A retrospective study of intramuscular clozapine prescription for treatment initiation and maintenance in treatment-resistant psychosis

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ABSTRACT

Background: Clozapine is uniquely effective in treatment-resistant psychosis but remains underutilised, partly due to psychotic symptoms leading to non-adherence to oral medication. An intramuscular (IM) formulation is available in the UK but outcomes remain unexplored.

Aims: This was a retrospective clinical effectiveness study of IM clozapine prescription for treatment initiation and maintenance in treatment-resistant psychosis over a 3-year period.

Methods: Successful initiation of oral clozapine after IM prescription was the primary outcome. Secondary outcomes included all-cause clozapine discontinuation two years following initiation, and one year after discharge. Discontinuation rates were compared with a cohort only prescribed oral clozapine. Propensity scores were used to address confounding-by-indication.

Results: Among 39 patients prescribed IM clozapine, 19 received at least one injection, while 20 accepted oral when given an enforced choice between oral and IM clozapine. Thirty-six (92%)

successfully initiated oral clozapine after IM prescription; 3 never transitioned to oral. Eight discontinued oral clozapine during the two-year follow-up, versus 83/162 in the comparator group (discontinuation rates of 24% and 50% respectively). Discontinuation rates at one-year post-discharge were 21%, compared to 44% in the comparison group. IM clozapine prescription was associated with a non-significantly lower hazard of discontinuation two-years after initiation and one-year after discharge (HR0.39,95%CI 0.14–1.06; HR0.37,95%CI 0.11-1.24). The only reported adverse event specific to the IM formulation was injection site pain and swelling.

Conclusions: IM clozapine prescription allowed transition to oral maintenance in a cohort initially non-adherent. Discontinuation rates were similar to patients only prescribed oral clozapine and comparable to existing literature.

INTRODUCTION

Clozapine has been considered the gold-standard for treatment-resistant psychotic disorders since the 1980s (1). It demonstrates a 50 to 75% response rate among those who fail to achieve remission with conventional first- or second-generation antipsychotics (2). Clozapine is associated with better long-term outcomes than other antipsychotics or no treatment, including lower long-term all-cause mortality rates (3), reduced violent offending (4) and readmission rates (5). Despite superior efficacy, clozapine remains significantly underutilized and its initiation is often substantially delayed. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study reported that only 14 to 50% of eligible patients were treated with clozapine (6). Furthermore, data from the United Kingdom (UK) shows that clozapine initiation is typically delayed by approximately 4 years (7).

One common problem occurs when treatment-resistant patients are not able to accept clozapine or associated blood tests due to symptoms of acute psychosis, including impaired insight and delusional beliefs. Although the Mental Health Act (MHA) in England and Wales gives the legal authority to administer involuntary drug treatment and ancillary investigations, including blood tests to support clozapine use (Mental Health Act. Nottingham: CQC; 2008), most patients who require but are non-adherent to antipsychotics are prescribed long-acting injections, due to the practical difficulties of enforcing oral treatment. However, since clozapine is not available as a long acting injection, an unwillingness to take the oral form of clozapine has hitherto precluded clozapine treatment. While compulsory administration of medication is not uncommon in psychiatric care, this is rarely employed with clozapine treatment, with only a few facilities worldwide reporting the use of nasogastric (8) and intramuscular (IM) clozapine (9,10,11,12,13).

In this study, we present our 3-year experience with short acting IM clozapine in the South London and Maudsley Hospital (SLaM) Foundation Trust.

METHODS

Study design

Observational data from SLaM were collected to follow-up a cohort of patients prescribed IM clozapine as a short-term strategy to initiate oral clozapine. Our aim was to evaluate its potential value in initiating and maintaining clozapine in patients initially reluctant to take oral clozapine. Transition from IM prescription to oral clozapine was the primary outcome. The secondary outcome was all-cause clozapine discontinuation, a widely used outcome measure in observational studies. Post-discharge discontinuation rates were investigated in order to assess long-term adherence to oral medication outside a hospital setting where concordance cannot be prompted and supervised by healthcare professionals. Finally, we compared all-cause clozapine discontinuation rates with those of a comparison group of patients started and maintained on oral clozapine, without IM prescription, while detained under the MHA in SLaM. This analysis was conducted to investigate whether addressing an initial reluctance to accept clozapine treatment by prescribing the IM formulation will lead to long-term compliance at rates similar to or different from patients who accepted oral clozapine from initiation.

