Clozapine as a First Treatment for Schizophrenia

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Objective: The authors' goal was to explore whether clozapine given as the first antipsychotic treatment favorably affects the course of schizophrenia.

Method: Thirty-four inpatients experiencing their first episode of schizophrenia or schizoaffective disorder were treated first with clozapine and then followed for up to 4 years. In a previous study, the authors followed patients experiencing their first episode of schizophrenia or schizoaffective disorder who were given fluphenazine as the first treatment. In the current study and the previous study, response criteria required sustained remission of positive symptoms.

Results: Nineteen of the 34 subjects met response criteria while taking clozapine. The median time to treatment response was 11 weeks (range=2–13). Using survival analysis, the authors determined that the cumulative response rate for the 34 patients was 66.4% at the end of 13 weeks, which is comparable to the response rate to fluphenazine in the previous study. All responses to clozapine occurred by 13 weeks. Eight (42%) of the clozapine responders discontinued clozapine before 6 months, and only six (32%) remained on clozapine for all of their time in the study.

Conclusions: The authors found no benefit for clozapine over conventional antipsychotics for acute treatment of the first episode of schizophrenia or schizoaffective disorder. Long-term benefits could not be studied because of the high rate of early discontinuation of clozapine treatment.

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Clozapine's efficacy for treatment-resistant schizophrenia is well-known, and there is evidence for its superiority to conventional antipsychotic agents for non-treatment-resistant schizophrenia as well (1). If clozapine has superior efficacy, might early treatment with this better drug have a beneficial effect on the initial course as well as the long-term course of schizophrenia?

As an initial attempt to explore this question, we followed the same study design used in our previous study of conventional antipsychotics as the initial treatment for first-episode schizophrenia (2) but changed the initial treatment to clozapine. In the current article, we report data for 34 patients diagnosed with schizophrenia or schizoaffective disorder who were given clozapine as their first antipsychotic treatment and followed prospectively for up to 4 years.

Method

Inpatient admissions at Hillside Hospital in Glen Oaks, N.Y., were screened, and eligible first-episode patients were offered participation in the study. Written informed consent was obtained from all subjects and available parents. Inclusion criteria were age 16–45 years; diagnosis of schizophrenia or schizoaffective disorder based on a Schedule for Affective Disorders and Schizophrenia (SADS) (3) interview and Research Diagnostic Criteria (RDC) (4); at least one psychotic symptom on the SADS—Change Version (SADS-C) (5), with psychosis and disorganization items rated moderate or higher at study entry; no more than 12 weeks of lifelong antipsychotic medication; and no medical conditions that might affect diagnosis or assessment or contraindicate treatment with clozapine.

Patients were treated openly with clozapine as follows: 12.5 mg/day on day 1; 25 mg/day on days 2 and 3; 50 mg/day on days 4 and 5; 75 mg/day on days 6 and 7; 100 mg/day on days 8 and 9, and increments of 50 mg/day every 2 days until treatment response or dose-related side effects occurred. Patients judged to be treatment nonresponders and those with substantial adverse events were switched to another antipsychotic medication (clinician's choice) and continued in the follow-up.

Assessments included the SADS-C, including the psychosis and disorganization items, and the Clinical Global Impression (CGI) (6) every 2 weeks during acute treatment and every 4 weeks following treatment response.

Treatment response was defined as having no psychotic symptoms rated more than mild on the SADS-C and being rated much improved or very much improved on the CGI. The improvement had to be maintained for at least 2 months.

Results

Subjects included 21 males and 13 females; their mean age at onset of psychosis was 21 years (SD=4.9), and their mean age at study entry was 23 (SD=5.2). Fourteen (41%) were white, 11 (32%) were African American, four (12%) were Hispanic, and five (15%) were of other ethnic backgrounds. Four (12%) were college graduates, 15 (44%) had completed some college, three (9%) were high school graduates, and 12 (35%) did not complete high school. Diagnosis at study entry (RDC) was schizophrenia for 29 (85%) and schizoaffective disorder for five (15%). According to DSM-III-R criteria, 13 (38%) were diagnosed as having schizophreniform disorder, 15 (44%) as having schizophrenia, and six (18%) as having schizoaffective disorder.

