Clozapine In Treatment of Schizophrenia

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Abstract— Clozapine is antipsychotic mediation which is mostly used in patients with treatment resistant schizophrenia and against the negative symptoms. In it the clinical response of 84 schizophrenic patients were examined, previous antipsychotic medication had been withdrawn, and patient were treated with clozapine according to standardization titration, we also observe the adverse effects, extrapyramidal symptoms, baseline pathology and literature of reviews. After all, these variables may have important for the use if clozapine and our understanding of the pathophysiology if treatment resistant – schizophrenia.

Objective: This study addressed the unique clinical properties attributed to the antipsychotic clozapine including its efficacy in patient with the treatment refractory psychosis and against negative symptoms.

Method: The clinical response of 84 schizophrenic patients is (66 related with treatment refractory illness and remaining 18 who were intolerant of antipsychotic treatment) were examined. After all previous antipsychotic medication had been withdrawn, and the patient were treated with clozapine according to a standardization titration and dosage schedule. Results: fifty percent patients with the treatment of refractory illness and seventy six percent of the treatment intolerant patients responded to clozapine in up to 52 weeks. The optimum period required for a trial of clozapine appeared to be 12-24 weeks. Clozapine exhibited the negative symptoms, but these were not clearly independent of its effect on positive symptoms and extrapyramidal side effects.

Index Terms— Antipsychotic, Schizophrenia, Extrapyramidal symptoms, adverse effect and Baseline pathology.

I. INTRODUCTION

Clozapine is the most significant development in the antipsychotic drug pharmacology since the advent of the chlorpromazine. In the preclinical study of the rodents, clozapine exhibited characteristics which is associated with the antipsychotic efficacy in the standard screening paradigms (1-3).At the same time, clozapine is differed significantly from standard antipsychotic drugs in that it neither caused catalepsy nor, chronic administration, induced the dopamine - agonist-stimulated behavioral hyperactivity(4-6).Clinical studies borne out the clozapine's having a typical properties. Earlier reports indicated that the clozapine had antipsychotic efficacy and few if any extrapyramidal side effects in typical chronic schizophrenia patients with the acute exacerbation and multiple episodes(6-16). In the multicenter collaborative study that was pivotal to the drug's development in the United States. clozapine was shown to be the superior to classic neuroleptics in schizophrenic patients with treatment of refractory symptoms(17). Primary among these is the generally accepted finding that clozapine is superior to classic antipsychotic for the patient with treatment of refractory schizophrenia. This superiority is

predominantly based on the clozapine's ability based to decrease positive psychotic symptoms.

Second, is that the clozapine has been said to have a therapeutic efficacy against the negative symptoms. Third, is that the clozapine has been reported to improve the patient's neurocognitive deficits and the functional capacities independent of its effects on formal schizophrenic psychopathology (18, 19-22). Fourth, it has been suggested that the clozapine may have a more variable and longer time course of therapeutic effects than classic antipsychotic drugs (23).Clozapine is also said to be a better tolerated than the classic antipsychotic drugs in terms of the extrapyramidal side effects. It is thought to produce the very little and dystonia and the less liability to tardive dyskinesia than classic antipsychotic drugs(24).These clinical properties that are attributed to clozapine have clearly distinguished it as atypical and unique among the antipsychotic drugs. However, evidence supporting these clinical properties is variable, only clozapine superior efficacy in patient with treatment refractory psychosis and the lower incidence of the extrapyramidal side effects have been incontrovertibly proven. To examine these question further we evaluate the clinical response of 84 patients treated with clozapine in a standardized open treatment protocol.