IM clozapine

The IM clozapine used in this study is manufactured by Apotheek A15® (formerly Brocacef®) in the Netherlands and was approved by the Drugs and Therapeutics Committee of SLaM NHS Foundation Trust in 2016. Owing to the need for daily administration, and the large volume that must be injected to achieve maintenance doses of clozapine, IM clozapine is not suitable as a long-term treatment. Although there is no upper limit, the protocol suggests not exceeding 14 days of injections; nonetheless previous data report safe use of IM clozapine for up to 96 days (9). Therefore, the SLaM protocol (see Supplementary material 1) allows for IM clozapine as a short-term intervention to initiate or re-initiate clozapine treatment in patients who refuse oral medication, with a view to converting to oral clozapine once compliance is achieved. The decision to prescribe IM clozapine is undertaken on an individual basis and our local protocol states that it must be agreed by a multidisciplinary team, Director of Pharmacy and a second opinion doctor appointed by the Care Quality Commission under the provisions of the MHA, 1983. The final decision is driven by a comprehensive assessment, which includes extensive information gathered from various sources

such as family discussions, capacity assessments and best interest meetings. The latter aims to reach a decision in the best interest of a patient who is assessed to lack capacity for the decision in question.

Once IM clozapine is prescribed, the choice of oral clozapine must be offered at every administration, and the injection is only administered as a last resort when oral clozapine is refused. The strength of IM clozapine is 25mg/ml and each ampoule contains 5ml (125mg). Current recommendations, based on clozapine pharmacokinetics, assume oral bioavailability of clozapine to be approximately 50% of the IM formulation (14). As the injection of larger volumes can be painful, it is suggested that the maximum volume that can be injected into each site is 4ml (100mg), which gives approximately equivalent bioavailability as 200mg oral clozapine. For doses greater than 100mg daily, the dose may be divided and administered into two sites based on individual preference. To minimise the number of injections, once daily dosing is preferred.

IM clozapine cohort

All individuals prescribed IM clozapine between 1st June 2016 and 7th March 2019 in an inpatient care setting within SLaM were included in the study. They all lacked capacity to treatment. Each patient prescribed IM clozapine was added to a register and linked to electronic medical notes and pharmacy dispensing records. Patients were followed-up with regard to concordance to oral clozapine treatment until clozapine discontinuation or two years after IM clozapine prescription or 31st July 2019, when the data collection ended, whichever occurred sooner. Time to all-cause post-discharge discontinuation was defined as the time from the date of discharge until the date oral clozapine was stopped, one year of treatment or end of data collection (31st July 2019), whichever occurred sooner. Treatment discontinuation was defined as a discontinuation for longer than seven consecutive days, even if clozapine was later re-initiated.

Patient demographics and clinical data such as the duration of illness, prior use of clozapine and the date of clozapine initiation, discharge and transition from IM to oral clozapine were collected from electronic medical records. Global clinical severity was rated retrospectively at IM clozapine prescription using the Clinical Global Impression Improvement scale (CGI-I) by manual analysis of patients notes in the electronic medical records by an experienced psychiatrist (CC). Further data included clozapine injection date(s) and dose(s), and use of restraints. Reasons for clozapine discontinuation where applicable were obtained from descriptive medical records. Patients who were discharged from SLaM were followed up through their registered pharmacies responsible for clozapine supply. A questionnaire was sent to respective pharmacists asking whether the patient under their care remained on clozapine treatment and, if not, the date and reason for discontinuation.

Comparison group: historical cohort

The comparison group included patients with a diagnosis of a treatment-resistant psychotic disorder (ICD-10: F20–F29) aged between 18 and 65 years old initiated on oral clozapine in a SLaM facility in routine clinical practice between 1st January 2007 and 31st December 2011. We selected patients who were initiated on clozapine while detained under the MHA (Section 2, Section 3 or Section 47/49) to represent compulsory treatment in the historical cohort. These data were collected as part of a previous study investigating reasons for clozapine discontinuation (15) from the Clinical Records Interactive Search (CRIS) system, an anonymized case register derived from SLaM electronic case records. Follow-up with regard to continuing clozapine was carried on until clozapine discontinuation or 2 years after clozapine initiation, whichever occurred sooner. Post-discharge follow-up was continued from the date of discharge until the date clozapine was stopped or one year of treatment, whichever occurred sooner. Global clinical severity was rated retrospectively at clozapine prescription using the CGI-I by manual analysis of the electronic medical records. No information on the use of restraints was available for the historical cohort.

