of clozapine was gradually increased to 450 mg per day over the next few weeks. Blood cell counts were monitored twice a week for the first 8 weeks and later once a week for the next one year. Filgrastim was discontinued after 3 weeks as total counts remained within normal limits. The patient was, and continues to be, followed up regularly; white blood cell counts have remained normal four years after re-challenge with clozapine. Psychotic symptoms have gradually reduced along with an improvement in personal and social functioning.

Case report 2: Mr. B, a 32-year-old male was diagnosed to have schizophrenia in 2005. Treatment resistance was considered as he remained symptomatic following adequate trials of risperidone and olanzapine. Clozapine was commenced in 2010, however he developed transient leucopenia (total white blood cell count dropped from 6900/cu mm to 3500/cu mm over a few days) necessitating discontinuation of the medication. No other potential causes for the leucopenia were evident. Following this he received several antipsychotic medication trials including Amisulpride 800 mg/day, Quetiapine 800 mg/day and Risperidone 8 mg/day, both individually, as well as in combinations.
In view of persistent psychotic symptoms with significant impairment in social and occupational functioning, the option of rechallenge with clozapine was considered. Treatment plans were made in consultation with the clinical hematologist. After written informed consent was obtained, all other psychotropic medications, except amisulpride were tapered and stopped. Clozapine was initiated and the dose increased to 400 mg per day. White blood counts were closely monitored twice a week initially and later reduced to once a week. The patient continues to be followed up regularly and white blood cell counts have remained normal three and half years after re-challenge with clozapine. He continues to have residual psychotic symptoms; therefore clozapine has been augmented with sodium valproate and amisulpride. There has been improvement in the areas of personal and social functioning.

Discussion
Clozapine re-challenge is not frequently considered an option in view of the increased potential for life threatening complications. This is more so in low and middle income countries where limited resources preclude such attempts(12,13). When considering a re-challenge with clozapine it is advised that monitoring be more frequent (twice a week for 3 months) to detect emergent dyscrasias, as these tend to appear earlier and in a more severe form(6,8). An extended period of hospitalization for intensive monitoring, avoiding the concomitant use of other medications with a potential for dyscrasias and liaison with a clinical haematologist are other essential considerations during the re-challenge. While medications such as lithium or colony-stimulating factor analogs are suggested as adjuvants, there is no consensus on the dose and duration of these medications to prevent dyscrasias. Recent reports suggest genetic susceptibility to dyscrasias with clozapine. Further research in this area is warranted. The two cases described above suggest that re-challenge with clozapine is a feasible option in patients with persisting psychosis; however this must be performed with caution and close monitoring.

References: