Safety of quetiapine fumarate extended release in the treatment of Korean patients with acute schizophrenia

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Introduction  The aim of this study was to evaluate the efficacy and safety of quetiapine fumarate extended release (XR) in the treatment of Korean subjects with acute schizophrenia.

Methods  This was an 8-week, multi-center, open-label, non-comparative study to evaluate the efficacy and safety of quetiapine fumarate XR at a daily dose of 400–800 mg. Changes in total scores on the Positive and Negative Syndrome Scale (PANSS) from baseline to week 8 were analyzed to evaluate the efficacy of quetiapine XR. Additionally, the Clinical Global Impression scale and the Montgomery–Asberg Depression Rating Scale were administered.

Results  The mean change in PANSS total scores was −26.8, and the mean PANSS total score at the endpoint was significantly lower than that at baseline. The mean PANSS positive score, negative score, and general score showed statistically significant reductions at the end of the study. Statistically significant changes were also observed in Clinical Global Impression-Severity and Montgomery–Asberg Depression Rating Scale scores. The most common treatment-related adverse events in the group receiving quetiapine XR were sedation (10.6%) and constipation (9.6%).

Conclusions  In this study of Korean patients with acute schizophrenia, quetiapine XR showed clinical efficacy and relatively good tolerability. Copyright © 2012 John Wiley & Sons, Ltd.

Key words—schizophrenia; quetiapine fumarate extended release; efficacy; tolerability; titration

INTRODUCTION

Schizophrenia is a severe, debilitating mental illness characterized by a progressive decline of the patient’s functioning and relationship with the outside world (Caldwell and Gottesman, 1992). The median lifetime prevalence estimate is 4.0 per 1000, and many patients require long-term treatment (McGrath et al., 2008). Although most patients are generally responsive to pharmacological treatment, they frequently have difficulty maintaining their therapy because of side effects, particularly extrapyramidal symptoms (EPS) (Brenner et al., 1990). Some first-generation antipsychotic drugs also induced unacceptable side effects, such as tardive dyskinesia (TD), in some patients (de Jesus Mari et al., 2004). Evidence suggests that some second-generation antipsychotic drugs (SGAs) provide significant improvement in positive symptoms, negative symptoms, functional capacity, cognitive function, and quality of life in patients with schizophrenia (Woodward et al., 2007). In several studies, some SGAs have also been shown to carry a reduced risk of acute EPS and TD compared with some first-generation antipsychotic drugs (Miyamoto et al., 2005). Quetiapine is one of the SGAs used for the treatment of patients with schizophrenia. Quetiapine is known to be effective in the treatment of positive and negative symptoms of schizophrenia and is generally well tolerated during long-term treatment (Kasper et al., 2001; Perez et al., 2008). The low incidence of side effects is very important, as side effects have been associated with poor adherence, exacerbation of symptoms, hospitalization, and poor clinical outcomes.
Quetiapine immediate release (IR) is administered twice daily and requires dose titration over 4 days to reach the target therapeutic dose (Figueroa et al., 2009). Some psychiatrists have suggested that the method of titration is complex and that some patients prefer less frequent administration (Fleischhacker et al., 2003; Osterberg and Blaschke, 2005). The extended-release form of quetiapine fumarate (quetiapine XR) was developed to provide more convenient once-daily administration as well as to allow simple and rapid dose escalation, with the aim of improving compliance. In several short-term clinical trials, once-daily oral quetiapine XR 400–800 mg was generally effective across a range of symptoms in the acute treatment of schizophrenia, and rapid dose titration of quetiapine XR, up to 800 mg/day during the first week, raised no concerns regarding adverse events (AEs) (Baldwin and Scott, 2009; Meulien et al., 2010). The aim of this study was to determine the efficacy and safety of quetiapine XR in the treatment of Korean patients with acute schizophrenia.

PATIENTS AND METHODS

Subjects

Patients aged between 18 and 65 years were recruited from nine centers in Korea. Written informed consent was obtained from each subject, and the institutional review board (IRB) of each of the eight centers approved the study protocol. One center used the IRB of Busan Paik Hospital as the central IRB for their region (approval no. 08-127). All subjects were diagnosed with schizophrenia according to the standard structured clinical interview for DSM-IV Axis I disorders (First et al., 1997) and had Positive and Negative Symptom Scale (PANSS) (Key et al., 1987; Yi et al., 2001) total scores of over 70 and Clinical Global Impression-Severity scale (CGI-S) scores over 4. Additionally, all subjects had multiple PANSS items with scores above 4 among items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), and P6 (suspiciousness/persecutions). Subjects with a history of comorbid conditions such as personality disorders, substance abuse or dependence, head trauma, severe neurological disorders, depression, or other medical problems were excluded.