Adverse events

All SLaM patient records were scrutinized for documented adverse events (including when they first occurred in relation to the initiation date). Adverse events were defined as any unfavourable and unintended sign, symptom or disease noted on the electronic records, which occurred during use of IM clozapine or within 3 days from administration, that are not recorded by the manufacturer's summary product characteristics (https://www.medicines.org.uk/emc/product/4411/smpc).

Statistical methods

Statistical analysis was carried out using Stata, version 15 (16). The percentage of patients who successfully initiated oral clozapine after IM prescription was calculated. Kaplan-Meier survival curves were used to estimate and graph the time to clozapine discontinuation from IM or oral clozapine prescription in both the IM cohort and the comparison group respectively. Patients were followed from the date of first IM clozapine prescription and were censored after 2 years follow up or 31st July 2019, whichever occurred sooner. All cause discontinuation of oral clozapine was calculated, and all patients who were prescribed IM clozapine were included, whether or not they received the drug intramuscularly. After checking proportional hazard assumptions, a Cox regression was employed to model the association between IM clozapine prescription and clozapine discontinuation. Propensity scores were used in order to address the issue of confounding-by-

indication and a fully adjusted Cox analysis was carried out with the propensity score included as a covariate. Propensity scores indicate the probability of being prescribed IM clozapine based on patient characteristics (age, gender, diagnosis, length of illness, CGI at clozapine prescription) and were calculated using logistic regression.

A separate survival analysis was set up to model post-discharge clozapine discontinuation rates, which were graphed using a Kaplan-Meier survival curve in both the IM and comparison group, with T0 at the date of discharge. Patients were censored after one-year follow up or 31st July 2019, whichever occurred sooner. The discontinuation rates in the two groups were analysed using a Cox regression model adjusted for propensity scores, which were included in the analysis as a covariate.

Post hoc analysis using Kaplan-Meier survival curves was conducted to evaluate differences in discontinuation rates after IM prescription between the subgroup of patients who were prescribed and administered IM clozapine and those who had it prescribed but not administered. Post-hoc Cox regression analysis was conducted to calculate the hazard of clozapine discontinuation in the two sub-groups.

Ethical standards

This clinical effectiveness study was approved by the Drugs and Therapeutics Committee (DTC) of the South London and Maudsley NHS Foundation Trust, the locally designated approval committee for all non-interventional prescribing outcome audits. The local SLaM protocol for the use of IM clozapine was approved by DTC.

Ethical approval for the use of CRIS as a research dataset was given by Oxfordshire Research Ethics Committee C (08/H0606/71). The service-user led CRIS oversight committee granted permission for the use of a previously identified anonymised cohort of patients commencing oral clozapine to provide the comparison group data. Informed consent was not required as CRIS is an anonymized case register.

RESULTS

Patient Characteristics: IM clozapine cohort

Data were available for 39 inpatients with a treatment-resistant psychotic disorder who had been prescribed IM clozapine. Of these, 19 (49%) were administered at least one injection (median 2,

range 1 – 56), while 20 (51%) preferred to receive oral clozapine when offered the enforced choice between oral and IM administration. Of the patients who received more than one injection, 7 (50%) were administered consecutively and 7 (50%) received IM intermittently with oral clozapine. 32 patients (82% of our sample) had previously taken clozapine. Cohort characteristics are presented in Table 1. Table 2 summarises characteristics of IM clozapine administrations in our sample.

Among the 19 patients who received IM clozapine, the median maximum daily IM dose was 75 mg (range 6.25 – 200mg), equivalent to 150mg of oral clozapine. Most patients (n=16, 84%) received the injection(s) during the titration period; either from the first dose (n=11, 58%) or after refusing later doses (n=5, 26%). Manual restraints by nursing staff were used in nine patients (47%) with a median of zero and a mean of two restraints per patient (0 restraints: 10 patients; 1 restraint: 5 patients; >1 restraint: 4 patients). No mechanical restraints were used. The most common adverse event associated with IM formulation was swelling at the injection site, which occurred in the three patients who had more than 29 injections (16%). Other side effects reported in the patients' notes were drowsiness in two patients (10%), urinary incontinence (one patient, 5%) and neutropenia (1 patient, 5%). No side effects associated with physical restraints were reported in the electronic notes, although psychological consequences were not explicitly investigated.

Patient Characteristics: Historical cohort

The comparison group included 162 patients who started oral clozapine while admitted to a SLaM hospital under the MHA. They all fulfilled the criteria for a treatment-resistant psychotic disorder, and their characteristics are summarized in Table 1.