II. METHOD

Patients were referred for clozapine treatment because of the treatment resistant psychosis, intolerance of standards pharmacotherapy (25). i.e., persistent psychotic symptoms for at least 2 years despite adequate separate the trials with three antipsychotic drugs from the two biochemical classes at dose greater than 1000 chlorpromazine equivalents fir a six weeks. Intolerance means the presence of moderate or the occurrence of extreme sensitivity to the extrapyramidal side effects of standard antipsychotic drug treatment such that a drug dose which might be expected to have the therapeutic effects can not be tolerated. The study patients also had to meet the following criteria: 1) age between 18 and 40 years, 2) a primary psychiatric diagnosis of schizophrenia disorder uncomplicated by the current substance abuse, and 3) no current or past history of the serious medical illness, particularly drug-induced blood dyscrasia. Eighty four patients were studied between 1985 and 1990. Patients were admitted to the inpatient service, and all medications were withdrawn for 14-28 days, depending on the patient's tolerance of the drug free period. The study group was the 67% male; it was 86% white, 10% black, and 4% Hispanic. The means age was 28.2 years .seventy nine patients means (94%) had diagnoses of schizophrenia, five patients (6%) had schizoaffective disorder. The group had been ill for a means of 8.8 years. Sixty six patients had treatment - refractory illness, and 18 patients were intolerant of treatment (where the sixteen had tardive dyskinesia and two had severe extrapyramidal side effects). Before the initiation of clozapine treatment, patients were given the baseline evaluations that the Brief psychiatric Rating Scale (BPRS) (26).

Following are the baseline evaluation, clozapine 25 mg/day p. o, was administered. According to a standard schedule, the dose was gradually titrated, and as tolerated, to a maximum of 500 mg/ day by treatment day 14 and then held steady for 1 week. Subsequently, the daily dose of clozapine was adjusted as clinically indicated up to maximum of 900 mg. Dose adjustment aimed to achieving optimal response to treatment for the patients in terms of alleviation of psychopathology with a tolerable level of the side effects. The mean dose during acute treatment phase was 411mg/day. Patients were evaluated for extrapyramidal side effects, psychopathology, and other side effects at weeks 3 and 6 during the time of acute treatment phase with the MINIDOTES, that is the shorter version of the dosage record and Treatment Emergent Symptom Scale that includes a 4- point symptom severity rating. They were subsequently assessed with this instrument at weeksb12, 26, 39 and 52 during the first year and at 13 – week intervals thereafter, patients could be discharged after week 6 of treatment and followed as a outpatients, depending on their clinical status. Continue treatment of clozapine determined by the patient's therapeutic response and tolerance of the drug, which is determined by the clinical judgement of the research team. During the follow up period, the dose was adjusted on clinical basis. The average dose during maintenance treatment was 458 mg/ day. Response to clozapine was analyzed statistically by various methods, repeated measure analysis of variance evaluated change from baseline to week 6, to 1 year and to endpoint. To measure time to

improvement, we used the survival analysis. Survival curves were estimated by the product limit formula. To quantify the rate of over a time, then we calculate the average acceleration between the BORS score and the weak of treatment for each subject individually, In addition, conditional probalities were used to summarize data regarding whether the patient would respond by week 52 if she or he had not responded to the date. Standard chi-square and paired and independent univariate t tests were also performed. Unless noted, all reported p values reflect two-tailed tests (27).

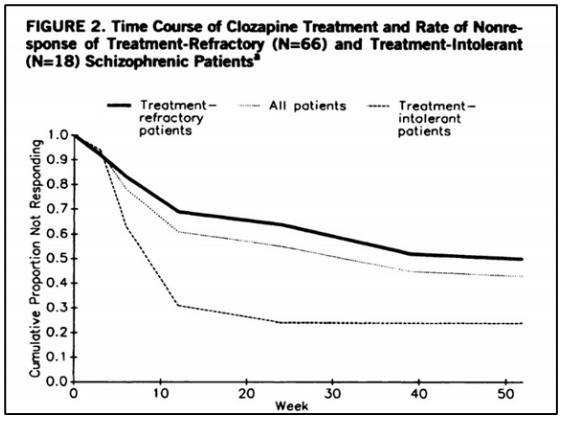

FIGURE 2. Time Course of Clozapine Treatment and Rate of Nonresponse of Treatment-Refractory (N=66) and Treatment-Intolerant (N=18) Schizophrenic Patients[a]

