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Continuing clozapine with granulocyte colony-stimulating factor in patients with neutropenia

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Abstract

Background: The current guidelines dictate that clozapine should be stopped following the emergence of neutropenia. Various alternative approaches have been tried in the past, among them one rarely used alternative being to continue treatment with clozapine with coprescription of granulocyte colony-stimulating factor (G-CSF).

Aim and method: In this case series we aim to describe the treatment and progress of a number of patients in a secure psychiatric hospital in the UK. These patients were restarted on clozapine in combination with G-CSF, in spite of previous neutropenia associated with clozapine treatment.

Discussion and conclusion: We hope that this case series will raise the profile of a potentially effective alternative to discontinuing clozapine after neutropenia.

Keywords: clozapine, clozapine-induced neutropenia, granulocyte colony-stimulating factor

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Introduction

The effectiveness of clozapine as therapy for treatment-resistant schizophrenia is well established [Kane *et al.* 1988; McEvoy *et al.* 2006; Lewis *et al.* 2006]. There is also extensive literature covering the effectiveness of clozapine in reduction of aggression [Glazer *et al.* 1998; Hector, 1998; Rabinowitz *et al.* 1996; Spivak *et al.* 1997; Volovka, 1999; Volovka *et al.* 2004; Buckley *et al.* 1995], self-harm and suicide [Duggan *et al.* 2003] and adverse incidents [Beer *et al.* 2006] in various psychiatric settings. However, in spite of superior efficacy to other antipsychotic medications, the use of clozapine had been reserved for treatment-resistant disease [National Institute for Health and Clinical Excellence, 2009] because of the risk of serious adverse reactions [Kilian *et al.* 1999]. The occurrence of agranulocytosis is a substantial hazard in the administration of clozapine, but this hazard can be reduced, or managed, by monitoring the white cell count [Alvir *et al.* 1993]. Of the patients taking clozapine about 3% develop neutropenia (neutrophil count $< 1.5 \times 10^9$/liter) and 1% develop agranulocytosis (neutrophil count $< 0.3 \times 10^9$/liter) [Alvir *et al.* 1993; Atkin *et al.* 1996]. Among those who have been rechallenged there is evidence that neutropenia occurs more quickly on rechallenge than the first episode of neutropenia, lasts longer and is more severe [Dunk, 2006]. Unsurprisingly the authors have not been able to find any case in the literature in whom a third rechallenge of clozapine following neutropenia was attempted.

Neutropenia is a frequent problem in patients with haematological malignancies; following cancer chemotherapy; with idiosyncratic drug reactions; and in some viral infections and autoimmune disorders. Granulocyte colony-stimulating factor (G-CSF) is a cytokine which increases the maturation of granulocytes within the bone marrow, and is known to greatly improve quality of life in patients with severe chronic neutropenia [Jones *et al.* 1993]. However, G-CSF has rarely been used to continue clozapine treatment in patients with neutropenia, as evidenced by the scant literature [Dunk, 2006; Chin-Yee *et al.* 1996; Conus *et al.* 2001; Sperner-unterweger *et al.* 1998; Majczenko and Stewart, 2008; Rajagopal *et al.* 2007; Joffe *et al.* 2009, Hagg *et al.* 2003; Mathewson and Lindenmayer, 2007]. None of the

patients described in this literature experienced significant side effects associated with G-CSF.

Aims

None of the patients described in the above case reports were in a secure psychiatric setting. We aim to describe the treatment of three patients with clozapine and G-CSF in a secure psychiatric hospital in the UK. All of the patients had previously developed neutropenia that was associated with clozapine treatment. For the purpose of this small case series the authors included patients who have 'treatment-resistant' schizophrenia, who had previously received clozapine and developed neutropenia associated with this treatment. All of the patients have a significant history of violence.

Method

Clinical data were collected from reviewing inpatient notes. Data were also obtained from pharmacy records, pertaining to prescription and administration of medications, and from the security department. All incident reports (incidents of aggression and violence are recorded within the hospital in a standardized way) were reviewed for each patient. For the purpose of anonymity some of the irrelevant details have been altered.

