Risperidone Long-Acting Injection (RLAI): The 12-Week Efficacy and Tolerability in Thai Patients with Chronic Schizophrenia

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Background: *Although oral atypical antipsychotics have improved the outcomes in schizophrenia, the patient medication adherence plays role as the important factor to clinical potential of the drugs. Therefore, the long-acting formulations of antipsychotics have been developed to improve the treatment compliance in patient with schizophrenia and risperidone long-acting injection (RLAI) is the first long-acting injectable drug since then.*
Objective: *To evaluate the efficacy and tolerability of long-acting risperidone injection in Thai patients with chronic schizophrenia for 12 weeks treatment.*
Material and Method: *This was a non-randomized, open-label, single-arm study, performed at 5 centers in Thailand. The eligible patients with schizophrenia diagnosed by DSM-IV criteria were enrolled. Patients received long-acting risperidone injection 25, 37.5 or 50 mg every 2 weeks. Efficacy assessments were measured by Manchester Psychiatric Rating Scale (MPS), CGI-S and SF-36 at baseline, week 6 and week 12 or end point visit. Tolerability assessments were measured by Yale Extrapyramidal Symptoms Rating Scale (YESS), Visual analogue scale 10-cm for pain at injection site, body weight (BW) and incidence of adverse events.*
Results: *Of 184 patients recruited, 160 patients (87%) completed the study. RLAI produced a significant improvement ($p < 0.001$) in MPS positive score from baseline to endpoint, 4.4 ± 3.7 to 1.6 ± 2.6. There was also significant reduction in MPS negative score, from 3.06 ± 2.68 to 0.93 ± 1.61 at endpoint ($p < 0.001$). The CGI-S score improved significantly from baseline to end point ($p < 0.001$), as reflected by the increase the proportion of patients rated as "not ill" or "borderline ill" from 5.9% at baseline to 53.2% at endpoint. Quality of life measured on the SF-36 scale was improved in all domains except bodily pain. Movement disorders, measured by YESS, were significantly reduced following RLAI introduction. Treatment with this drug was well tolerated and no significant weight gain occurred during the study.*
Conclusion: *This study suggests that RLAI produces symptomatic improvement in chronic schizophrenia patients, along with improvement of movement disorders and had a good tolerability and adherence to treatment.*

Keywords: *Risperidone long acting injection, Schizophrenia, Thai*

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Schizophrenia continues to be a devastating and costly disease, despite recent advances in treatment. People with schizophrenia have psychotic episodes characterised by delusions, hallucinations, unusual thought content, aggression and excitement, which often result in hospitalisation. However, other symptoms that may continue during periods of relative wellness create much of the disability associated with the disease. Declining social and occupational functioning is an extension of such symptoms as poor executive functioning, restricted affect and poverty of speech, disorganisation and lack of motivation,

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cognitive impairment, and poor self-care. These symptoms are often called negative symptoms and are an important focus of new drug development. While classical neuroleptics suppress and control positive symptoms of schizophrenia, there is no clear evidence from controlled studies that they are effective for ameliorating the negative symptoms of schizophrenia, such as alogia, affective flattening, anhedonia or asociality, depressed appearance, avolition or apathy, psychomotor retardation and attention impairment[1].

The atypical antipsychotics like risperidone have been shown not only to be effective for suppressing positive symptoms but have improved efficacy on negative symptoms as well[2]. But non-compliance is still very common among patients with schizophrenia or other psychotic disorders and is a frequent cause of relapse.

In Thailand, lifetime prevalence of schizophrenia is 0.17%[9] and non-compliance rate is about 54%[10]. The non-compliance to treatment medication can lead to increasing risk of relapse, rehospitalization, suicidal thinking, length of hospitalization stay and cost of treatment[11]. The long-acting injection delivery system was developed to improve this problem. Even the risperi-done long-acting injection (RLAI) is available in Thailand for many years, the local efficacy and safety data have not been established. Therefore, this study is conducted with aiming to reveal the efficacy and tolerability of RLAI in the treatment of schizophrenia in Thailand.