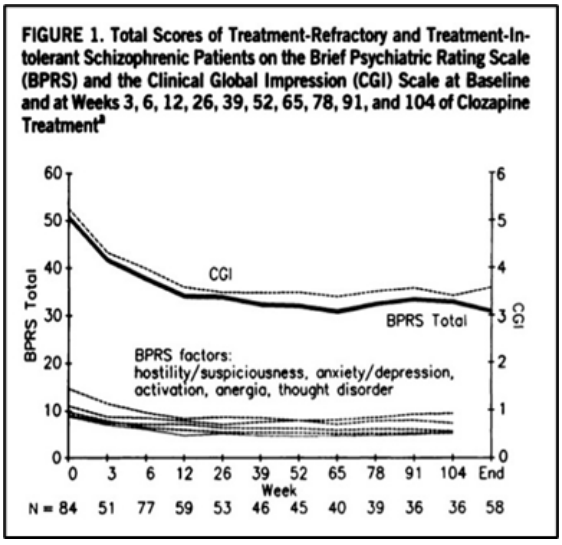

FIGURE 1. Total Scores of Treatment-Refractory and Treatment-Intolerant Schizophrenic Patients on the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression (CGI) Scale at Baseline and at Weeks 3, 6, 12, 26, 39, 52, 65, 78, 91, and 104 of Clozapine Treatment[a]

III. EFFECTS OF CLOZAPINE

"Significant changes from baseline were seen at each time point. The five factors of the BPRS in the course of clozapine treatment are depicted by curves in the lower part of figure. Although the baseline severity levels of the factors varied, the patterns of the change were similar to all".

"Response was defined as 20% or greater decrease Psychiatric Rating Scale to greater than 35 that persisted for at least 12 weeks".

IV. RESULT

Duration of the trial and response for continuation

The means duration of clozapine treatment for the group was 127 weeks with 94 weeks of median duration. Thirty eight of the 84 patients eventually have the clozapine discontinued for the following reasons: 1) Insufficient therapeutic effect 2) lack of compliance with treatment regimen 3) Agranulocytosis 4) other side effects 5) Unrelated medical problems. Seventy -seven patients followed during clozapine treatment for at least 6 weeks, 59 were followed for at least 12 weeks, 53 for 26 weeks and 45 for 52 weeks and lastly 36 for more than 104 weeks.

Baseline Pathology and Clinical Research

The mean phycopathology ratings of the patients at baseline were as follows: BPRS total score, 50.7 (SD = 14.6); SANS global item score, 2.7 (SD = 0.8) and CGI severity score, 5.3 SD = (1.2). Fifty (59.6%) of the patients and tardive dyskinesia; among these patients mean Simpsons Dyskinesia Scale global item score was 2.8 (SD =0.9). To examine the rate and time course of response to treatment, were determined the proportions of the patients who were classified as responders at each week of clozapines treatment for the 45 patients who received at least 52 weeks of treatment. Response to treatment was defined as a 20% or more decrease in total BPRS score to a score of greater than 36 and a CGI severity of illness rating of 3 or less. It was required that this level of response to maintained for at least two observations over a period of spanning at least 12 weeks. Since whether patients had a continued in treatment for 52 weeks was influenced by multiple factors since, patient who responded well to clozapine were more likely to have a continued treatment, we examined the response rate of the entire study group by using survival analysis (figure 2) and determined the response rates seperately

for the treatment -refractory and treatment intolerant subgroups. By this method we determined the 52 week response rate for the total group was 57%. When subgroups were examined seperately , the cumulative response rates at 3,6,12,26,39 and 52 weeks were 8%,17%,31%,36 % and 50%,respectively, for the patients with refractory illness and 6%,37%,69%,76%,76% and 76%, respectively, for the treatment – intolerant patients.