Because the use of G-CSF as a treatment for clozapine-related neutropenia is not a licensed indication, the authors were careful to follow a process of discussion and consultation prior to implementing this novel treatment regime. The plans were discussed and formulated with the patients' multidisciplinary care teams and then discussed with the patients themselves. If possible, informed consent was obtained from the patients. When this was not feasible, a discussion of best interests included the views and opinions of patients' families and carers. In the latter case the view of a second opinion appointed doctor was also sought, in line with the provisions of the Mental Health Act. All patients were formally detained under the Act.

In the interests of peer review, and because of the use of a nontrust formulary treatment, the opinion of the appropriate clinical director was sought and agreement obtained prior to commencing the trial. In addition, the case histories were presented for further peer review at local academic meetings. Owing to the specialist nature of the proposed intervention, the opinion and involvement of a haematologist was sought at an early stage. This involvement was essential in terms of excluding other specific, treatable causes of neutropenia as well as advising on the technical use of G-CSF.

Case 1

Mr X is a white British man in his 20s with a diagnosis of treatment-resistant paranoid schizophrenia. He first became unwell in his early 20s while he was at university. Since then, he had spent the majority of the intervening time in hospital. His presentation included persistent grandiose and persecutory delusions and distressing auditory hallucinations in different modalities. He has a history of alcohol and cannabis misuse. Because of a gradual escalation of aggressive behaviour (including fashioning a weapon and assault on staff members) he had been moved to hospitals with a higher degree of security.

Mr X responded poorly to first-line antipsychotics, including first- and second-generation agents (experiencing severe dystonic reactions with the former). A trial with clozapine initially produced positive results but had to be discontinued after a few months when Mr X developed neutropenia. This was followed by deterioration in his mental state and aggressive behaviour.

After consultation with the Clozaril Patient Monitoring Service (CPMS) and a local haematologist, the decision was taken to attempt a rechallenge with clozapine with lithium cover to boost his white cell count. An initial improvement was again seen, with a reduction in Mr X's agitation and challenging behaviour. Unfortunately, however, he again developed neutropenia leading to agranulocytosis and a chest infection, requiring hospital admission to receive intravenous antibiotics. Both lithium and clozapine were discontinued and Mr X's mental state again deteriorated with challenging behaviour, including specific persecutory beliefs about staff, fashioning weapons and further assaults.

Following a full review of his treatment history the decision was taken to attempt a retrial of clozapine with G-CSF cover in the event of neutropenia. The process of consultation and review which has been described above was followed.

A pre-clozapine neutrophil level of 1.6 was treated with 30 million units filgrastim (G-CSF) with almost immediate results, pushing his neutrophil

count into the acceptable 'green' range. Clozapine was subsequently started. Within several weeks the ward had noticed a considerable change in Mr X's behaviour, including a correction of his reversed sleep pattern; a reduction (in fact almost complete amelioration) in his reporting of persecutory delusions; and improved compliance with ward rules and boundaries. Mr X required two further doses of G-CSF over the following 2 weeks. In light of his continued positive response and absence of adverse effects, the decision was taken, in conjunction with pharmacy personnel and the haematologist, to start regular weekly dosing of 30 million units G-CSF (with frequent blood monitoring as required for clozapine treatment).

Mr X's clozapine dosage was stabilized at 400 mg daily with continued improvement in his mental state as well as markedly reduced aggressive behaviour. He was on the combination of clozapine and G-CSF for a year before he was transferred to a lesser secure unit where he continues to be treated with the combination. His neutrophil count during treatment with this regime ranged between 1.9 and 5.6 $\times$ 10^9/liter and no adverse effects associated with the use of G-CSF were noted.

Case 2

Mr Y is a white British man in his 30s known to the psychiatric services for 16 years. He has severe, mixed personality disorder (with predominantly antisocial, paranoid and narcissistic traits), as well as schizophrenia. In spite of receiving care in a secure psychiatric hospital, he presented with serious challenging behaviour and increasingly frequent and serious violence.

In high security Mr Y continued to display high levels of aggression with frequent threats to harm or kill staff. He was violent towards staff and other patients, in the context of paranoid ideation and auditory hallucinations which were resistant to trials of different antipsychotics. Treatment with clozapine (at a dose of 700 mg/ day) resulted in significant improvement in psychotic symptoms and marked reduction in violent incidents. However, clozapine was discontinued about nine months later following significant weight gain and concern over compliance, and a long-acting depot antipsychotic medication was initiated. However, this resulted in further deterioration in mental state and clozapine was reinitiated after the weekly depot was discontinued. However, this was again discontinued after only a few weeks when Mr Y developed neutropenia believed to be related to the clozapine. Despite treatment with a first-generation depot antipsychotic and an alternative, oral second-generation agent, Mr Y's behaviour once more deteriorated.

