Case Report
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Efficacy of Asenapine in Schizophrenia Resistant to Clozapine Combined with Electroconvulsive Therapy: A Case Report

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Schizophrenic patients resistant to antipsychotics are diagnosed as having treatment-refractory schizophrenia, and they are treated with clozapine. However, clozapine is sometimes combined with electroconvulsive therapy (ECT) if clozapine monotherapy fails. In this report, a severe treatment-refractory schizophrenic patient who did not respond to clozapine even with ECT, but who recovered with asenapine monotherapy, is presented. Asenapine, considered a serotonin spectrum dopamine modulator, is a new atypical antipsychotic with unique pharmacological features that is used not only for schizophrenia, but also for bipolar disorder. The unique features of asenapine may be effective for some treatment-refractory schizophrenic patients.

KEY WORDS: Asenapine; Treatment-refractory schizophrenia; Clozapine; Electroconvulsive therapy; Suicide; Recurrence.

INTRODUCTION

Schizophrenia is a complex and chronic mental disorder resulting from genetic, social, and psychological influences. Generally, antipsychotics are effective for the treatment of schizophrenia. However, it is well known that about 30% of schizophrenic patients do not respond adequately to antipsychotics [1], and they are diagnosed as having treatment-refractory schizophrenia (TRS). TRS is defined as an insufficient response to at least two sequential and different antipsychotic medications with adequate doses and durations [2]. Although it is well established that clozapine is the most effective antipsychotic for the treatment of TRS [3], it sometimes fails to diminish mental symptoms, or it cannot be continued because of severe adverse events [4]. On the other hand, as a non-pharmacological therapy for TRS, electroconvulsive therapy (ECT) is useful and is used in combination with antipsychotics. A meta-analysis reported that combined therapy with ECT and clozapine is more effective for TRS than clozapine alone [5].

Asenapine is a new atypical antipsychotic with unique features that was introduced in Japan in 2016. Asenapine is the only antipsychotic used by the sublingual route, and it has a specific pharmacological profile: it shows high binding affinity for dopamine receptors (D_1, D_2, D_3, and D_4), serotonin receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_5, 5-HT_6, and 5-HT_7), adrenalin receptors (α_1, α_{2A}, α_{2B}, and α_{2C}), and histamine receptors (H_1 and H_2). However, asenapine shows little binding affinity for muscarinic receptors [6]. Thus, asenapine is sometimes called a serotonin spectrum dopamine modulator because of its high binding affinity for 5-HT receptors [7].

The efficacy and tolerability of asenapine have been shown in both acute and long-term treatment for schizophrenia [8,9]. Previous reports suggested that augmentation therapy with asenapine may be effective for TRS and for catatonia in patients who showed an insufficient response to clozapine [10,11]. However, no previous studies have reported the efficacy of asenapine monotherapy for TRS in patients who showed insufficient response to clozapine combined with ECT. In this report, the case of a 40-year-old female with TRS who failed to respond sufficiently to clozapine combined with ECT, but improved

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significantly by switching to asenapine monotherapy, is presented. Informed consent for publication of this case report was obtained from the patient.