V. ADVERSE EFFECTS

Some patients exhibited motor agitation, although it was not clear that this represent a akathsia (28). Preexisting symptoms of tardive dyskinesia is also decrease in the severity with the clozapine treatment. the mean Simpson Dyskinesia Scale global item score was 2.8 at baseline, at week 6 the mean score was 1.9 and at week 12 the mean score was 1.7. Clozapine's effects on tardive dyskinesia in a subgroup of patients have been previously reported indetail (29).Treatment -emergent side effects as recorded on the MINIDOTES at scheduled clinical rating assessments and by the systemic cardiovascular and also hematologic monitoring are shown in table 1. The mean period of observation for which of the side effects were evaluated was 27 days for the acute phase and 418vdays for the maintainance phase. Seven of the 77 patients exposed to clozapine for at least 6 weeks developed agranulocytosis .possible reason for high rate in patients , specially large proportion of patients with Ashkenazi Jewish ancestry have been previously discussed (30,31).

TABLE 1. Side Effects of Clozapine in the Acute and Continuation Phases of Treatment of Patients With Schizophrenia

	Percentage of Patients With Symptom			Percentage of Visits in Which Patients Complained of Symptom			
				During Acute Phase[a]		During Continuation Phase[b]	
Symptom	At Least Once During Entire Treatment Period	During Acute Phase[a] (N=12)	During Continuation Phase[b] (N=57)	Mean	SD	Mean	SD
Agranulocytosis[c]	9.1	—	—	—	—	—	—
Anergia	53.3	66.6	15.7	61.8	46.9	18.7	27.1
Decreased appetite	16.6	8.3	1.7	8.3	28.8	2.2	8.0
Increased appetite	46.6	33.3	12.2	25.0	40.5	15.3	26.3
Blurred vision	18.3	25.0	1.7	15.2	31.3	5.0	15.9
Catalepsy	3.3	0.0	0.0	0.0	0.0	0.7	4.7
Confusion	13.3	8.3	1.7	5.5	19.2	3.6	14.2
Constipation	53.3	33.3	22.8	27.0	44.5	20.9	31.0
Depression	31.6	8.3	5.2	4.1	14.4	10.5	24.3
Dermatitis	10.0	0.0	1.7	0.0	0.0	3.0	11.2
Diarrhea	15.0	0.0	3.5	0.0	0.0	3.5	13.8
Dizziness	40.0	50.0	3.5	40.2	46.8	9.5	16.9
Drowsiness	63.3	66.6	24.5	50.6	44.1	22.9	28.8
Dry eyes	1.6	0.0	0.0	0.0	0.0	0.3	2.5
Dry mouth	5.0	0.0	0.0	0.0	0.0	0.3	1.5
Dyspepsia and heartburn	8.3	0.0	0.0	0.0	0.0	1.3	5.1
Excitement	10.0	16.6	1.7	13.8	33.2	2.4	13.4
Fainting	3.3	8.3	0.0	4.1	14.4	0.1	0.9
Headache	25.0	8.3	0.0	2.7	9.6	3.2	8.5
Hypersalivation	91.6	58.3	78.9	44.1	41.3	71.7	32.5
Insomnia	16.6	0.0	1.7	0.0	0.0	2.9	12.7
Menstrual irregularity	8.3	8.3	0.0	8.3	28.8	0.9	4.0
Myoclonus	13.3	8.3	0.0	2.7	9.6	1.9	6.6
Nausea	35.0	16.6	5.2	9.7	22.9	8.6	18.3
Nightmares	3.3	0.0	1.7	0.0	0.0	1.8	11.6
Restlessness (objective)	26.6	8.3	3.5	6.6	23.0	4.7	11.4
Restlessness (subjective)	30.0	8.3	5.2	6.6	23.0	6.1	14.2
Seizures[c]	7.1	—	—	—	—	—	—
Urinary hesitancy/retention	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Urinary incontinence	16.6	25.0	0.0	22.2	41.0	2.1	6.0
Urination—increased frequency	33.3	8.3	10.5	2.7	9.6	13.6	27.5
Vomiting	13.3	0.0	1.7	0.0	0.0	3.6	11.4
Weight gain	53.3	33.3	10.5	22.2	36.6	13.7	23.9
Weight loss	28.3	16.6	1.7	10.4	29.1	3.6	10.1
Heart function							
Abnormal systolic blood pressure[d]	23.3	16.6	0.0	6.9	16.6	1.8	4.8
Abnormal diastolic blood pressure[e]	43.3	33.3	0.0	20.8	34.1	4.7	7.2
Abnormal pulse rate[f]	28.3	16.6	1.7	6.9	16.6	4.0	13.8
Extrapyramidal effects[g]							
Rigidity	6.2	1.5	3.4	1.0	10.0	3.0	15.0
Cogwheeling	4.9	1.5	1.7	0.0	2.0	2.0	13.0
Tremor	37.8	14.7	10.2	11.0	25.0	13.0	23.0
Akinesia	31.7	20.3	8.5	15.0	32.0	10.0	24.0
Akathisia	30.5	11.6	8.5	11.0	28.0	10.0	20.0