In light of his previously good response to clozapine a further retrial was initiated and the dose gradually increased to 650 mg daily. Once again the clinical response in terms of mental state and reduced aggression was swift and marked. Mr Y again developed a neutropenia of 1.4 $\times$ 10^9/liter several months later in January 2010. However, on this occasion he was treated with 30 million units of filgrastim (G-CSF) with immediate response, his neutrophils returning to an acceptable level. Mr Y required only this single dose of G-CSF and has otherwise maintained his neutrophil count between 1.8 and 8.8 $\times$ 10^9/liter. He has continued to respond well to clozapine with a marked reduction in violence. After an extended period of weekly monitoring he has since been able to reduce to less frequent monitoring.

Case 3

Mr Z is a white British man in his early 20s with a diagnosis of paranoid schizophrenia and severe borderline and antisocial personality disorders. He was treated with first- and second-generation antipsychotics but showed a poor response. He committed the offence of armed robbery following escaping from a locked ward and had psychotic symptoms at the time of his offence. In the secure hospital there were incidents of multiple assaults on staff and patients.

Following initiation of clozapine Mr Z reported a reduction and then cessation of auditory hallucinations and his aggression reduced. However, after approximately 2 months of treatment he received two 'red alert' neutrophil levels over 2 days and clozapine was discontinued. This was followed by an immediate deterioration of Mr Z's mental state, including the re-emergence of command hallucinations to kill. Although Mr Z continued to be treated with alternative antipsychotic agents he remained guarded and complained of ongoing hallucinations with associated homicidal thoughts and fantasies. This culminated in a serious assault on a member of staff with a fashioned weapon.

Treatment with high doses of a second-generation antipsychotic resulted in some improvement in the intensity of Mr Z's psychotic symptoms. However, he retained a troubling and pervasive sense of paranoia and continued to describe violent fantasies and preoccupations. In discussion with Mr Z it was decided that a retrial of clozapine would be warranted in light of the initial positive response and the highly worrying behaviour associated with his psychotic symptoms. He was able to give informed consent for this intervention, including the use of G-CSF in the event of neutropenia. A specialist haematological review indicated that Mr Z presented with a low baseline neutrophil level, similar to the pattern seen in benign ethnic neutropenia, although Mr Z is of white British origin. All relevant investigations were conducted and these revealed no underlying, treatable cause of neutropenia. In conjunction with this apparent idiopathic low neutrophil count it was considered likely that Mr Z's previous 'red alerts' were induced by the clozapine. As such it was considered that G-CSF treatment should be considered rather than lithium due to the risk of clozapine-induced agranulocytosis with lithium [Gerson *et al.* 1991; Whiskey and Taylor, 2007; Valevski *et al.* 1993].

Due to this relatively low baseline neutrophil level Mr Z was started first on filgrastim (G-CSF) in December 2009 with the aim of prophylactically boosting his count. After three weekly doses of 30 million units his neutrophil level was considered robust enough to commence clozapine, which was done in early January 2010. He responded as he had previously done to the clozapine, with a rapid reduction in his symptoms. He again experienced side effects including hypersalivation and constipation which responded to adjunct pharmacological treatment. Several days after initiation of clozapine he received another low neutrophil level (an 'amber' blood result) and was given another 30 million units of filgrastim with good effect. Over the following 2 weeks he required filgrastim on two further occasions, each time boosting his neutrophil count into an acceptable range. Within 3 weeks he reported a significant reduction in his paranoia and feeling 'clearer headed' and more relaxed on the ward. As a result of careful (several times weekly) monitoring of his neutrophil level and consultation between the treating psychiatrists, pharmacy personnel and the haematologist, he was commenced on a weekly schedule of 30 million units of filgrastim by intramuscular injection.

