Influence of time to clozapine prescription on the clinical outcome

ABSTRACT

Background: We investigate whether an earlier use of clozapine is related to a better response in different clinical domains, namely positive, negative, functioning and well-being.

Material and methods: We used data from a carefully characterised cohort of 254 clozapine-treated patients, which were evaluated using the positive subscale of the *positive and negative syndrome scale (PANSS), the Brief Negative Symptom Scale (BNSS), Global Assessment of Functioning Scale (GAF)"* and the short version *Warwick-Edinburgh Mental Well-being Scale (SWEMWBS)*. We then used logistic regression models (for positive and negative symptoms remission) and linear regression (for functioning and wellbeing) to evaluate the influence of time to clozapine initiation (TCI; above or below three years), age at the first episode of psychosis (AFE), duration of clozapine treatment (DCT) and gender.

Results: Proportion of negative symptoms remission and higher functioning scores were associated with earlier treatment with clozapine in the first three years after the first episode of psychosis (exp (B)=0.38; p=.02; β=-0.12, p=.046, respectively). No effect of time to clozapine initiation was found on positive symptoms remission rates or well-being scores.

Conclusions: Starting clozapine treatment within the first 3 years of illness decreases the severity of negative symptoms and improves functioning in clozapine-treated patients. Clozapine effect on positive symptoms remission rates was not influenced by the time to clozapine initiation.

Keywords: Treatment-resistant schizophrenia, delay, duration of psychosis, remission, negative symptoms.

1. Introduction

Clozapine is the only effective medication for treatment-resistant schizophrenia (TRS) [1], the severe end of the disorder affecting third cases of all cases. Clozapine is indicated after a lack of response to two antipsychotics, but the prescription is often delayed.

A study showed that clozapine has been prescribed an average of 47.7 months[2]. About half of the patients respond to clozapine, but how the delay impacts the response is unclear. To date, two studies have shown that an earlier prescription of clozapine (within three years of TRS criteria) was associated with a better outcome[3,4], defined by the improvement in the *Brief Psychiatric Rating Scale* (BPRS).

It is relevant to replicate this finding. Setting a threshold of clozapine efficacy might have a double-sword impact. On the one hand, it might prompt clozapine prescription in the early intervention in psychosis services. Still, it might also lead to therapeutic neglect for those with a longer duration of illness.

A key element is the poor definition of response. The recent TRIPP consensus suggests that patients may have persistent positive, negative, or cognitive symptoms. Clozapine differs from other antipsychotics in terms of better results for psychosis but has also been suggested a superior efficacy for negative, cognitive and affective symptoms [5 6].

In this study, we examined the effect of time to initial clozapine prescription from first episode psychosis over the positive, and negative symptoms as well as general functioning and self-perceived well-being. In a cohort of carefully characterised 254 clozapine clozapine-treated patients in Cambridgeshire, United Kingdom (UK), we used logistic and multiple regression to define response(s) and the influence of clozapine and a range of other clinical and sociodemographic variables.

2. Material and methods

2.1 Design

A retrospective naturalistic study using electronic records from the clozapine clinic from Cambridgeshire and Peterborough NHS Foundation Trust (CPFT). This is the only mental health (MH) care provider for an area of about 800,000 population (Office National Statistics, 2012) covering mostly rural or small cities (Cambridge, Peterborough and Huntingdon).

2.2 Electronic records

The Clinical and Research Database (CRD) for Persistent Schizophrenia is an ethically approved electronic database (13/EE/0121 and 18/EE/0239) with anonymised clinical formation, from January 12 to December 12), with a range of sociodemographic and clinical data, including psychometrics scales described below.

2.3 Variables

For this study, we used database variables on gender, date of birth (month/year), date first contact with mental health services (as proxy for date of first episode of psychosis or illness onset) and date of first clozapine prescription, and date of psychometric assessment. We then calculated variables of interest:

- Age at first episode (AFE, in years): Year of birth – year of first contact with MH services.
- Time to clozapine initiation (TCI, in year): Year of clozapine initiation - year of first contact with MH services.

- Duration of clozapine treatment (DCT, in years): date last appointment - Year of clozapine initiation.

The key variable to study was TCI, which was subsequently categorised as early clozapine (=0, up to 3 years from first episode psychosis) and late (=1, more than 3 years). AFE and DTC has been treated as continuous variables.

Lack of response was defined using the last recorded assessment on psychometric scales. For positive symptoms/psychosis, any item scoring three or above in the positive subscale (P1 to P7) of the *Positive and Negative Syndrome Scale (PANSS)* was considered as no-response (=0). Additionally, anyone on clozapine augmentation with a second antipsychotic was considered as non-responsive (=0). For negative symptom, any item scoring 2 or above in the *Brief Negative Symptom Scale (BNSS)* was considered as non-response (=0). *The General Assessment of Functioning (GAF)* scale and the *Short Version Warwick-Edinburgh Mental Well-being Scale (SWEMWBS)* were used for analysis, using the score as a continuous variable.

