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Early treatment response predicted subsequent clinical response in patients with schizophrenia taking paliperidone extended-release

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ABSTRACT

This 6-week open-labeled study investigated whether early treatment response in patients receiving paliperidone extended-release (paliperidone ER) can facilitate prediction of responses at Week 6. Patients with schizophrenia or schizoaffective disorder were administered 9 mg/day of paliperidone ER during the first 2 weeks, after which the dose was adjusted clinically. They were assessed on Days 0, 4, 7, 14, 28, and 42 by the Positive and Negative Syndrome Scale (PANSS). The serum concentrations of 9-hydroxyrisperidone were examined on Days 14 and 42. Among the 41 patients enrolled, 26 were classified as responders (≥50% improvement on total PANSS scores at Week 6). In the receiver-operator curves (ROC) analyses, the changes in total PANSS scores at Week 2 appeared to show more accurate predictability compared to Day 4 and Day 7. At Week 6, no significant correlation was observed between blood 9-hydroxyrisperidone concentration and the total score or changes of PANSS scores. The results suggest that early treatment response to paliperidone ER, particularly at Week 2, can serve as a suitable outcome predictor at Week 6. Using 9 mg/day paliperidone ER as an initial dose for schizophrenia treatment exhibited relatively favorable tolerability and feasibility.

1. Introduction

Previous treatment guidelines have recommended that clinicians monitor antipsychotic responses for at least 4–6 weeks before changing medications (National Collaborating Centre for Mental Health, 2009). However, early prediction of treatment outcomes can prevent unnecessary delays in decision making and reduce the occurrence of medication side effects. Recent studies have suggested the possibility of predicting antipsychotic responses early in the course of treatment, and this strategy has been adopted by the prescribed guidelines (Taylor et al., 2012). In meta-analysis, a more substantial improvement in psychopathology was observed during the first 2 treatment weeks than in the weeks subsequent to the first 2 treatment weeks (Agid et al., 2003). Studies examining the treatment response of first and second generation antipsychotics, such as fluphenazine (Correll et al., 2003), risperidone (Chang et al., 2006; Leucht et al., 2007), amisulpiride (Leucht et al., 2007), and zotepine (Lin et al., 2007, 2012), have also determined that using the first 2 week's treatment result to predict the fourth or sixth weeks' treatment outcomes was acceptable in terms of specificity, sensitivity, and predictive power. Clinical response has been defined by a 20% to 50% reduction in the scores of the Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Syndrome Scale (PANSS) (Lin et al., 2007; Kinon et al., 2010; Schennach-Wolff et al., 2010, 2011) in the research field for schizophrenia. Recently, a reduction of more than 50% of baseline PANSS scores, instead of absolute score reduction, has been suggested to define a clinically significant improvement (i.e., response) in subjects with various severity of illness such as acutely-ill and non-refractory patients (Leucht et al., 2009).

Paliperidone extended-release (paliperidone ER) is a new psychotropic medication enabling controlled delivery of the active metabolite of risperidone (Citrome, 2012). The recommended treatment dose for schizophrenia ranges from 3 to 12 mg/day (Fowler et al., 2008; Citrome, 2012). The optimal dosing strategy remains uncertain, with a starting dose having been used as 6 mg/day (Marino and Caballero, 2008; Citrome, 2012), 9 mg/day (Kramer et al., 2010), and 12 mg/day (Canuso et al., 2010) in relevant literature. Fixed dose of paliperidone 3, 6, 9, 12 or 15 mg/day have also been used in previous clinical trials (Davidson et al., 2007; Kane et al., 2007; Marder et al., 2007). These earlier 6-week trials

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suggested that fixed dose of 9 mg/day paliperidone ER, compared to 6 mg/day, has a greater completion rate (66% vs. 56%) and lower or similar dropout rate (4% vs. 7%) despite higher extrapyramidal adverse effects (25% vs. 10%) (Meltzer et al., 2008). Furthermore, the only one study using 9 mg/day as the starting dose enrolled patients with stable condition (Kramer et al., 2010). In this study, we would like to test whether 9 mg/day paliperidone would be a feasible starting dose for patients in acute exacerbation.