Discussion

The cases presented here illustrate the different potential approaches to the use of G-CSF in treating clozapine-induced neutropenia: a single 'rescue' dose; occasional, responsive dosing; or regular prophylactic dosing. There are potential pifalls and benefits when contemplating any of these approaches. For example, a single 'rescue' dose in response to unexpected neutropenia, such as in case 2, can be given effectively on license as this is a recognized treatment for sudden neutropenia for which the cause is not determined. However, the clinician will then face the dilemma of whether or not to continue treatment with clozapine: while discontinuation may lead to rapid relapse and even 'rebound' psychosis, continued use may lead to further neutropenia and more difficult considerations about the use of clozapine/G-CSF cotherapy. However, with prophylactic prescription, or long-term responsive dosing, the indication must certainly be considered 'off license' and the prescribing clinician must face questions over how long to continue therapy (possibly indefinitely) and the potential for adverse effects associated with long-term G-CSF use. These can include enlarged spleen and hepatomegaly; urinary abnormalities; and, very rarely, splenic rupture [Jones *et al.* 1993; Chin-Yee *et al.* 1996; Conus *et al.* 2001; Sperner-unterweger *et al.* 1998; Majczenko and Stewart 2008; Rajagopal *et al.* 2007; Joffe *et al.* 2009; Hagg *et al.* 2003; Mathewson and Lindenmayer, 2007]. There is also a theoretical increased risk of myeloid malignancy with long-term exposure to G-CSF. Although this has not yet been seen in the limited experience of clinical practice, it is a potentially serious possibility which should not be dismissed. In light of these possible adverse effects close collaboration with a haematologist is important as these specialists have experience of regularly prescribing G-CSF in their clinical practice (although for different indications).

In light of these potential risks, there must be a persuasive rationale for following this approach. The authors argue that such a rationale can be found: while the intervention is uncommon there has been support for such an approach in the limited case reports in the literature; there is also a wealth of support in the literature and clinical experience for the long-term use of G-CSF in patients with nonpharmacologically associated neutropenia [Jones *et al.* 1993; Joffe *et al.* 2009; Hagg *et al.* 2003; Mathewson and Lindenmayer, 2007]. Furthermore the authors argue that severe,

intractable psychotic illness, especially when associated with significant risk of violence and concomitant high levels of containment and security, has a major negative impact on individual quality of life, in addition to conferring significantly increased levels of morbidity and mortality. When combined with patients' own requests and family and carer support for such an approach, these factors may amount to a persuasive argument.

In our own experience, as described above, the patients responded well to reintroduction of clozapine, in terms of clinical improvements in mental state and reduction in aggression and violence. This is, perhaps, unsurprising given the previous rapid responses shown by this group of patients. In addition, this admittedly small group of patients have not displayed clinically significant side effects associated with the use of G-CSF and the adverse effects reported in association with clozapine appear to be of a similar frequency and intensity as previously described.

The authors acknowledge that this is a small case series conducted in the highly specialized environment of a secure psychiatric hospital and, as a result, questions could be raised about the applicability of such an approach in other patient populations. However, the authors contend that it would be difficult to design a randomized controlled trial to measure the effectiveness of such a treatment approach for the following reasons: the interventions are novel and unlicensed; the seriousness of the potential risks involved; difficulty in gaining consent from patients (given that they would be at the severe end of the spectrum of psychopathology); and the difficulty of getting an adequate sample size to provide sufficient statistical power. Therefore case reports and case series, like this one, may provide the only evidence available to clinicians in this area.

Conclusion

This series builds on a number of previous case reports, in addition to more extensive literature on the use of G-CSF in other fields, which broadly show positive results. Further, more robust, investigations with appropriate methodology would be able to give a clearer picture of the benefits that the authors have observed in the sample patient group. However, because of the practical and ethical difficulties of designing such studies (such as a randomized controlled trial) it would be helpful if clinicians who have experience of using G-CSF share their experience with their peers by publishing their findings.

The authors are of the opinion that this select group of patients, who have responded to clozapine in the past but experienced neutropenia, are unresponsive to other interventions and remain significantly distressed with poor quality of life and florid psychotic symptoms, and who pose a significant risk to others, should be considered for clozapine rechallenge in combination with G-CSF. Not doing so may mean that these patients are deprived of a potentially effective treatment approach. However, given the risks involved, the authors would advocate that for each individual patient a risk–benefit analysis should be performed, along the lines discussed above. The authors accept that, at this stage, there is not enough evidence to justify or recommend incorporating the general use of G-CSF within clinical guidelines. However, mention of the approach in the guidelines would raise clinician awareness of this alternative and potentially lead to fewer practical and administrative challenges when it is appropriately considered.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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