Material and Method

Patients

There eligible 210 patients both inpatients and outpatients were required from 5 centers in Thailand that were approved by Ethic Committee (EC) at each center. This study was restricted to the patients above 18 years of age who had been diagnosed with Schizophrenia by DSM-IV criteria, chronically. The patients who have just started pharmacological antipsychotic treatment with unstable medical condition, had the history of tardive dyskinesia, neuroleptic malignant syndrome (NMS) and known history of risperidone allergic were excluded from this study. Oral risperidone had been used for drug sensitivity testing during run-in period (3 days).

By protocol and investigator judgment, patients were switched from their previous anti-psychotic medication to flexible-dose treatment with 25, 37.5 or 50 mg of RLAI given by intramuscular gluteal injection every two weeks for three months. While other psychotropic medications for sleep induction or sedation had to be remained stable. Anticholinergic medication had continued up to eight weeks and then be tapered off at the discretion of the investigator.

Efficacy assessments

The efficacy was assessed by Clinical Global Impression Severity Scale (CGI-S)[12] to assess overall change in clinical status and Manchester Psychiatric Rating Scale (MPS). Psychiatric rating scale is the simple 5-point scale using for assessment of clinical thera-peutic progression of chronic psychotic patients[13].

Health-related quality of life assessment

HRQoL was measured using the Medical Outcomes Study Short Form 36-item questionnaire (SF-36) Thai version[14]. The SF-36 consists of 8 domains that assess the following: bodily pain (BP), general health, general mental health, physical functioning, role emotional, role physical, social functioning and vitality[15].

Safety assessment

The safety was evaluated at baseline, 6-week and 12-week visit by Yale Extrapyramidal Symptoms Rating Scale (YESS), an eight-item with easy-to administer scale for assessing emergence, severity and type of side effects that commonly occur during acute treatment[16]. The pain at injection site was measured using Visual Analogue Scale (VAS). For bodyweight and descriptive report of adverse events were assessed at every schedule visits for the entire study period.

Statistics

Data analysis was done regarding to intention-to-treat (ITT) principle using last-observation-carried-forward (LOCF) analysis with respect to end point visits. The MPS, CGI-S, SF-36 and YESS mean scores at each visit were analysed to determine changes from baseline to endpoint using the general linear model for repeated measure ANOVA tests of within subject effects at the 5% significance level and adjusted multiple comparisons by Bonferroni.

Results

Patient demographics

A total of 184 patients were recruited in the study and received at least one dose of long acting

risperidone microspheres. The demographic patient data were tabulated in Table 1.

The 86.4% of enrolled patients completed the 3 months study period with twenty-four patients dropped out. The most common reason for discontinuation were adverse events and lost to follow-up (Table 2). All patients received 25-mg RLAI as the initial dose and at the second week, there were 37 patients who increased the dose to 37.5 mg (20.1%). At end point, 35.22% of patients were receiving the 25 mg dose, whereas 30.19% and 34.59% were receiving 37.5 mg and 50 mg, respectively.

Table 1. Baseline demographic and clinical characteristics

Characteristics (n = 184)	n (%)
Age (mean ± SD), years; range 18-56 years	32.23 ± 9.81
Sex	
Male	127 (69.0)
Female	57 (31.0)
Race	
Thai	181 (98.4)
Thai-Chinese	2 (1.1)
Thai-India	1 (0.5)
Diagnosis	
Schizophrenia	175 (95.1)
Schizoaffective disorder	9 (4.9)
Schizophrenia type	
Paranoid	100 (54.3)
Disorganized	55 (29.9)
Undifferentiated	11 (6.0)
Residual	6 (3.3)
No specified	12 (6.5)
Clinical course	
Continuous	91 (49.5)
Episodic with residual	57 (31.0)
Episodic no residual	17 (9.2)
Single episode with partial remission	11 (6.0)
Single episode with full remission	2 (1.1)
Unspecified	3 (1.6)
Missing	3 (1.6)
Baseline MPS total score (mean ± SD), range 0-21	8.74 ± 5.14
Baseline body weight (mean ± SD), range 47-103	64.57 ± 13.26

Table 2. Reasons for treatment discontinuation

	RLAI patients (n = 184)
Discontinued, n (%)	24 (13.0%)
Reason, n (%)	
Adverse event	8 (4.3%)
Lost to follow-up	8 (4.3%)
Insufficient response	3 (1.6%)
Serious adverse event	1 (0.5%)
Any reason	4 (2.2%)