Remarkably, a significant improvement in the total PANSS scores has been observed on the fourth day of paliperidone ER administration in most trials (Davidson et al., 2007; Chwieduk and Keating, 2010). One recent report has shown that paliperidone ER treatment response at Week 6 could be predicted by an early response at Week 2 in hospitalized schizophrenia patients (Heres et al., 2014). However, the study was based on secondary analyses of clinical trial data which had also included subjects taking concomitant treatment with other antipsychotics and tested specifically the predictability of the Week-2 response. Whether an even earlier prediction model can be applied to Day 4 or 7 drug response remains to be determined. Previously, Riedel et al. (2005) observed a correlation between active moiety plasma levels of risperidone (risperidone plus 9-hydroxyrisperidone) and clinical responses in patients receiving risperidone treatment. In addition, despite using similar doses, the responders to risperidone treatment have been shown to exhibit significantly lower active moiety plasma levels of risperidone than did the nonresponders (Riedel et al., 2005). Paliperidone (9-hydroxyrisperidone), as a metabolite of risperidone, has similar but not identical, pharmacology and pharmacokinetics (Chue et al., 2012; Suzuki et al., 2014; Corena-McLeod, 2015). Current data on the relationship between the plasma level of paliperidone and its clinical effects after paliperidone ER treatment (Suzuki et al., 2014) are relatively fewer than that of risperidone (Lopez and Kane, 2013). Moreover, the plasma concentrations of risperidone in Taiwanese patients have been reported to be higher than those of Caucasian patients (Lai et al., 2009), suggesting a possible ethnic difference in the drug metabolism of paliperidone.

The aim of this 6-week open-labeled study was to investigate whether early symptom improvement in PANSS score reduction on Days 4, Day 7, or Day 14 after paliperidone ER treatment in patients with schizophrenia can predict their ultimate clinical response at Week 6. This study also tested whether the starting dosage of 9 mg/day of paliperidone ER was feasible in the schizophrenia patients with acute exacerbation, and evaluated the associations of paliperidone levels with clinical responses as well as adverse effects at Week 6.

2. Methods

This study was conducted at the Taipei City Psychiatric Center, Taipei City Hospital, Taiwan. It was approved by the Institutional Review Board of Taipei City Hospital before case enrollment and registered on www.clincaltrials.gov (NCT02075528).

2.1. Participants

Eligible patients admitted to an acute psychiatric ward were screened and evaluated by the researchers. Written informed consent was obtained from patients before participation. The ability to provide informed consent was first evaluated by psychiatrists other than the researchers.

The inclusion criteria were: (1) age between 18 and 65 years, (2) diagnosis of schizophrenia or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), (3) baseline total PANSS score≧60 (Chang et al., 2006; Canuso et al., 2010), (4) not having received long-acting antipsychotic injections in the preceding 6 months, and (5) no major systemic illnesses based on physical examinations and laboratory test results. The exclusion criteria were: (1) diagnoses of substance (except nicotine) dependence in the previous 6 months, (2) a medical condition that could affect absorption, metabolism, or excretion of the study drug, (3) substantial risks of suicide or violent behavior, (4) pregnancy or breastfeeding, (5) documented organic diseases of the central nervous system, (6) unstable or critical untreated medical illness, (7) history of clozapine treatment in the previous 3 months, and (8) participation in an investigational drug trial in the 30 days before screening.

2.2. Study design

The participants were assigned to receive a fixed dosage of 9 mg/day of paliperidone ER for the first 2 weeks. The paliperidone ER dosage was adjusted flexibly after 2 weeks according to the clinical judgment of the physicians in charge. The patients were allowed to use lorazepam (maximum of 4 mg/day) for insomnia or agitation, and benztropine (maximum of 6 mg/day) for managing extrapyramidal side effects. No other psychotropic agents were used during the 6-week study. The compliance and safety of participants were monitored by the research psychiatrists.

