The aim of the study was to assess the clinical response to clozapine. The patients included in this study were those participating in a prospectively designed clozapine monitoring program (n = 202 subjects) who completed at least 52 weeks of treatment and had complete data records at Psychiatric Hospital, University Hospital Centre “Mother Theresa” in Tirana, Albania over the period 2013 -2014. In the study participated 102 subjects with a mean age 44.2 (±10.7) years with a range 22 -74 years old. Thirty five (34.3%) were women and 67 (65.7%) men meeting both DSM-IV criteria for schizophrenia and Kane’s criteria for drug-resistance. 27 (26.8%) patients were classified as responders, 45 (44%) being refractory (Clozapine responders) and 30 (29.2%) super-refractory. The super-refractory group had the highest scores for totals of BPRS (p<0.01) in all visits. Treatment resistant schizophrenia remains a major personal tragedy and a public health problem.

Keywords: schizophrenia, clozapine, super refractory, response,

1. Introduction

Clozapine is an early atypical antipsychotic, first synthesized in 1958. Although it was formulated as part of an effort to develop new antidepressants, preclinical work established its similarities to chlorpromazine, and it was ultimately evaluated for its potential antipsychotic properties(1). Even then, clozapine established itself as unique, as its low liability for extrapyramidal symptoms challenged widely held notion at the time that clinical response was integrally linked to induction of extrapyramidal symptoms (2). Shortly after its release in the early 1970s, clozapine was linked to a risk, albeit a low one, of agranulocytosis (1). As a result, its use was markedly curtailed and a requirement for mandatory blood monitoring was established in most countries. A seminal study in the late 1980s demonstrating clozapine’s clinical superiority in refractory schizophrenia (3) established its position in North America as a treatment of “last resort,” permitted only after the failure of other antipsychotics and only in conjunction with routine hematological monitoring. Despite the introduction of a number of newer atypical antipsychotics over the past two decades, clozapineremains the treatment of choice in refractory schizophrenia, a position endorsed by various guidelines (4–7). As a rule, clozapine is recommended only after incomplete response to two adequate antipsychotic trials, which is reflected in some product monographs. For example, in Canada clozapine can be prescribed only as a third-line treatment (8), although in the United States it is permitted (although not recommended) as a second-line treatment (9). The criteria that define treatment resistance have been modified to reflect changes in recommended antipsychotic dosing guidelines that now advocate somewhat lower dosages (10). Also, treatment criteria have been proposed for “ultra-resistant schizophrenia,” applicable to patients who demonstrate a suboptimal response to clozapine (11). It is noteworthy that there remains hesitancy in prescribing clozapine for individuals with refractory schizophrenia. For example, a review of the Veterans Affairs databases for 1999–2006 indicated that while the atypical antipsychotics were rapidly supplanting their conventional counterparts, clozapine use remained flat at 2%–3% (12). Other researchers have reported an average delay of 5 years in moving to clozapine in the face of treatment resistance (13). Schizophrenia is characterized by a differential response to antipsychotic treatment based on stage of illness, with evidence that shorter duration of untreated psychosis is associated with greater antipsychotic response. The aim of the study was to assess the clinical response to clozapine.

Abstract: Schizophrenia is characterized by a differential response to antipsychotic treatment based on stage of illness, with evidence that shorter duration of untreated psychosis is associated with greater antipsychotic response. The aim of the study was to assess the clinical response to clozapine. The patients included in this study were those participating in a prospectively designed clozapine monitoring program (n = 202 subjects) who completed at least 52 weeks of treatment and had complete data records at Psychiatric Hospital, University Hospital Centre “Mother Theresa” in Tirana, Albania over the period 2013 -2014. In the study participated 102 subjects with a mean age 44.2 (±10.7) years with a range 22 -74 years old. Thirty five (34.3%) were women and 67 (65.7%) men meeting both DSM-IV criteria for schizophrenia and Kane’s criteria for drug-resistance. 27 (26.8%) patients were classified as responders, 45 (44%) being refractory (Clozapine responders) and 30 (29.2%) super-refractory. The super-refractory group had the highest scores for totals of BPRS (p<0.01) in all visits. Treatment resistant schizophrenia remains a major personal tragedy and a public health problem.