2.4 Statistical analysis

We use two different logistic regressions for assessing response, using the response criteria defined above for positive and negative symptoms. Lack of response was coded as 0, and response as 1. For The GAF and the SWEMWBS scale two linear regressions have been done.

Dependent variables included gender, age of first episode of psychosis (AFE), time to clozapine initiation (TCI) as the two categories (early and late) and duration of clozapine treatment (DCT). Reference categories were male and early TCI. All other variables were continuous.

We used SPSS v28.0 for conducting the analyses and significance was set as p=0.05.

3. Results

There were a total of 254 clozapine-treated in the sample, 197 (77.6%) of them were men and 57 women (22.4%). The overall mean age of first episode was 22.41 years (Standard deviation (SD) =7.2 and time to clozapine initiation was 9.81 years (SD=8.3). Regarding TCI, 44 (17.3%) were early treated and 210 (82.7%) late. The average duration of clozapine treatment was 17.16 years, with 29 (11.4%) people prescribed clozapine for over 20 years.

Among the four models (**Table**), an early use of clozapine was associated to greater proportion of negative symptoms compared to late. In addition, it was related that early use of clozapine improved global functioning measured by the GAF scale. Time to clozapine initiation did not predict psychosis response or wellbeing. Other variables, such as age of psychosis onset, gender and time on clozapine treatment did not influence response.

4. Discussion

We found that earlier clozapine initiation, within three years of first episode psychosis, predicted a greater proportion of negative symptoms remission and level of functioning. We also found that time of clozapine initiation after first episode of psychosis did not influence proportion of psychosis remission or wellbeing. This suggests that efficacy of clozapine in psychosis control does not weaken over time.

Our study has some strengths and limitations. It is the largest sample analysed to date and we used specific psychopathological, functioning and wellbeing scales, whereas the previous study only used a general scale such as BPRS. Regarding the limitations, patients were not

psychometrically evaluated before clozapine. However, it is reasonable to assume all cases experienced significant positive symptoms at the time of clozapine initial prescription. We also used time from first contact with mental health services (as proxy for first episode of psychosis) to calculate the time to clozapine initiation, rather than from the moment resistance criteria were met. Our strategy mimics current thinking of resistance being present at the time of the first episode. Other limitation is inherent to the study, such as being a single site and relatively small sample to draw definitive conclusions.

To our knowledge, only two studies has focused on the role of time to clozapine and clinical outcome. Üçok et al did a retrospective study of 162 patients in clozapine, they found that the delay in starting clozapine was an independent contributor to the response to clozapine treatment, albeit the remission criteria were not clearly specified [3]. Yoshimura et al found significant greater decrease in total BPRS in these starting within three years of meeting resistance criteria[4]. We used specific psychopathology scales for positive and negative symptoms, and different criteria (time from first contact with mental health instead of time to meet the resistance criteria), but all three studies suggest a better outcome the sooner the clozapine is initiated, by rates of remission (Üçok), improving of a general scale (Yoshimura) or in global functioning. Our study suggest that the improvement might be due to a better effect on negative symptoms and resembles Varghese et al study that found duration of treatment with other antipsychotics before clozapine was associated with a higher incidence of negative symptoms, measured by the PANSS scale[7].

We could not find a difference in effect on positive symptoms. Noteworthy, our sample included 40% of responders to clozapine, like what is widely reported in clozapine. The interpretation is that clozapine effect on positive symptoms does not decrease after three years of the first diagnosis. Our study is also in line with meta-analytic evidence indicating that younger age was not a predictor for better response[8]. A delay in the time from TRS to the start of clozapine may reflect poorer functioning, greater severity of symptoms, and poorer adherence to treatment [9 10]. We did not find gender differences in remission rates for positive or negative symptoms but found a greater wellbeing in males. This finding needs further replication.

5. Conclusions

Our study might have a practical consequence in the United Kingdom, which is to stimulate early intervention services to promote clozapine initiation. Negative symptoms in schizophrenia are currently one of the main barriers to recovery and there is no effective treatment. Most teams are funded for three years of treatment and would be sensible to use this time to carefully evaluate the criteria for resistance and the presence of significant negative symptoms.

To conclude, our study suggests that clozapine remains effective for controlling psychotic symptoms throughout the illness, but the impact on negative symptoms and functioning is greater if prescribed within three years of illness onset. Our findings might encourage early intervention services to offer this therapeutic option more often.

6. Appendices

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