The efficacy and safety of drug were assessed by experienced researchers on Days 0, 4, 7, 14, 28, and 42. Efficacy was measured using the PANSS, Personal and Social Performance Scale (PSP) (Wu et al., 2013), and Clinical Global Impression-Severity (CGI-S). Drug safety was evaluated using routine physical and neurological examinations, laboratory tests, the Drug-Induced Extrapyramidal Symptom Scale (DIEPSS) (Kim et al., 2002; Knol et al., 2010) and the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (Knol et al., 2010). Any new event or worsening of an existing condition that required concomitant therapy to be administered as treatment was documented on an adverse-event form. Serum concentrations of 9-hydroxyrisperidone were assessed on Days 14 and 42. Venous blood was collected into an EDTA-tube and centrifuged at 3000 rpm for 15 minutes. The plasma samples were stored at −80 °C until they were assayed. Determinations of risperidone and 9-hydroxyrisperidone levels were performed using high-performance liquid chromatography (HPLC) and ultraviolet detection. The lower limit of quantification (LLQ) of HPLC was 5 ng/dL. Detailed procedures have been described elsewhere (Lai et al., 2009).

2.3. Statistical analysis

The primary endpoint was set for identifying responders and nonresponders. Responders were defined as those patients who exhibited a reduction of 50% or more in total PANSS scores after 6 weeks' treatment. The percentage of total PANSS score reduction was calculated as $(PANSS_{baseline} - PANSS_{endpoint}/PANSS_{basline} - 30)$ *100% (Leucht et al., 2009). The secondary endpoints were set for documenting changes in other clinical measurements (PANSS, CGI, PSP, DIEPSS, and UKU), and serum concentrations of 9-hydroxyrisperidone at Week 6.

At Week 6, responders and nonresponders were initially compared regarding demographic data, age of onset, and total baseline PANSS scores and subscores at Days 4, 7, and 14. The Pearson χ^2 test or Fisher exact test were used to compare categorical variables, and an independent *t* test was conducted for continuous variables. The last-observation-carry-forward (LOCF) method for the clinical rating data was applied in the analysis to provide a conservative estimate for the dropouts.

We used receiver operating characteristic (ROC) analysis

(shown in Fig. 1) to examine whether PANSS score reduction at Day 4, Week 1, and Weeks 2 could differentiate responders from nonresponders at Week 6 and thus serve as a predictor for Week-6 response (Somoza and Mossman, 1991; Perry et al., 2001; Lin et al., 2007). Then we used Youden index, which is an indicator for the balance between sensitivity and specificity, to determine the optimal cutoff score of PANSS reduction. The formula is Youden index = sensitivity (%) + specificity (%) − 1. The ROC analysis was also applied to explore the possible cutoff concentration of paliperidone at Week 2 for predicting the responder/nonresponder at Week 6.

Regarding other outcome measures, including total PANSS scores and subscale scores, DIEPSS, CGI-S, and PSP, we analyzed the changes from the baseline by using repeated-measure analysis of covariance that was adjusted for baseline variables. The correlations between pharmacokinetics and clinical outcomes or adverse effects at Week 6 were analyzed using Pearson's correlation. A p value less than 0.05 was statistically significant. All of the analyses were conducted using the SPSS software package, Version 12.0.

Table 1
Demographic data and clinical characteristics of the sample at baseline.

	Total (N=41)	Responders* (N=26)	Non-responders (N=15)	p Value*
Age (y/o)	39.98 ± 9.91	40.92 ± 9.55	38.33 ± 10.64	0.427
Female (n; %)	19 (46.3%)	11 (42.3%)	8 (53.3%)	0.495
Education years (years)	12.98 ± 2.97	12.85 ± 3.17	13.20 ± 2.68	0.718
Age of onset (age)	25.46 ± 7.71	26.46 ± 7.81	23.73 ± 7.48	0.281
Time of admission	2.63 ± 1.64	2.69 ± 1.49	2.53 ± 1.92	0.769
Height (cm)	164.02 ± 10.65	164.65 ± 10.74	162.92 ± 10.75	0.622
Body weight (kg)	64.82 ± 16.81	61.94 ± 15.46	69.80 ± 18.39	0.152
BMI (kg/m^2)	23.91 ± 4.90	22.64 ± 4.04	26.09 ± 5.59	0.028

* The p values represent the difference between responders and non-responders by independent t test.