Transition from IM to oral clozapine and discontinuation rates

In total, 36 patients (92%) eventually started oral clozapine after being prescribed the IM formulation. Among those who received at least one injection, 16 (84%) were later switched to oral. The remaining three either continued to refuse oral clozapine despite IM administrations or discontinued IM clozapine due to adverse effects (neutropenia, recurrent pneumonia). The median number of days of injection before transition to oral was 2 (range 1-47).

In the IM cohort, median follow-up was 694 (IQR 481 – 720) days from IM prescription date and 296 (IQR 0 – 365) days from discharge date. In the comparison group, mean follow up was 720 days from the date of clozapine initiation and 365 days from discharge. In the subgroup of patients who were prescribed and administered IM clozapine median follow up was 509 (IQR 302 – 720) days from prescription and 236 (IQR 0 – 365) days from discharge, while in the subgroup of patients who

were prescribed but not administered IM clozapine mean follow up was 683 (IQR 534 – 720) days from prescription and 287 (IQR 0 – 365) days from discharge.

Fig. 1A displays a Kaplan-Meier survival curve for the clozapine discontinuation rates after clozapine prescription in the cohort of patients who were prescribed IM clozapine and in the comparison group. Discontinuation rates at two-year follow up were lower in the cohort of patients who were initially prescribed IM clozapine than in the comparison group (24% and 50% respectively), with a reduced hazard of clozapine discontinuation (HR 0.39, 95% CI 0.19 – 0.80) although this became non-significant after the model was adjusted for propensity scores (HR 0.39, 95% CI 0.14 – 1.06). In a post-hoc analysis, higher discontinuation rates were found in those who received the injection compared to those who chose to receive oral clozapine after being offered the enforced choice between the two formulations (52% and 6% respectively; HR 10.34, 95% CI 1.26 - 84.70). The Kaplan-Meier survival curve is shown in Fig. 1B. Table 3 summarizes the results of the Cox regression analyses.

Data were available after discharge for 29 of the IM patients (74%; 5 of which had received at least 1 injection) as the remaining 10 (26%) were still in hospital at the end of the study. Twenty-two (76% of those discharged) patients were maintained on oral clozapine until the end of follow-up; in the comparison group 81/162 patients remained on clozapine one year after discharge. Among the seven patients who were clozapine-naïve at IM prescription, three (43%) were still on oral clozapine at the end of follow-up.

Patients included in the post-discharge survival analysis are shown in Fig. 2. Discontinuation rates at one year after discharge for the IM cohort and the comparison group were 21% and 44% respectively (Fig. 1C). Fig. 1D graphs the post-hoc survival analysis for the subgroup of patients who were administered and those who were not administered IM clozapine. Compared to oral, IM clozapine prescription was associated with a non-significantly reduced risk of clozapine discontinuation after discharge after adjusting for propensity scores (HR 0.37, 95% CI 0.11 - 1.24). Post-hoc Cox regression analysis showed an increased risk of clozapine discontinuation after discharge in the subgroup of patients who were administered IM clozapine compared to those prescribed but not administered IM clozapine, although this was not statistically significant (adjusted HR 5.35, 95% CI 0.62 - 45.87).

In the entire cohort of 39 patients, eight (20%) discontinued clozapine treatment during the follow-up period. Four (10%) were due to non-adherence or unknown reasons and four due to adverse effects (10%) unrelated to the IM formulation but rather to clozapine's established adverse effect profile (neutropenia, recurrent pneumonia).

On a practical level, the majority of patients who received IM clozapine were administered less than 10 injections (n=13; 68%), with a discontinuation rate of 39% after 2 years of treatment. However, amongst the 6 patients who received more than 10 injections, two (33%) switched to oral clozapine and remained on it at the end of follow-up, whilst four discontinued it. The maximum number of injections administered before successful transition to oral treatment was 47.

Among the nine patients who required manual restraints during IM clozapine administration, seven remained on clozapine at follow-up, whilst two discontinued, one of which never agreed to transition from IM to oral clozapine.

DISCUSSION

In this retrospective clinical effectiveness study of patients prescribed IM clozapine, 92% of patients were successfully initiated on oral clozapine after IM prescription after a median of two IM administrations. Of patients with sufficient follow-up data, 76% remained on clozapine at two years from initiation. Clozapine discontinuation rates at two-year follow up were similar to a comparison group of patients who were prescribed only oral clozapine under the MHA in routine clinical practice. Correspondingly, clozapine discontinuation rates of 21% were observed at one-year follow-up post-discharge. This is at the lower end of that shown in previous studies, which demonstrate clozapine discontinuation rates between 16 and 66% across various countries (17).

