Supplementary Table 7. Clozapine-induced inflammation

Hypothetical model with 3 phases[27,28,76]
• In the first phase, the titration is too fast for a specific patient, as the psychiatrist was too aggressive with it, and/or due to the patient's clozapine PM status; this leads to a release of cytokines. • In the second phase, a positive feedback loop develops, the cytokines inhibit CYP1A2, which further increase the plasma clozapine concentrations. • In the third phase, if the titration continues, the inflammation becomes complicated by the development of auto-antibodies (or another auto-immune phenomenon) which leads to myocarditis or other inflammations.
Extension of the concept
In a literature review, Verdoux et al.[103] proposed that manifestations of clozapine-induced inflammation due to rapid titration may include a wide variety of presentations including: • systemic inflammatory processes: - fever - fever with isolated CRP elevation - lupus • localized signs of inflammation: - myocarditis, - serositis, - pneumonitis/alveolitis, - hepatitis, - pancreatitis, - nephritis, - colitis, and - dermatological disorders
Overlap among definitions
• The above classification is somewhat arbitrary since these presentations may lie on a continuum with no clear-cut boundary between them, and several conditions may co-occur. • Moreover, it overlaps with manifestations associated with eosinophilia; the typical clozapine-induced myocarditis is associated with eosinophilic infiltrations. A recent review from a European pharmacovigilance database identified 51, of which 47 were new cases of clozapine-related DRESS syndrome which appear to have associated variables similar to clozapine-induced myocarditis.[104]

CRP, c-reactive protein; CYP1A2, cytochrome P450 1A2; DRESS, drug reactions with eosinophilia and systemic symptoms; PM, poor metabolizers