Study design

Ninety-six subjects were enrolled in an 8-week, multicenter, open-label, non-comparative trial (D1443L00062). After the baseline evaluation, subjects received treatment with quetiapine XR. The dosing schedule consisted of two periods. During the titration period, spanning the first 3 days of treatment, the quetiapine XR dose was fixed. The day 1 dose was 300 mg, followed by 600 mg on day 2, and 800 mg on day 3. After this initial titration period, the quetiapine XR dose became more flexible according to the needs of the specific patient. The flexible doses in this phase ranged from 400 to 800 mg/day (Figure 1). Primary (total psychopathology score) and secondary outcome (psychopathology subscale scores, global impression, depressive symptoms, and global functioning) variables were assessed at baseline and at week 8. The checklist for AEs was completed weekly after baseline evaluation.

Assessment

The PANSS score was used to assess the severity of psychiatric symptoms. PANSS positive, PANSS negative, and PANSS general psychopathology scores were also calculated for all subjects. The CGI-S was used to assess the overall clinical status of subjects. The
Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979; Ahn et al., 2005) was administered to evaluate depressive symptoms, and the Global Assessment of Functioning (GAF) (Endicott et al., 1976; Yi et al., 2003) was administered for the evaluation of functional capability. Serum prolactin and cholesterol levels, the Simpson–Angus Akathisia Rating Scale (SAS; Simpson and Angus, 1970), the Abnormal Involuntary Movement Scale (AIMS; Munetz and Benjamin, 1988), and the Barnes Akathisia Rating Scale (BARS; Barnes, 1989) were used for the evaluation of adverse effects. All scales were completed weekly after baseline evaluation.

Analyses

The efficacy analysis was performed using modified intention to treat (MITT) and per protocol (PP) populations. The MITT population consisted of all patients who received at least one dose of study treatment and who had measurements at baseline and at least one treatment assessment. The PP population was defined as all MITT patients with no major protocol violations and/or deviations. The safety population consisted of all patients who received at least one dose of study treatment. A last-observation-carried-forward (LOCF) method was used in the MITT analysis for missed efficacy data. The changes from baseline to week 8 in PANSS total scores were analyzed using paired t-tests. The changes in PANSS positive, PANSS negative, and PANSS general psychopathology scale scores and in CGI, MADRS, and GAF scores were also analyzed using a paired t-test or Wilcoxon’s signed rank test. A p-value of ≤0.05 was considered statistically significant.

RESULTS

Study subjects

Of the 96 subjects enrolled, 94 were treated. The two subjects not treated were screening failures. Ninety-four subjects received study medication and therefore constituted the safety analysis set. Five subjects were excluded from the MITT analysis set on the grounds of having no recorded post-dose efficacy results. The MITT analysis set thus comprised 89 subjects. Major protocol violations occurred with seven subjects. These subjects were excluded from the PP analysis; therefore, this set included 82 subjects (Figure 2). Table 1 shows the demographic and disease characteristics of the MITT set. The results of the PP analysis did not differ significantly from those of the MITT set (data not shown.)

Efficacy results

Change from baseline in PANSS total scores. The mean PANSS total score at baseline was 99.7, and the mean PANSS total score at endpoint was 72.9. The mean change in PANSS total scores was −26.8 (95% CI: −31.0, −22.6%). The mean PANSS total score at endpoint was significantly lower than that at baseline, and this change was clinically relevant (Figure 3) (Table 2). The proportion of patients achieving reductions of 30% in PANSS total scores was 43.8% (95% CI: 33.5%, 54.1%).

Changes in PANSS subscales. Eighty-nine subjects had measurable scores on the PANSS subscales at both baseline and endpoint (LOCF). The mean PANSS

<table>
<thead>
<tr>
<th>Enrolled</th>
<th>n = 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening failure</td>
<td>n = 2</td>
</tr>
<tr>
<td>Treated</td>
<td>n = 94</td>
</tr>
<tr>
<td>Discontinued</td>
<td>n = 27</td>
</tr>
<tr>
<td>Adverse event (n = 4)</td>
<td></td>
</tr>
<tr>
<td>Lack of therapeutic response (n = 11)</td>
<td></td>
</tr>
<tr>
<td>Protocol non-compliant or protocol deviation (n = 5)</td>
<td></td>
</tr>
<tr>
<td>Subject not willing to continue study (n = 6)</td>
<td></td>
</tr>
<tr>
<td>Subject lost to follow-up (n = 1)</td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>n = 67</td>
</tr>
</tbody>
</table>

Figure 2. Disposition of subjects
positive score was 24.5, the mean PANSS negative score was 25.6, and the mean PANSS general score was 49.6 at baseline. Furthermore, the mean PANSS positive, negative, and general scores were 17.1, 19.4, and 36.4, respectively, at the end of the study. Significant reductions in the PANSS positive, negative, and general scores were observed at the end of the study (13.2, 6.2, and 13.2, respectively) (Table 2).

