264 - Severe neutropenia or agranulocytosis

Severe neutropenia or agranulocytosis

Schizophrenia and related psychoses CHAPTER 1 Clozapine, neutropenia and lithium Mild neutropenia Around 3.8% of patients treated with clozapine develop neutropenia.1 Most of these cases are unrelated to clozapine treatment, and clozapine in fact may not cause neutropenia per se.2 The risk of neutropenia (<1.5×109/L) in patients treated with clozapine is broadly similar to the cross-sectional prevalence of neutropenia in otherwise healthy individuals (0.4– 4.5% depending on ethnicity).3 Indeed, a meta-analysis comparing the risk of neutropenia between clozapine and other antipsychotics found that clozapine did not have a stronger association with neutropenia than other antipsychotic medications.4 Most people developing mild neutropenia will not develop severe neutropenia or agranulocytosis. Risk factors for neutropenia include being Afro-Caribbean, younger age and having a low baseline white cell count (WCC).5 The vast majority of patients who stop clozapine because they have developed neutropenia can be successfully rechallenged.6 Adopting the US monitoring criteria would eliminate the requirement to discontinue clozapine treatment in cases of mild neutropenia (absolute neutrophil count [ANC] between 1 and 1.5×109/L). Confusion arises because of the various possible reasons for a low neutrophil count in people taking clozapine. A single low count might just be a coincidental finding of no clinical relevance, as is common with all drugs. Several low counts (consecutive or intermittent) might be seen in people with BEN (see below) or as a result of clozapine- associated bone marrow suppression (especially if consecutive and progressively falling). Full-blown agranulocytosis can probably always be interpreted as being the result of severe bone marrow suppression caused by clozapine. Severe neutropenia or agranulocytosis The risk of agranulocytosis during clozapine treatment is 1 in 250 (0.4%),7 lower than previously thought, and risk of death resulting from this is 0.05% – a rare event. Most cases of agranulocytosis develop within the first 18 weeks of treatment. Thereafter, the risk diminishes steeply.8 The mechanism of clozapine-induced agranulocytosis is not fully understood but is thought to be immune mediated, given the significant association with certain human leucocyte antigen variants.9 Identifying with certainty whether an episode of severe neutropenia is clozapine-related may be difficult. However, the pattern of neutrophil count change is important. A single episode of a below-threshold ANC <0.5×109/L may be unrelated to clozapine but would normally promptly lead to treatment cessation. In patients without BEN, agranulocytosis is generally preceded by normal neutrophil counts, which are then

followed by a precipitous fall in neutrophils (usually over a week or less) and a prolonged period of counts near to zero (assuming that it has not been treated).10 Neutrophil counts that do not follow this characteristic pattern are difficult to interpret. The Netherlands Clozapine Collaboration Group11 considers the risk of agranulocytosis so low that a mentally competent patient may stop routine haematological monitoring after 6 months of treatment. The group still nevertheless recommends low-frequency testing (for example four times a year if routine monitoring is stopped).

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