Keywords: schizophrenia, clozapine, super refractory, response,

2. Material and Methods

The patients included in this study were those participating in a prospectively designed clozapine monitoring program (n = 202 subjects) who completed at least 52 weeks of treatment and had complete data records at Psychiatric Hospital, University Hospital Centre “Mother Theresa” in Tirana, Albania over the period 2013 -2014. In an effort to have consistent baseline conditions, before entering into the study, all the patients’ psychoactive drugs except for typical antipsychotics were tapered and discontinued. After patients had been taken on this drug regimen for at least 2 weeks, baseline assessment was completed. Then, clozapine treatment was started with dose increments of 25–50 mg every 2 days to bring patients to the dose of 400 mg/day by the end of the week 2. Patients were taken at this dose regimen up to the end of week 4, when a second clinical assessment was performed. Those subjects meeting the response criteria (see below) were maintained on the 400 mg/day dose regimen up to the end of the study, whereas the remaining patients received further dose increments of 50 mg every 2 days to reach the maximum established dose of 600 mg/day by the end of week 6, and then were kept on this dose regimen up to week 52. Typical antipsychotics were rapidly tapered and discontinued during the first week of clozapine treatment. Clozapine was administered in 2–3 divided (and approximately equal) doses, with the last dose of the day given between 7:00 P.M. and 8:00 P.M. Patients were hospitalized up to the achievement of their maximum clozapine daily dose; then,
they were discharged and clozapine was administered at home by staff nurses, who carefully checked patients' compliance up to the end of the study. Psychopathological assessment was performed by means of the Expanded Brief Psychiatric Rating Scale (BPRS: 24 items and a scoring from 1 to 7) both before starting clozapine (baseline) and every 2 weeks up to week 52. Patients were a priori defined responders as they attained a 20% decrease in the BPRS total score plus a post-treatment BPRS score of 47 or less. These criteria had to be met at two consecutive rating points; responders were classified as such when they first met a priori criteria. The aim of the study was to assess the clinical response to clozapine. Results were expressed as mean ± SD and statistically assessed by analysis of variance (ANOVA) with or without repeated measures, post-hoc Tukey's test and χ² (Chi-square) test with Yate's correction, where appropriate.

3. Results and Discussion

In the study participated 102 subjects with a mean age 44.2 (±10.7) years with a range 22-74 years old. Thirty five (34.3%) were women and 67 (65.7%) men meeting both DSM-IV criteria for schizophrenia and Kane's criteria for drug-resistance except one patient who did not met the Kane's criterion of duration of illness of at least 5 years. The mean duration of their illness was 23.4 years. Of the 102 patients, 27 (26.8%) were classified as responders, 45 (44%) being refractory (Clozapine responders) and 30 (29.2%) super-refractory (fig. 1). The super-refractory group had the highest scores for totals of BPRS (p<0.01) in all visits (table 1). To date, only a few studies have addressed the characteristics of patients with super-refractory schizophrenia. An incomplete response to clozapine is the persistence of psychotic symptoms despite a trial of clozapine with adequate doses (i.e. 300-900 mg/day) during a minimum of 8 weeks up to 6 months. Thus, the improvement of psychotic symptoms considered the main treatment target and, as an apparent consequence, it has been proposed the addiction of high potency antipsychotics to clozapine for the treatment of these symptoms. It is estimated that approximately 30% of patients treated with clozapine do not respond adequately, remaining with persisten psychotic symptomatology, despite having received adequate treatment for sufficient periods. Such patients are called partial responders to clozapine", "-clozapine resistant" or even "super-refractory", and represent a challenge for the treatment of RS, as well as a great economic burden (17). The treatment of these patients is problematic and pharmacological and non-pharmacological augmentation strategies remain the only options for this population, despite the lack of adequate evidence for efficacy (18). Many reviews have been published describing in detail such strategies that will be summarized. Various antipsychotics were used supposedly to augment the antipsychotic properties of clozapine: amisulpride, aripiprazole, haloperidol, loxapine, olanzapine, pimozide, and ziprasidone. The benefits of these augmentation strategies remain inconclusive since they were tested in case series or case reports, which have a low strength of evidence, as compared with controlled trials (19). More robust evidence is derived from four placebo controlled trials, one with sulpiride and three with risperidone and, due to their importance, they are summarized below (20). A study showed a significant improvement on positive and negative symptoms in the group that received sulpiride added to clozapine when compared with placebo group, and it was proposed that this effect could be explained by the selective enhancement of D2 blockage by sulpiride (21). However, it is well known that risperidone has a strong affinity for D2 receptors and the hypothesis that blocking these receptors would improve persistent positive symptoms in patients resistant to clozapine was only supported by some studies which found no differences between risperidone placebo groups (22). Therefore, the hypothesis that adding a more potent antipsychotic to enhance or optimize D2 affinity, and thus improving psychotic symptoms in poor clozapine responders, was not supported by the previous studies, and it is also interesting to point out that in the study the placebo group showed a greater reduction in the PANSS positive scores than the risperidone group (23). Finally, when clozapine augmentation with antipsychotics fails, it has been proposed to switch to another antipsychotic. This strategy is considered to have a weak level of evidence and olanzapine was the antipsychotic most frequently tested in some open trials.