Changes in CGI-S, MADRS, and GAF. Mean and median values of the absolute reduction in the CGI-S scores were 1.46 and 1.10, respectively, reflecting statistically significant reductions among these subjects. The proportion of patients with a CGI global improvement rating ≤3 at week 8 (LOCF) was 84.3% (95% CI: 76.7%, 91.8%). With LOCF used, the mean change and median change from baseline in MADRS total scores at day 57 was –9.44 and –8.0, respectively, which reflects a statistically significant reduction (Figure 4). The mean baseline GAF value was 35.4, and the mean GAF at endpoint was 53.3. The mean (median) change in GAF was 17.9 (16.0), which also indicated statistically significant improvement (Figure 5) (Table 2).

Safety results

Adverse events. The proportions of subjects reporting at least one AE was 69.1%. During the treatment period, 221 AEs were reported by 65 subjects in the safety set (Table 4). Fifty-three treatment-related AEs occurred in 29 subjects (30.9%). Four subjects discontinued participation because of AEs. No serious adverse consequences resulted from AEs. The most common treatment-related AEs in the quetiapine XR group were sedation (10.6%) and constipation (9.6%) (Table 3).

Table 1. Demographic and disease characteristics (MITT population)

<table>
<thead>
<tr>
<th></th>
<th>Male (N=52)</th>
<th>Female (N=37)</th>
<th>Total (N=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>42.4 (9.8)</td>
<td>35.8 (13.0)</td>
<td>39.7 (11.6)</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>66.6 (11.4)</td>
<td>59.1 (13.0)</td>
<td>63.5 (12.6)</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>168.7 (6.6)</td>
<td>158.0 (5.9)</td>
<td>164.2 (8.2)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>23.4 (3.5)</td>
<td>23.7 (5.4)</td>
<td>23.5 (4.4)</td>
</tr>
<tr>
<td>DSM-IV diagnosis criteria, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorganized</td>
<td>1 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catatonic</td>
<td>1 (1.1)</td>
<td></td>
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<tr>
<td>Paranoid</td>
<td>45 (50.6)</td>
<td></td>
<td></td>
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<tr>
<td>Undifferentiated</td>
<td>42 (47.2)</td>
<td></td>
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<tr>
<td>Family members with known diagnosis of schizophrenia, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>76 (85.4)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>13 (14.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject has a known history of diabetes mellitus, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>86 (96.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (3.4)</td>
<td></td>
<td></td>
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</tbody>
</table>

Table 2. Summary of major efficacy results (MITT population)

<table>
<thead>
<tr>
<th>Efficacy variables</th>
<th>N</th>
<th>Mean (SD)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS total score change</td>
<td>89</td>
<td>–26.8 (–31.0, –22.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Positive score change</td>
<td>89</td>
<td>–7.4 (–8.6, –6.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Negative score change</td>
<td>89</td>
<td>–6.2 (–7.5, –5.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>General score change</td>
<td>89</td>
<td>–13.2 (–15.5, –10.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CGI-S score change</td>
<td>89</td>
<td>–1.46 (–1.71, –1.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MADRS total score change</td>
<td>89</td>
<td>–9.44 (–11.44, –7.43)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GAF score change</td>
<td>81**</td>
<td>17.9 (15.0, 20.8)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

PANSS, Positive and Negative Symptom Scale; CGI-S, Clinical Global Impression-Severity scale; MADRS, Montgomery–Åsberg Depression Rating Scale; GAF, Global Assessment of Functioning.

*Paired t-test or Wilcoxon’s signed rank test. **Eight patients had no post-baseline GAF score.
Clinical laboratory evaluation

Prolactin level. Prolactin levels at endpoint differed significantly from those at baseline in both sexes. The median changes in prolactin levels were $-8.6$ ng/mL in men and $-7.7$ ng/mL in women.

Figure 4. Changes in CGI-S, MADRS, and GAF scores

Lipid profiles. Mean changes from screening in levels of total cholesterol, triglycerides, HDL, and LDL at week 8 were $8.7$ mg/dL, $9.6$ mg/dL, $-0.4$ mg/dL, and $7.1$ mg/dL, respectively. All of these blood levels were within normal range.
Body weight. The mean weight change since screening was 0.55 kg. The mean weight of subjects remained essentially unchanged over the course of the study. The proportion of patients who had a ≥7% weight gain compared with baseline was 7 (7.9%) (Table 3).