Clozapine has consistently been shown to provide superior therapeutic benefits in treatment-resistant psychotic disorders (1) and should therefore be offered to all patients that meet these criteria. NICE guidelines highlight the importance of involving patients in decisions about the choice of medication (18). Nonetheless, some people diagnosed with a psychotic disorder lack insight and capacity to make an informed decision about optimal treatment options, particularly during acute illness, and may therefore make a non-capacitous decision to decline medication. Moreover, patients may be non-adherent as a direct response to delusional beliefs. There is compelling evidence to suggest that patients' refusal of clozapine in treatment-resistant psychotic disorders may have a significant negative impact on their long-term outcomes, and in the best interest of selected cases, enforced treatment may be the most appropriate option.

Presently, few naturalistic studies have demonstrated the potential of IM clozapine in initiating treatment, with a total enrolment of approximately 100 patients (9,10,11,12,13). To our knowledge, this is the largest study in the UK to report the use of short-acting IM clozapine for treatment initiation

and maintenance in patients with a treatment-resistant psychotic disorder. Our study further adds to the evidence for IM clozapine as a viable tool to allow patients whose illness is compromising their capacity to consent to appropriate treatment for their resistant psychotic disorder to access and benefit from clozapine.

Post-discharge discontinuation rates were as good as, or better than, a comparison group prescribed only oral clozapine. This suggests that the prescription of IM clozapine may achieve long-term clinical improvement and adherence to oral medication, even in those patients who are initially reluctant to engage with clozapine treatment, and that this is maintained even in a less restrictive setting. Consistent with previous studies (9,11,13), our data found no evidence that IM clozapine differs markedly from oral clozapine tolerability and adverse effects, with the one reported adverse event related to its formulation being swelling at the injection site. However, the lack of additional side effects reported may be attributed to its short-term use, often during titration and therefore at low doses, and this study was not powered nor designed to assess safety.

In the observational cohort, over half of those who had been prescribed IM clozapine chose to accept oral clozapine after being offered the choice between the two formulations. This finding is in line with an observational study by Hoge *et al.,* (20), according to which drug refusal developed into voluntary acceptance of treatment by most patients. Although preliminary, our data on discontinuation rates among those who did not require IM administrations is in line with previous findings (9,11) that the mere prescription of IM clozapine can increase adherence to clozapine without the need of IM administration. Post hoc analysis also showed that those patients who accepted oral clozapine when offered the IM had lower discontinuation rates compared to patients who declined oral and were administered IM clozapine. Although this result should be interpreted with caution due to small numbers, this may be attributed to a more entrenched attitude towards medication in the latter subgroup. Nevertheless, future qualitative work is required to understand the decision-making process underpinning a patient's decision to accept oral treatment when there is a choice between IM and oral dispensation.

Enforcement of treatment in psychiatry remains an ethically and clinically contentious practice. Previous literature has raised questions about the risks and benefits of enforcing clozapine treatment (22). This debate is ongoing, and it is beyond the scope of this article. However, in an investigation on patients' perception towards their involuntary admission, O'Donoghue *et al.,* (23) found that prior to discharge 72% of patients reported admission to have been necessary and almost 80% felt that the received treatment had been beneficial. Furthermore, previous studies have demonstrated improvement in inpatients with schizophrenia, irrespective of whether they received treatment voluntarily or involuntarily (24). Of interest, patients treated involuntarily tended to show even greater

symptom improvement than voluntary patients (24). Consistent with our findings, a recent small-scale study in the UK demonstrated positive outcomes with compulsory clozapine treatment by nasogastric administration. Nevertheless, the IM route remains well-established in clinical practice and avoids the considerably more invasive and distressing nature of nasogastric administration and its greater resource requirements (8).

While our sample is too small to draw any firm conclusions, our findings may justify safely persisting with IM clozapine to achieve transition to oral, despite a prolonged refusal of oral treatment. Nevertheless, individual-based decisions are paramount to ensure the best interest of every patient. In our study, the use of manual restraints by nursing staff did not appear to influence clozapine discontinuation rates. Clozapine treatment has been shown to demonstrate a reduction in incidents of aggression and subsequent restraints, but whether this is comparable with IM administration remains unanswered. Furthermore, due to the lack of a formal evaluation, the psychological impact of restraint on both patients and nursing could not be investigated in our study.

Our experience also suggests IM clozapine can be used to achieve oral clozapine initiation and avoid treatment interruption when used both consecutively and intermittently with oral clozapine. Previous authors have shown clozapine to be a cost-effective therapy in TRS (21), it is likely that an economic evaluation will demonstrate that IM clozapine prescription is highly cost-effective, especially in light of the absence of alternative treatments for this population.