3. Results

A total of 41 patients diagnosed with schizophrenia (n=38) or schizoaffective disorder (n=3) participated in this study. Eight patients withdrew from the study before Week 6 (completion rate 82.9%) for various reasons: exacerbation of psychotic symptoms (n=3); adverse effects of insomnia, anxiety, agitation, or extrapyramidal side effects (n=4); and subjective unsatisfactory treatment response (n=1). Regarding patients who completed the study, the final dose of paliperidone ER was 9 mg/day for 18 patients (54.5%), 12 mg/day for 11 patients (33.3%), and 6 mg/day for another 4 patients (12.1%). At the end of the study, 25 participants (75.8%) were concomitant with benzodiazepine and 17 participants (51.5%) with anticholinergic agents. The most frequent adverse effects were insomnia (29.3%), followed by restlessness (26.8%), anxiety (24.4%), dizziness (17.1%), drowsiness (7.3%), headaches (7.3%), dysmenorrhea or amenorrhea (7.3%), and palpitation (4.9%).

At the end of the study, 26 patients (63.4%) were classified as responders. As shown in Table 1, no difference in demographic data or clinical characteristics between responders and nonresponders were observed except the responders exhibited higher BMIs. Table 2 shows the comparisons of the rating scale scores between responders and nonresponders. At the baseline, the nonresponders exhibited higher positive PANSS scores and CGI-S scores (higher means more severe). No differences for the other measurements between responders and nonresponders were observed. At Week 6, the responders yielded significantly lower total PANSS scores, subscale scores, and CGI-S scores, and higher PSP scores than the nonresponders after adjusting for baseline data. Although the DIEPSS scores at Week 6 were lower in the responder group than in the nonresponder group, no difference in the UKU scores between the two groups was observed.

The ROC analysis (Fig. 1) and the Youden index were applied to determine the optimal cutoff point of score changes as a predictor for treatment response at Week 6. Table 3 summarizes the results of ROC analyses and Youden index. We found a score reduction of 8 points in the total PANSS score on Day 4 and 9 at Week 1 appeared to be able to predict the response at Week 6, with good sensitivities (81% and 92% respectively), whereas the specificities (53% and 53%) and Youden index scores (0.34 and 0.46) were low. In contrast, a score reduction of 24.5 points (27% reduction from baseline) in the total PANSS score at Week 2 yielded not only

Table 2
Comparison of rating scales between the responders and the non-responders groups at baseline and 6 weeks.

	Time	Total sample(N=41)	Responders (N=26)	Non- responders (N=15)	p Value*
PANSS total score	At baseline	90.68 ± 16.98	86.88 ± 14.83	97.27 ± 18.91	0.058
	At Week 6	61.07 ± 25.31**	46.65 ± 6.26	86.07 ± 26.54	< 0.001
PANSS-positive score	At baseline	22.44 ± 5.36	21.12 ± 4.97	24.73 ± 5.41	0.036
	At Week 6	13.34 ± 6.92**	9.42 ± 2.16	20.13 ± 7.10	< 0.001
PANSS-negative score	At baseline	23.41 ± 4.28	23.58 ± 4.44	23.13 ± 4.12	0.754
	At Week 6	16.39 ± 6.90**	13.00 ± 3.54	22.27 ± 7.42	< 0.001
PANSS-general score	At baseline	38.00 ± 8.84	36.00 ± 6.69	41.47 ± 11.09	0.098
	At Week 6	26.78 ± 10.89**	20.73 ± 2.75	37.27 ± 11.81	< 0.001
CGI-S	At baseline	4.73 ± 0.81	4.54 ± 0.76	5.07 ± 0.80	0.042
	At Week 6	3.37 ± 1.11**	2.81 ± 0.75	4.33 ± 0.98	< 0.001
PSP	At baseline	54.68 ± 10.76	55.27 ± 11.27	53.67 ± 10.09	0.652
	At Week 6	66.10 ± 9.92**	70.81 ± 5.10	57.93 ± 11.04	< 0.001
DIEPSS	At baseline	1.88 ± 2.65	1.58 ± 2.12	2.40 ± 3.40	0.406
	At Week 6	1.44 ± 3.01	0.58 ± 1.55	2.93 ± 4.22	0.021
UKU	At baseline	10.29 ± 9.43	9.42 ± 9.37	11.80 ± 9.66	0.444
	At Week 6	7.15 ± 9.97	4.92 ± 10.65	11.00 ± 7.48	0.088