4. Conclusion

TRS remains a major personal tragedy and a public health problem. However, because so little is known about TRS and because the results of treatment are so variable, it is essential to weigh carefully the risk-benefit ratio. Although atypical novel antipsychotics are better tolerated than older drugs and may be more effective in some but not most TRS patients, no proven treatment exists for TRS. It is essential that, instead of increasing the dose and relentlessly adding and changing medications, or embarking upon unproven interventions, psychiatrists acknowledge to themselves and explain to frustrated patients and family members, the limits of pharmacological treatment. Otherwise, we run the risk of making abad situation worse by adding the suffering of adverse effects to that of the illness.

References


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**Table 1:** Mean BPRS score at baseline and at 1 year

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 52</th>
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<tbody>
<tr>
<td>BPRS Total Score</td>
<td>70.1 ± 13.1</td>
<td>54.2 ± 10.2</td>
<td>50.4 ± 9.9</td>
<td>42.3 ± 9.2</td>
<td>36.0 ± 6.9</td>
<td>35.1 ± 8.7</td>
</tr>
<tr>
<td>All responders</td>
<td>63.0 ± 4.7</td>
<td>40.5 ± 5.5</td>
<td>40.5 ± 8.3</td>
<td>35.5 ± 7.8</td>
<td>33.0 ± 7.9</td>
<td>33.0 ± 6.6</td>
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<tr>
<td>New responders</td>
<td>69.2 ± 10.8</td>
<td>52.1 ± 4.6</td>
<td>43.2 ± 2.3</td>
<td>38.6 ± 6.7</td>
<td>35.1 ± 9.1</td>
<td>31.0 ± 6.9</td>
</tr>
<tr>
<td>New responders</td>
<td>66.6 ± 5.1</td>
<td>58.1 ± 7.3</td>
<td>54.6 ± 5.1</td>
<td>39.2 ± 7.2</td>
<td>36.0 ± 7.2</td>
<td>34.4 ± 10.3</td>
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<tr>
<td>New responders</td>
<td>79.6 ± 19.7</td>
<td>62.1 ± 12.7</td>
<td>61.4 ± 13.4</td>
<td>54.4 ± 10.1</td>
<td>39.4 ± 7.6</td>
<td>41.3 ± 7.2</td>
</tr>
<tr>
<td>Super refractory</td>
<td>77.4 ± 18.5</td>
<td>68.6 ± 10.8</td>
<td>67.6 ± 12.5</td>
<td>61.6 ± 12.3</td>
<td>54.6 ± 4.8</td>
<td>60.0 ± 11.3</td>
</tr>
</tbody>
</table>

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**Figure 1:** The response to treatment