CASE

The patient was a 40-year-old female. Her past history only included iron-deficiency anemia. At 26 years of age, she presented with auditory hallucinations, persecutory delusions, and thought insertion. She was then diagnosed with schizophrenia and took antipsychotic medications as an outpatient. However, her symptoms, especially auditory hallucinations and persecutory delusions, did not improve. She first visited our hospital at 28 years of age. First, she took risperidone 6 mg/day until 31 years of age. However, she sometimes had auditory hallucinations and persecutory delusions and she could barely work with her family's help. The Global Assessment of Functioning scale was 35. Thus, it was concluded that her symptoms had not improved sufficiently. Furthermore, extrapyramidal symptoms, hyperprolactinemia, amenorrhea, and galactopoiesis appeared as adverse effects. Therefore, her antipsychotic medication was switched from risperidone to quetiapine. Quetiapine was started at a dose of 200 mg/day and gradually increased to 750 mg/day. While taking quetiapine, her adverse effects improved, but her psychotic symptoms did not improve sufficiently. From 35 years of age, she attempted suicide on several occasions because of worsening of her symptoms. She was then diagnosed as having TRS, and clozapine was recommended, but it took her a while to make a decision because clozapine treatment must be started in an inpatient setting for at least 18 weeks in Japan. She was finally admitted to our hospital to start clozapine at 39 years of age. At the time of admission, organic causes of her psychosis were investigated by blood examinations, electroencephalogram, and head computed tomography, but none was found. The Positive and Negative Symptom Scale (PANSS) [12] total score was 98 points at the time of admission. The initial dose of clozapine was 12.5 mg/day, which was increased to 50 mg/day after a week. The dose of clozapine was adjusted with a weekly increment around 25 to 50 mg/day. As for adverse effects of clozapine, she showed temporary eosinophilia when clozapine was increased to more than 250 mg/day, and she had slight somnolence. Then, 14 weeks after starting clozapine, we increased the dosage to 500 mg/day but unfortunately she developed convulsive seizures the very next day. The dose was then reduced by about 100 mg/day per week. Finally, 18 weeks after starting clozapine, we reduced and maintained the dose of clozapine at 200 mg/day, but her symptoms did not improve sufficiently. However, 23 weeks after starting clozapine, she unexpectedly attempted suicide by jumping during an overnight stay in her home. Therefore, clozapine showed insufficient efficacy. Then she was treated with the combination of clozapine and ECT since the 30th week after clozapine initiation. She received ECT twice a week, 12 times in all. During the initial course of ECT, her symptoms improved, and she was discharged 39 weeks after starting clozapine. At the time of discharge, her PANSS total score was 78. She was followed in the outpatient clinic, with continued maintenance ECT every 2 weeks and clozapine 200 mg/day. However, her symptoms gradually worsened, and one month after discharge, she again attempted suicide by jumping and was quickly brought to our hospital. Her right arm and pelvis were fractured, and the fractures were treated surgically. After surgery, she was transferred to our psychiatric unit, with a PANSS total score of 117. At that time, it seemed that combination therapy was ineffective for her, and it was decided to switch her to another antipsychotic. Based on her drug and medical history, asenapine was selected. Clozapine was stopped on the day that asenapine was started at 10 mg/day. With 20 mg/day of asenapine, her symptoms gradually improved without any adverse effects such as extrapyramidal symptoms and hyperprolactinemia. Two months after switching to asenapine, she was discharged from our hospital. At the time of discharge, her PANSS total score was 62. As for the course of her symptoms, not only delusions and hallucinations, but also especially mood symptoms such as excitement, grandiosity, suspiciousness, hostility, guilt feelings, and depression were improved. The changes of PANSS scores with each admission are shown in Table 1. While the same dose of asenapine was continued for more than one year, she could work regularly and continue follow-up visits without any adverse effects.

DISCUSSION

In this report, the case of a female with TRS who failed to respond to clozapine combined with ECT in which ase-

Table 1. Changes in the PANSS score before and after each treatment

Contents of therapy	PANSS score			
	Total	Positive symptoms	Negative symptoms	General psychopathology
First admission (ECT and clozapine 200 mg/day)				
At admission	98	28	20	50
At discharge	78	18	18	42
Second admission (asenapine 20 mg/day)				
At admission	117	31	24	62
At discharge	62	15	12	35

First admission showed changes in the Positive and Negative Symptom Scale (PANSS) total and each sub-scale score before and after treatment with electroconvulsive therapy (ECT) combined with clozapine. Second admission showed in the PANSS total and each sub-scale score before and after treatment with asenapine monotherapy.

napine showed efficacy and safety was presented.