The subjects were followed for a mean of 114 weeks (SD=74, range=4–221). Mean time in treatment with clozapine was 50 weeks (SD=47). Nineteen (56%) of the 34 subjects met response criteria while taking clozapine. The

median time to treatment response was 11 weeks (range=2–13). Using survival analysis, we determined that the cumulative response rate for the 34 patients was 66.4% (95% confidence interval=48.3%–84.5%) at the end of 13 weeks. No patients responded to clozapine after 13 weeks, although eight of the 15 nonresponders were treated with clozapine beyond 13 weeks; the range of treatment time for these patients was 15 to 61 weeks. Clozapine dose at the time of response ranged from 37.5 to 600 mg/day; the mean dose was 206 mg/day (SD=133). The mean highest clozapine dose for responders was 234 mg/day (SD=126); the mean highest dose for nonresponders was 297 mg/day (SD=153).

Our patients discontinued clozapine relatively early, undermining our ability to examine long-term benefits. Treatment responders took clozapine longer (mean=75 weeks, SD=70) than did nonresponders (19 weeks, SD=17). However, eight (42%) of the 19 responders discontinued clozapine before 6 months, and 10 (53%) did so before 1 year. Only six clozapine responders (32%) and two nonresponders (13%) took clozapine throughout their study participation. At study termination, seven responders (37%) and four nonresponders (27%) were taking olanzapine or risperidone, two nonresponders (13%) were taking haloperidol, and six responders (32%) and seven nonresponders (47%) were not taking any antipsychotic medication.

Six (46%) of the 13 responders who discontinued clozapine did so because of low WBC (one patient) or other adverse effects (rash, urinary retention, weight gain) (three patients), two (15%) refused to take blood tests, and seven (54%) discontinued in the context of refusal of any medication. The 13 nonresponders who discontinued clozapine did so because of low WBC (five patients), refusal of blood tests (three patients), lack of improvement (three patients), or refusal of any medication (two patients). None of the patients with low WBC progressed to agranulocytosis.

Only one clozapine responder relapsed while still taking clozapine (at 1 year). Three clozapine responders who switched to another atypical antipsychotic relapsed while taking the second drug. Two responders relapsed after discontinuing antipsychotic treatment.

Discussion

The cumulative response rate after 13 weeks of clozapine treatment (66.4%) is similar to the response rate in our earlier study of patients treated with typical antipsychotics (7). The median response time was actually longer for the clozapine group (11 weeks) than for those in the previous study (9 weeks), possibly because of the slow titration required for clozapine. Although these results might suggest no benefit for clozapine over conventional drugs for acute treatment of the first episode, it should be emphasized that the number of patients in our study group was very small, and the comparison group was not concurrent. Patients' characteristics or other cohort differences may be important. The two groups of patients differed in terms of the proportion of males (62% in the current study compared with 52% in the previous study) and diagnostic composition (85% schizophrenia and 15% schizoaffective disorder in the current study compared with 70% schizophrenia and 30% schizoaffective disorder in the earlier study). These differences might suggest a poorer prognosis for patients in the current study than the earlier study. In contrast, duration of untreated psychosis was shorter for subjects in the current study (mean=49.9 weeks, SD=119) than in the previous one (mean=71 weeks, SD=150).

In a double-blind 52-week trial, Lieberman et al. (8) studied 164 patients in China who were experiencing their first episode of psychosis. They found a 71% cumulative response rate at 12 weeks for clozapine-treated patients compared with a 62% rate for chlorpromazine-treated patients but no difference between the drugs at 1 year (cumulative response rates were 81% for clozapine and 79% for chlorpromazine). The 71% early response rate is consisent with our finding.

The fact that only one patient in our study relapsed while taking clozapine, compared with three patients who relapsed while taking other antipsychotics, hints at support for a clozapine advantage in long-term outcome. However, the high rate of discontinuation of clozapine treatment—53% (N=18) by 6 months and 71% (N=24) by 1 year—rules out conclusions about long-term benefits. We have found that unwillingness to continue antipsychotic treatment is a serious problem among first-episode patients, whether treated with conventional or first-line new-generation drugs. The additional burden of clozapine side effects and WBC monitoring probably contributes to the very high rate of discontinuation found in this study group.

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