BARS, SAS, and AIMS. For a large majority of patients in the study, no change in BARS total scores was observed over the treatment period due to the high rate of “0” scores at baseline. Approximately 80% of patients showed no change from baseline in BARS total scores, and 16.8% percent of patients showed improvement. For SAS total scores, the percentages of patients showing improvement, no change, and worsening compared with baseline were 40.4%, 56.2%, and 3.4%, respectively. A large majority of patients in the study showed no change in AIMS total scores over the treatment period due to the high rate of “0” scores at baseline. Thus, 72% patients showed no change from baseline in AIMS total scores; 23.6% of patients showed improvement in AIMS total scores compared with baseline (Table 4).

DISCUSSION
The results of this study suggest that a once-daily dose of quetiapine XR is relatively effective for the treatment of schizophrenia. The mean change in PANSS total scores was \(-26.8\%\) (95% CI: \(-31.0\%, -22.6\%\)). The mean PANSS total score at endpoint was significantly lower than that at baseline, and this change was clinically relevant. Reductions in PANSS positive, negative, and general scores were observed at the end of the study (mean changes, –7.4, –6.2, and –13.2, respectively). Furthermore, statistically significant changes were seen in CGI-S, MADRS, and GAF scores. Importantly, we observed significant improvement in mean total GAF and MADRS scores with quetiapine XR treatment. Because recovery from impaired psychosocial functioning in patients with schizophrenia is very difficult and may be the most severe challenge in the treatment of schizophrenia (Swartz et al., 2007), this improvement in GAF scores is an important finding of this study. Recently, it has been reported that quetiapine XR may have an antidepressant effect, and the US Food and Drug Administration has approved quetiapine XR as an adjunct treatment for major depressive disorder (McIntyre et al., 2009; El-Khalili et al., 2010; Pae et al., 2010).

Quetiapine XR was relatively well tolerated by the Korean population in this study, and the incidence of treatment-related AEs was reasonably low. No serious AE and no death due to AE occurred, and no new safety issues were identified. Laboratory safety data were generally unremarkable. The most common treatment-related AEs were somnolence (10.6%), constipation (9.6%), and dizziness (4.3%). However, this AE profile was similar to that for quetiapine IR (Kahn et al., 2007). Meulien et al. (2010) also reported that once-daily treatment with quetiapine XR at doses between 400 and 800 mg/day is relatively well tolerated and showed AE profiles similar to those for the equivalent total daily doses of the quetiapine IR formulation. A fixed titration method was used in this study. However, no serious AE was observed, and only one subject dropped out because of AEs in the titration period. These findings suggested that rapid titration of quetiapine XR, reaching 300 mg by day 1, 600 mg by day 2, and 800 mg by day 3, is relatively well tolerated in Korean populations. Kahn et al. (2007) also reported the tolerability of rapid titration of quetiapine XR in the treatment of acute schizophrenia. Other AEs that we observed in this study were related to EPS, prolactin levels, body weight, and metabolic parameters. Bushe et al. (2010) reported that treatment with quetiapine led to decreased serum prolactin levels in patients with schizophrenia. In this study, serum prolactin levels were decreased in both
male and female subjects after 8 weeks of quetiapine XR treatment. The incidence of EPS was low in this study. Quetiapine XR treatment significantly decreased scores on the SAS, BARS, and AIMS scales. Additionally, a number of subjects with previously existing drug-induced TD showed improvements in TD symptoms during the study. These results are similar to those of previous studies with quetiapine IR in the treatment of acute schizophrenia (Kahn et al., 2007). The mean body weight increased by 1 kg in male subjects, with no significant changes in the body weight of female subjects. In total, five male subjects and two female subjects showed body weight increases greater than 7% at the end of the study. The change of mean body weight with quetiapine XR was not as small as in a previous study (Kahn et al., 2007). Small changes in fasting cholesterol and triglyceride levels were also observed. Blood cholesterol and triglyceride levels were slightly elevated at the end of the study, but they remained within normal ranges. This study had a general limitation in that the study design was open and non-comparative. Therefore, generalizations from the results of this study should be made cautiously. Overall, quetiapine XR was generally safe and well tolerated in the treatment of Korean patients with schizophrenia. The rapid dose titration of quetiapine XR was not associated with any severe AEs. These tolerability profiles of quetiapine XR may imply that patient adherence can be potentiated.

CONCLUSIONS
Quetiapine XR showed significant efficacy for the treatment of Korean subjects with acute schizophrenia. The efficacy of quetiapine XR treatment was confirmed by improvement in PANSS total and subscale scores, CGI-S scores, and MADRS scores. GAF scores were also significantly improved. In general, quetiapine XR showed good tolerability and safety profiles. The titration method used in this study was also well tolerated.

CONFLICT OF INTEREST
No conflict of interest declared.

ACKNOWLEDGEMENT
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