One meta-analysis reported that combined therapy with clozapine and ECT was the most effective treatment for TRS [5]. In the present case, we maintained the dose of clozapine at 200 mg/day, because the dose could not be increased due to the adverse effect of seizures. A previous study reported that the rate of seizures was increased with higher doses of clozapine and rapid dose titration [13]. Furthermore, it has been reported that, regarding high doses, 300 to 600 mg/day has a higher risk of seizures than a dose of less than 300 mg/day [13]. Although we increased the dose of clozapine according to the standard protocol in Japan, slower titration and staying at a lower dose might have prevented her seizures. In fact, when the dose was decreased and kept at 200 mg/day, she did not have seizures. On the other hand, 200 mg/day was a comparatively low dose. However, a previous study reported the effectiveness of combined use of ECT and clozapine at a mean dose of 287 mg/day [14]. This was about the same as the dose in the present case. Furthermore, it has been reported that the prevalence of side effects of the clozapine-ECT combination, especially delirium and prolonged seizures, were associated with a dose of clozapine higher than 250 mg/day [14]. In the present case, the patient had already had a seizure, and it was necessary to avoid increasing the risk of seizures. Therefore, the appropriate dose was used in this case.

In some cases, the augmentation strategy of clozapine with ECT could fail, which is why we selected a trial of asenapine. The reasons why we selected asenapine were as follows. First, we focused on the similarities of the receptor binding profiles between clozapine and asenapine. Furthermore, it has been reported that the efficacy of asenapine was evaluated in treatment of not only schizophrenia, but also bipolar disorder, and asenapine showed small changes in mean prolactin levels and weight gain [9]. The present patient had not only delusions and hallucinations, but also mood symptoms, and she had adverse effects caused by other antipsychotics. Furthermore, Potkin [15] reported that the risk of seizures was extremely low. It has been reported that the causes of seizures with clozapine might be associated with D_4 receptors and anticholinergic receptors. Asenapine has lower binding affinities for these receptors than clozapine. In particular, asenapine shows much less binding affinity for muscarinic receptors than other antipsychotics [6,16]. These may be the reasons for the safety of asenapine in relation to seizures compared to clozapine. It is well known that clozapine is the most effective choice for TRS. To clarify the mechanism by which asenapine was effective for TRS in the present case, we focused on the similarities and differences of receptor binding profiles between clozapine and asenapine. According to the similarities of the receptor binding profiles [6,16], both clozapine and asenapine have higher binding affinities for 5-HT_{1A}, 5-HT_6, and 5-HT_7 than other antipsychotics, which may improve anxiety, depression, and cognitive functions [7]. According to the 5-HT_{1A} receptor agonist activity of asenapine, it may improve not only positive, but also psychopathological symptoms in schizophrenia [17]. With respect to the 5-HT_6 receptor in schizophrenia, it has been reported that a selective 5-HT_6 inhibitor significantly improved the PANSS total score only in female schizophrenic patients in a double-blind, placebo-controlled study [18].

Regarding the association between the 5-HT_7 receptor and schizophrenia, previous studies reported that the 5-HT_7 receptor level was decreased in the prefrontal cortex of schizophrenic patients, and that the genetic poly-

morphism of Japanese schizophrenic patients was positively associated with the 5-HT_7 receptor gene [19], even with studies showing that 5-HT_7 receptor polymorphisms were not associated with antipsychotic improvement in Japanese schizophrenic patients [20]. Because the affinity of asenapine for these serotonin receptors is higher than that of other antipsychotics, it may be more effective for psychotic symptoms and suicidal behavior. Although the dose of clozapine could not be increased to the maximum dose in the present case, the maximum dose of asenapine could be used with no adverse effects. This also may have led to greater efficacy in this case. The synergistic effects between these 5-HT receptors and a sufficient dose of asenapine may have greater efficacy than clozapine treatment, but controlled studies are needed. Furthermore, previous studies suggested that asenapine may improve depressive symptoms and reduce suicidal risk [21]. We concluded that asenapine was effective for not only psychotic symptoms, but also mood symptoms, such as suicidal ideation, in the present TRS patient who failed to respond to clozapine combined with ECT. Further clinical studies are needed to confirm the effects of asenapine, but this case provides much important information for the treatment of TRS.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Writing—original draft: Shinichiro Ochi. Data acquisition: Saori Inoue, Yuta Yoshino. Writing—review & editing: Hideaki Shimizu, Jun-ichi Iga. Supervision: Shu-ichi Ueno.

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