Positive and Negative Symptoms and Extrapyramidal Symptoms

When we examined the five BPRS factors individually, the patterns of response of each was similar to that of the activation which shows the most improvement (figure 1). The response curves on the SANS global item was parallel to the BPRS anergia

factors response curves as well as the curves of the other BPRS factors. A survival analysis comparing the time to diminution of both positive and negative symptoms indicate that the positive symptoms responded to treatment approximately 7 weeks before the negative symptoms. The data are not consistent with the notion that improvement of negative symptoms occurs independent of change in positive symptoms. At that same time, the data are consistent with the suggestion that the converse is true, i.e., that the improvement of positive symptoms is responsible for the change in the severity of the negative symptoms. To examine the improvement in positive symptoms and extrapyramidal side effects as a predictors of improvement of negative symptoms, multiple regression analysis was done. When we used extrapyramidal side effects and positive symptoms as independent variables and improvement of negative symptoms as the independent variables, akinesia and rigidity (32)

VI. DISCUSSION

The findings of this study have the important implications for the use of the clozapine and our understanding of the pathophysiology of treatment-resistant schizophrenia. The result are consistent with the prior studies which demonstrated that clozapine has therapeutic efficacy in some but not all the schizophrenic patients who are resistant to standard antipsychotic drugs. The proportion of patients who responded to treatment is comparable to the proportion in previous reports (33-43). In their 6- week acute treatment study of an older, more chronic group of the patients. At that same time, the maximum response rate of 57% in our study group at 52 weeks is comparible to that reported in other long term treatment studies (44,45,46).Although negative symptoms reflected by the BPRS anergia factors and the SANS appeared to improve with clozapine treatment ,we can not conclude that clozapine is effacacious against negative symptoms, because almost all improvement of negative symptoms occurred together with improvement in other clusters of phycopathology and improvement in extrapyramidal side effects (47,48).

Biases may affect the outcome of Meta -analyses as well as those of original studies. Every effort was made to reduce biases in this overview. A visual inspection of dustribution of the odds ratios among studies gave the no indication of publication bias influencing that overview. Generally poor quality of reporting in regard to both trial performance and trial outcome may have confounded our aim to avoid biases (49, 50). our results are consistent with prior studies which found that younger age at onset with prior studies which found that younger age at onset was associated with a more severe course of illness and poor outcome, and longer duration of illness and more psychotic episodes were associated with poorer response to treatment(51,53) .The implications of these findings are that younger age at onset reflects a more severe form of the disease, while duration of illness and number of episodes reflects the progression of the illness. Thus, over the course of illness and with successive psychotic exacerbations progressions of the schizophrenia occurs to treatment diminishes (53-55).The phenomenology of schizophrenia and the subtype of diagnosis may evolve over the course of the illness, with paranoid schizophrenia occuring more often in the first stage of illness and nonparanoid forms more often in the larger stages (56).

CONCLUSION

This systematic review confirmed that clozapine is more effective to reducing the symptoms of schizophrenia. We also found that about 50% of patients with treatment -refractory psychosis and a greater proportion of treatment intolerant patients have substantial clinical responses to clozapine, with various side effects. Many side effects abate with long -term treatment. The extrapyramidal side effects response to classic neuroleptics and the diagnosis subtype of the paranoid schizophrenia being possible predictors of better response to clozapine treatment, and the younger age at onset of disease and female gender being predictors of poor therapeutic response. These variables may have important implications fir the use of clozapine and our understanding of the pathophysiology if treatment -refractory schizophrenia.

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