Abbreviation: Positive and Negative Syndrome Scale (PANSS); Personal and Social Performance Scale (PSP); Clinical Global Impression-Severity (CGI-S); Drug-Induced Extrapyramidal Symptom Scale (DIEPSS); and the Udvalg for Kliniske Undersogelser Side Effect Rating Scale (UKU).

* The p values represent the differences of the measurements between responders and non-responder at baseline or at Week 6 (after adjustment for baseline data).

** Significant difference of these measurements between baseline and Week 6 in total samples ($p < 0.05$).

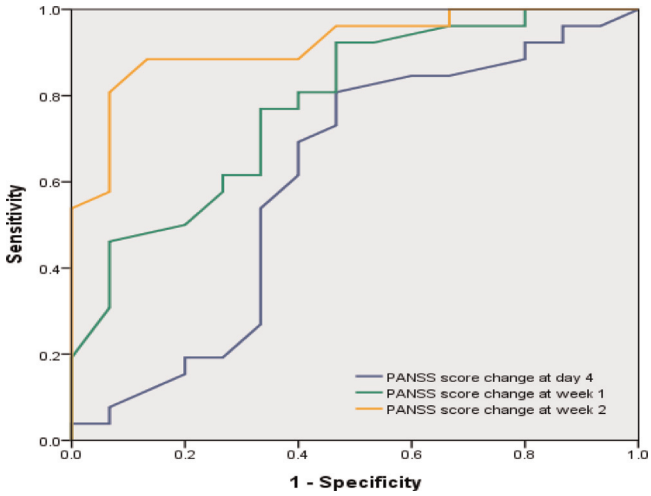

Fig. 1. ROC curve for PANSS total score change at Day 4, Week 1 and Week 2 to predict the response at Week 6.

Table 3
Prediction of responders at Week 6 using PANSS total score change at Day 4, Week 1 and Week 2.

Predictor	Cutoff point	Sensitivity	Specificity	Area under ROC curve	Youden index
Day 4	8.0	0.81	0.53	0.605	0.34
Week 1	9.0	0.92	0.53	0.778	0.46
Week 2	24.5	0.88	0.87	0.917	0.75

favorable sensitivity and specificity (88% and 87%, respectively) but also significantly high Youden index (0.75). However, when the score reduction of positive PANSS subscale scores was applied using the same method, the result was not as satisfactory as the total score reduction (data not shown).

The plasma level of 9-hydroxyrisperidone, after 2 weeks of fixed-dose paliperidone administration (9 mg/day), did not differ between responders (41.1 ± 18.2 ng/dL, $n = 23$) and nonresponders (66.7 ± 58.5 ng/dL, $n=9$) ($p=0.23$). At the endpoint (Week 6), the drug levels were also comparable between responders and nonresponders (41.6 ± 34.1 ng/dL, $n=25$ vs. 55.4 ± 22.3 ng/dL, $n=5$; $p=0.40$). Three participants did not provide blood samples and eight had dropped out from the study. Therefore, only 30 participants received the measurement of paliperidone levels at Week 6. No correlations were observed between levels of 9-hydroxyrisperidone and the scores of PANSS, CGI, PSP, DIEPSS, and UKU (data not shown). In addition, we find no association between 9-hydroxyrisperidone levels at Week 6 and changes in these rating scales. When the ROC curve was applied, very low area under ROC curve (0.377) was found under the cutoff of paliperidone concentration equaling to 7.8 ng/dL.

4. Discussion

The principal findings of this study are the early changes in total PANSS scores at Week 2 in patients with schizophrenia treated by paliperidone ER can be used to predict the ultimate response at Week 6. In addition, using 9 mg as a starting dose of paliperidone ER to treat schizophrenia during acute exacerbation appeared to be clinically feasible with a relatively favorable tolerability. We did not observe a significant correlation of plasma paliperidone (9-OH risperidone) levels with clinical outcomes or function assessment variables in this sample.