Despite the encouraging evidence generated from our study, it must be emphasized that those who declined treatment do not form a homogenous group and might have done so for a variety of reasons that warrant further examination before any actions are taken. Similarly, different factors could have played a role in favouring a transition from IM to oral clozapine, such as clinician-patient relationship or familiarity with nursing staff providing medication. In addition, relevant differences were observed between the two study groups. The patients offered IM clozapine had greater severity (CGI: mean 6.18, SD 0.45) and longer duration of illness (mean years 21.32, SD 11.18) than the comparison population (CGI: 5.35 ± 0.64; DOI: 9.42 ± 8.01). However, previous studies on patients with a schizophrenia-spectrum disorder have suggested that those who refuse treatment tend to be more symptomatic and with worse functioning than those who agree to treatment (25). Furthermore, only 18% of our patients were clozapine naïve at IM clozapine prescription, which might reflect the fact that IM clozapine is more likely to be recommended in patients with a previous good response to clozapine. Nevertheless, previous work has demonstrated clinical effectiveness in clozapine-naïve patients (11).

Limitations and future research

The most important limitation of our study is the small sample size; however, this is consistent with previous studies evaluating IM clozapine use (9,11,13). This limits the interpretability of our results, as evidenced by the fairly large confidence intervals around the results. The limited number of patients included in the study has also prevented us from conducting further post-hoc analysis which could be useful in order to identify specific sub-groups of patients who could benefit from IM clozapine administration. Secondly, as follow-up data collection ended in July 2019, 26% (n=10) of patients could not be followed up after discharge since they were still in hospital. In addition, not all patients who were discharged had sufficient follow-up, as they were in the community for less than one year at data collection. Furthermore, the naturalistic nature of our study meant that clozapine continuation post-discharge was confirmed by prescription refills of oral clozapine and adherence to haematological monitoring requirements opposed to the more objective method of measuring serum clozapine levels. Equally, the quality of data available for reasons for clozapine discontinuation were limited to the information provided in electronic clinical record systems by the patient's clinical team. Our study needs to be replicated prospectively in a larger sample size possibly with a longer follow-up period.

Another limitation lies in the comparator group. Patients who are prescribed IM clozapine are intrinsically different from those who accept oral clozapine, being less compliant and willing to accept any kind of treatment. Our comparator group differed from the cohort in age, and they had longer length of illness and higher CGI at clozapine initiation. We addressed this confounding-by-indication by calculating and adjusting for propensity scores in the Cox regression analyses, although some potential confounders may not have been measured and hence not included in the adjustment. Nonetheless, as the IM clozapine cohort included more severely unwell patients than the historical comparator, this would have, if anything, biased the results in favour of the latter. Another difference to highlight in the comparator group is the involvement of patients who were clozapine-naïve, whilst our IM clozapine cohort only had 18% of patients who had never taken clozapine before. It could be argued that the historical cohort covers a different timeframe compared to the IM clozapine cohort. Although this should be highlighted as a limitation, there hasn't been any major recent implementation of clozapine-focused services in SLaM,

Due to the retrospective nature of the study, we did not have standardised scales on side effects, nor could we collect data on patients' subjective experience of IM clozapine treatment, which would have enhanced the study findings. Further research is needed to explore patients' perspectives on IM treatment both at the time of administration and longer term. In particular, qualitative analysis would add to our understanding and reveal avenues for more focused quantitative work. Finally,

future work should focus on which sub-groups of patients are more likely to benefit from IM clozapine prescription to support more targeted approaches to interventions.

CONCLUSIONS

The main finding of our study is that most of patients prescribed IM clozapine were able to successfully initiate oral clozapine after IM prescription, with half of patients not requiring administration of the injection. Discontinuation rates after initial IM clozapine prescription were consistent with current literature and similar to the comparison group. Discontinuation rates post discharge did not differ from those who were only prescribed oral treatment with clozapine from initiation. Our data, though preliminary, suggest that prescribing IM clozapine is a viable short-term tool to allow patients to access oral clozapine, the most effective available treatment for treatment-resistant psychotic disorders. Pain and swelling at injection site were the only reported side effects specific to the IM formulation and occurred only in a minority of patients. Additional evidence, possibly derived from robust prospective studies, is needed to provide new and more definite insights about the transition from IM to oral formulations of clozapine.

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Conflict of interest:

The authors declare that they have no conflict of interest.