In this study, although the total PANSS score reduction on Day 4 and at Week 1 yielded satisfactory sensitivity to predict future responses, a poor specificity (around 50%) was observed. If the score reduction at Day 4 or Week 1 was used as a predictor, nearly half of the nonresponders would be misclassified as responders. By contrast, using an absolute score reduction by 24.5 points of the total PANSS score (27% reduction from baseline) at Week 2 as a predictor for treatment outcomes produced both favorable sensitivity and specificity, suggesting the clinical response at Week 2 could serve to identify responders and nonresponders at the end of this study. But we did not replicate the findings in some studies that demonstrated the reduction of positive symptoms could predict future responses (Lin et al., 2007). A Korean study (Lee et al., 2011) found that the early response of paliperidone ER treatment at Weeks 2 or 4 in patients with schizophrenia could predict subsequent responses at Week 12; however, the clinical response was only measured by CGI-S. The results from secondary analysis of paliperidone ER clinical trial data also support the Week 2 response could significantly predict final response at Week 6 (Heres et al., 2014). Likewise, previous studies on other second-generation antipsychotics suggest that early psychotic symptom reduction at Weeks 1 or 2 is a suitable predictor for future responses at Weeks 4 or 6 (Chang et al., 2006; Leucht et al., 2007; Lin et al., 2007). Thus, we propose that using the response at Week 2 rather than Day 4 or Week 1 of paliperidone ER treatment to guide the clinical decision on continuing current medication or switching to other antipsychotics is a plausible strategy. For patients discharged or leaving treatment before 2 weeks of assessment, a continued observation up to 2 weeks may be required to ascertain the early response.

Previously, a starting dose of 6 mg/day has been suggested for paliperidone ER in acute treatment of schizophrenia patients (Marino and Caballero, 2008; Citrome, 2012). Expanding on the early dose-finding studies (Davidson et al., 2007; Kane et al., 2007; Marder et al., 2007) and the only one study using 9 mg/day as a starting dose for patients in stable conditions (Kramer et al., 2010), we determined to use 9 mg/day as the starting dose to treat patients with acute exacerbation. Interestingly, the baseline PANSS total and CGI scores of the responders in our study were lower than those of the nonresponders (as shown in Table 2), suggesting a possibility that less severely ill patients might respond better to paliperidone with a starting dose of 9 mg/day. Although 4 participants withdrew from our study because of adverse effects (two due to intolerable extrapyramidal side effects) and 3 patients reported hyperprolactinemia-related adverse events, most of the side effects appeared tolerable. The completion rate in this study is comparable to previous studies using paliperidone ER to treat schizophrenia (Meltzer et al., 2008; Lee et al., 2011. Arakawa et al., 2008) estimated that the D2 receptor occupancy of 9 mg of paliperidone ER was between 70% and 80%, which lay within the optimal therapeutic range of antipsychotics proposed in previous studies (Nordstrom et al., 1993; Kapur et al., 2000; Nord, Farde (2011). Recently, Canuso et al. (2010) indicated that a higher starting dose of paliperidone ER (12 mg/day), compared with 6 mg/day, was more effective despite with a similar tolerability in patients with schizoaffective disorder. However, it has been noted that higher doses paliperidone (≧9 mg/day) may be associated with higher rates of extrapyramidal symptom side effects (Meltzer et al., 2008). In our study half of the participants had received anticholinergic agents. Collectively, these observations support the benefit and safety profile of using 9 mg/day of paliperidone ER as an initial dose followed by a flexible adjustment of dosage after 2 weeks to manage acute exacerbation in patients with schizophrenia, but clinicians should be cautious about the occurrence of extrapyramidal side effects.