Authors contributions:

CC, EW, DT, AS and JM contributed to the conception and design of the study; CC, EO, SL and OD collected and analysed the data; FG, SS and JO took part in to the interpretation of the data; all authors contributed to the drafting and revision of the manuscript.

Data Availability Statement

Authors had free access to the study data. All data will be available upon request to the authors.

482 Table 1. Demographic and clinical characteristics

Characteristic	IM clozapine cohort			Comparison group
	Total sample (n=39) n (%)	**IM clozapine prescribed and administered (n=19) n (%)**	**IM clozapine prescribed, not administered (n=20) n (%)**	**Oral clozapine prescribed (n=162) n (%)**
Male gender	26 (56)	10 (53)	12 (60)	102 (63)
Ethnicity				
Caucasian	22 (56)	11 (58)	11 (55)	55 (34)
African or Caribbean	14 (36)	8 (42)	6 (30)	73 (45)
Others	3 (8)	0	3 (15)	33 (21)
Age at IM clozapine prescription (years ± SD)	46 ± 10.86	48 ± 9.25	44 ± 12.03	31 ± 11.54
Length of illness (years ± SD)	21.32 ± 11.18	23 ± 12.08	19.63 ± 10.31	9.42 ± 8.01
Diagnosis				
F20 Paranoid Schizophrenia	18 (46)	9 (47)	9 (45)	154 (95)
F32 Bipolar disorder / F25 Schizoaffective disorder*	21 (54)	10 (52)	11 (55)	8 (5)
CGI score at clozapine prescription (mean ± SD)	6.18 ± 0.45	6.26 ± 0.45	6.10 ± 0.45	5.32 ± 0.66
Hospital setting				
Acute ward	16 (41)	7 (37)	9 (45)	*na*
Psychiatric Intensive Care Unit	8 (20)	5 (26)	3 (15)	*na*
National psychosis Unit	14 (36)	7 (37)	7 (35)	*na*
Forensic ward	1 (3)	0 (0)	1 (5)	*na*
Concomitant medication				
Antipsychotic polypharmacy	9 (23)	5 (26)	4 (20)	*na*
Antidepressants	4 (10)	2 (11)	2 (10)	*na*
Mood stabiliser	9 (23)	4 (22)	5 (25)	*na*
Antihypertensive	13 (31)	6 (32)	7 (35)	*na*
Anticholinergic	7 (18)	2 (11)	5 (25)	*na*
Other	23 (60)	12 (63)	11 (55)	*na*

Length of admission (days ± SD)**	387.07±296.42	415.27 ± 281.16	369.83 ± 312.07	444.95 ± 712.21
Length of admission after clozapine prescription (days ± SD)**	280.07±225.41	232.18 ± 185.75	309.33 ± 246.98	239.16 ± 297.39
No previous trial with clozapine	7 (18)	5 (26)	2 (10)	162 (100)

** Schizoaffective disorder and Bipolar disorder combined to avoid presenting identifiable data*

*** Only included patients who were discharged during the study period*

Table 2. Characteristics of IM clozapine administrations

Characteristic	**Median (min-max)**
Number of days of injection	2 (1 - 56)
Number of injections	- 1 injection: 6 patients - 2 injections: 4 patients - 3 – 10 injections: 3 patients - >10 injections: 6 patients
Maximum IM daily dose (mg)	75 (6.25 - 200)
Physical restraints required (n, %)	9 (47)
Number of restraints	- 0 restraints: 10 patients - 1 restraint: 5 patients - >1 restraint: 4 patients
Titration (n, %)	16 (84)
IM administered consecutively (n,%)	7 (50)
Patients who did not transition to oral clozapine (n,%)	3 (16)
Patients still in hospital at data collection (n,%)	8 (42)

Table 3. Results from the Cox regression analyses

Cox regression analysis	**Hazard ratio (95%CI)**	**Hazard Ratio adjusted for propensity scores (95%CI)**
IM clozapine cohort vs oral clozapine comparison group		
Clozapine discontinuation at 2-year follow-up	0.39 (0.19 – 0.80)	0.39 (0.14 – 1.06)
Clozapine discontinuation at 1-year post-discharge follow-up	0.54 (0.23 - 1.28)	0.37 (0.11 - 1.24)
Post-hoc analysis: IM clozapine administered vs non-administered		
Post-hoc analysis: Clozapine discontinuation at 2-year follow-up	10.34 (CI 1.26 - 84.70)	*Not applicable*
Post-hoc analysis: Clozapine discontinuation at 1-year post- discharge follow-up	5.35 (0.62 - 45.86)	*Not applicable*

Fig. 1. Kaplan-Meier survival curves - A. Clozapine discontinuation rates after IM (IM cohort) or oral (comparison group) clozapine prescription. B. Post-hoc analysis of clozapine discontinuation rates after IM or oral (comparison group) clozapine prescription after subdividing patients according to whether they were administered and not administered IM clozapine. C. Clozapine discontinuation rates after discharge in the cohort and the comparison group. D. Clozapine discontinuation rates after discharge subdivided by whether IM clozapine was administered, versus the comparison group of patients prescribed oral clozapine.