Paliperidone has been suggested to yield a similar therapeutic range as risperidone, and the blood levels of paliperidone in

patients demonstrating increased clinical improvement were reported to be approximately 20–52 ng/mL (25th–75th percentiles) (Nazirizadeh et al., 2010). In the current study, both responders and nonresponders exhibited a comparable range of paliperidone levels at Week 2 (e.g. 27.0–54.4 ng/dL and 27.0–92.0 ng/dL). In addition, the drug levels were neither correlated with the rating scales scores nor the changes in these scores at Week 6. These findings seem not favoring a link between blood levels of paliperidone and clinical outcomes (good or poor response). In fact, existing findings in literature regarding the associations between clinical response and plasma levels of risperidone and its metabolites are inconsistent. Riedel et al. (2005) observed a correlation between the plasma level of risperidone's active moiety and clinical response, in which responders exhibited low plasma levels. However, other studies have not observed this correlation (Spina et al., 2001). Similarly, our previous report determined no association between levels of the active moiety and the total PANSS or subscale scores in subjects receiving long-acting risperidone injections (Lai et al., 2009). We believe more studies with a larger number of subjects are needed to evaluate the clinical significance of the pertinent pharmacokinetic data.

The strength of this study is that we adopted a more stringent criteria to define the responder (i.e., a 50% or more reduction of total PANSS score) (Chen et al., 2009; Leucht et al., 2009). In addition, although ROC curve is not a prediction model, optimal cutoff point could maximize the changes of PANSS scores at Week 2 as a predictor via balancing errors and correct judgment for final response at Week 6 Somoza and Mossman (1991). However, some limitations should be considered. First, this was an open-labeled study, which might have influenced the objectivity of raters. Second, only 41 patients were enrolled in this study, which was a small sample size compared with that of previous studies on early prediction models. However, the results of this study revealed comparable predictive power with these studies (Chang et al., 2006; Lin et al., 2007). Third, because the dose of paliperidone ER was fixed for the first two weeks, it is possible some patients require a dose lower than 9 mg/day, thereby with a lower blood level of paliperidone, to achieve clinical improvement. So our results cannot be generalized to patients who receive dose adjustment flexibly. Fourth, the clinical significance of absolute PANSS score reduction might vary between patients exhibiting different baseline severity (Mortimer, 2007). The average total PANSS score of our patient group was 90.68 ± 16.98, which indicates a substantial severity of schizophrenia. The cutoff score obtained from this study might be unsuitable for patients whose baseline severity lies within other score ranges. Fifth, we defined clinical response according to score reduction at Week 6, but the duration required for determining the response remains undetermined and response is in fact not equal to remission. Previous evidences suggest that early improvement is a predictor of response and remission at discharge with various duration of hospitalization in the treatment of schizophrenia (Jäger et al., 2009; Schennach-Wolff et al., 2011). Higher disorganization symptoms may also be negatively associated with remission (Ortiz et al., 2015). Whether early response to paliperidone treatment would be a predictor for remission in the long run should be examined in future studies.

In conclusion, this study supports the early prediction model of clinical response in schizophrenia patients treated with paliperidone ER, and the first 2 weeks might be an adequate time for predicting future responses. Using 9 mg/day of paliperidone ER as an initial dose for schizophrenia treatment exhibited relatively favorable tolerability and feasibility. No association between paliperidone levels and measurements of clinical responses and adverse effects was observed in this study. Additional studies investigating the prediction model of remission, adequate dosing strategy, and sequential effects of hyperprolactinemia in schizophrenia patients treated with paliperidone ER are warranted.

Author contribution

The author's responsibilities were as follows: MCH, CJT and CCC designed the study design and performed the data analysis; all the authors recruited the participants, collected the blood samples, and assisted with the editing of the manuscript; and ECY, MCH and CCC wrote the first draft and finalized the manuscript. All authors participated in the analytic discussion of the results and approved the final version of the manuscript.

Conflict of interest

Dr Chiu CC has received a research grant from Janssen-Cilag Taiwan, Taipei; Johnson & Johnson Corporation, Taipei to conduct this study. Johnson & Johnson Corporation is the parent company of Janssen Pharmaceuticals which markets Paliperidone ER. They did not involve the study design, case enrollment, data analysis and manuscript preparation. Other Drs do not have personal affiliations or financial relationships with any commercial interests related to the article to disclose.

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