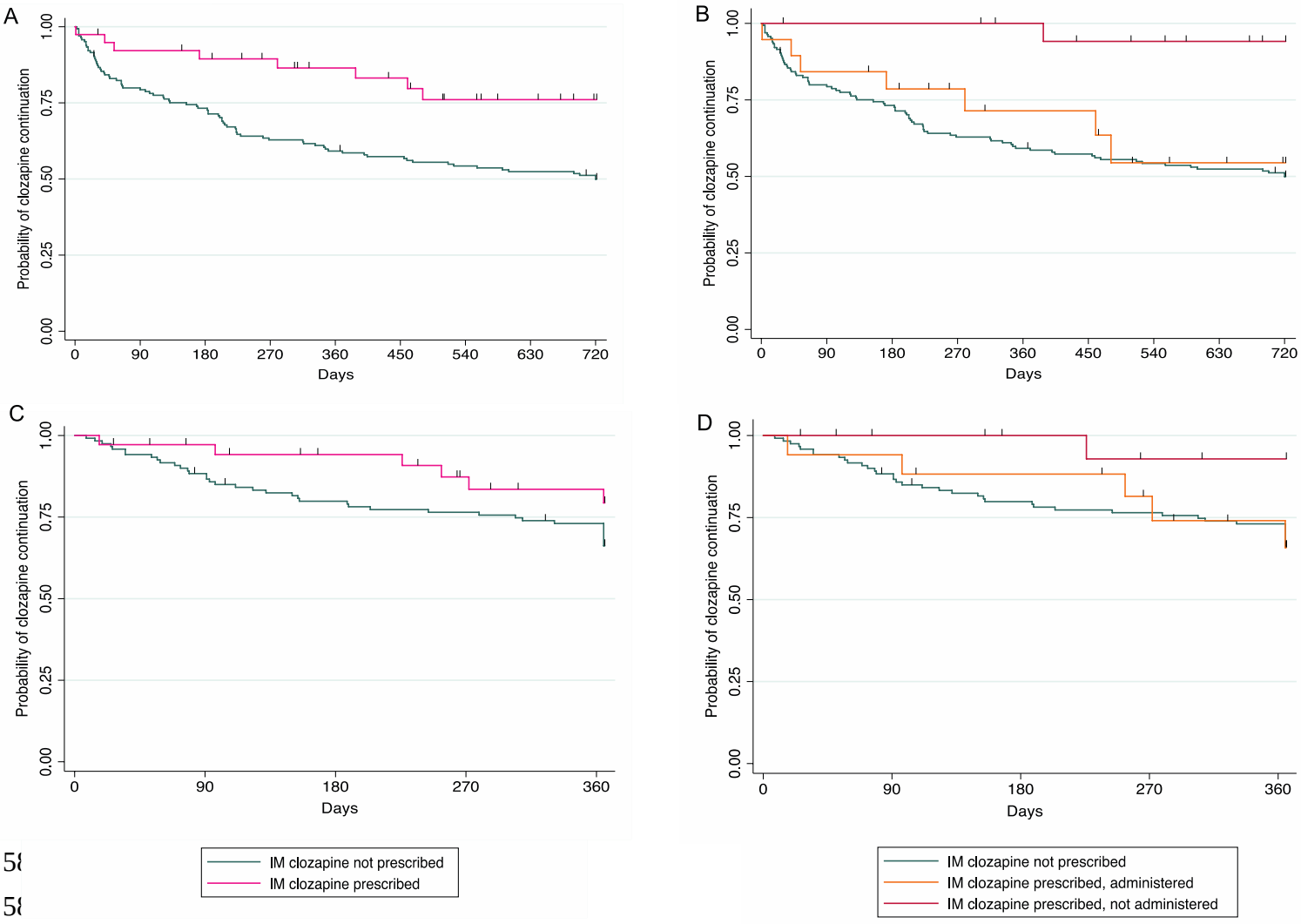

Fig. 2. Study Profile for post-discharge survival analysis