Efficacy

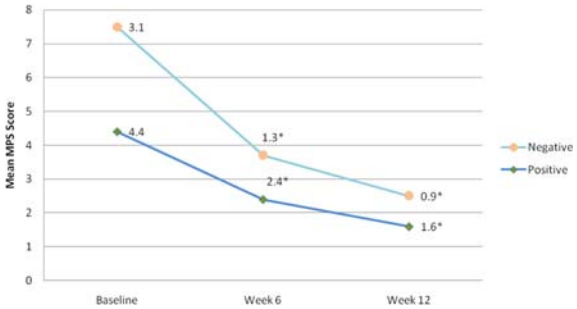
At baseline the mean MPS total score was 7.5 ± 6.5; mean positive score was 4.4 ± 3.7; mean negative score was 3.1 ± 2.8. A significant improvement was apparent after 6 weeks of treatment and further improvements were observed with continued treatment during the 12 weeks of the study (Fig. 1). Significant improvement ($p < 0.001$) in MPS positive score was shown 4.4 ± 3.7 at baseline to 1.6 ± 2.6 at endpoint. There was also significant reduction in MPS negative score, 3.06 ± 2.68 at baseline to 0.93 ± 1.61 at endpoint ($p < 0.001$).

There was an overall improvement in health-related quality of life during the 12-week treatment period, with significant improvements from baseline to endpoint reported for all factors of the SF-36 (55.38 to 66.90, $p < 0.01$). Clinically significant improvements that defined by at least 5 points improvement from baseline[17], were observed for all area of SF-36 questionnaire except Bodily Pain (-4.98 points), as shown in Table 3 and Fig. 3.

For CGI-S, there was a significant improvement from baseline (2.944) to endpoint (0.959, $p < 0.001$) following to RLAI introduction (Fig. 2). The proportion of patients rated as 'not ill' or 'borderline ill' increased from 5.9% at baseline to 53.2% at endpoint.

Tolerability and safety

Totally 68 adverse event episodes had been reported for the entirely study duration. But only 35



* p-value < 0.001 when comparing to baseline

Fig. 1 Positive and negative subscale of MPS at baseline, week 6 and week 12 (endpoint)

Table 3. Mean change of SF-36 score from baseline to 12-week (mean ± SE)

	Physical functioning	Role physical	Role emotional	Vitality	Emotional well-being	Social functioning	Bodily pain	General health
Baseline	66.26 ± 1.99	40.66 ± 3.24	34.60 ± 3.19	52.69 ± 1.52	57.81 ± 1.66	61.23 ± 2.28	77.50 ± 1.82	52.28 ± 1.74
Week 12	72.04 ± 2.17	56.80 ± 3.40	53.38 ± 3.53	62.92 ± 1.43	69.17 ± 1.57	73.73 ± 1.89	82.48 ± 1.59	64.71 ± 1.54
Mean pair difference	-5.79 ± 2.18	-16.14 ± 4.04	-18.78 ± 3.86	-10.23 ± 1.81	-11.36 ± 1.80	-12.50 ± 2.25	-4.98 ± 2.02	-12.44 ± 1.80
p-value	.009	.000	.000	.000	.000	.000	.015	.000

Fig. 2 Clinical global impression scale (CGI-S) at baseline and week 12 (endpoint)

** p-value < 0.05 and * p-value, 0.001

Fig. 3 Clinically significant improvements in 8 domains of SF-36 questionnaire from baseline to week 12 (endpoint)

* p-value < 0.001 when compared with baseline

Fig. 4 Mean YESS scores by domain at each visit

adverse event reports that investigator judged the relationship to the RLAI treatment as possible, probable and very likely (Table 4). The movement disorders were evaluated by YESS score at screening, baseline, week 6 and week 12. The YESS score improvement had been

shown at week 6 for parkinsonian, akathisia and total YESS scores (Table 5). The improvements have been prolonged until week 12 for total YESS score as shown in table 6 and Fig. 4.

Table 4. Adverse events that relating to the RLAI treatment

Event	n (%)
Extrapyramidal symptoms	9 (4.9%)
Insomnia	6 (3.2%)
Agitation	4 (2.1%)
Vomiting	2 (1.0%)
Euphoria	2 (1.0%)
Headache	1 (0.5%)
Nausea	1 (0.5%)
Irritable mood	1 (0.5%)
Aggression	1 (0.5%)
Myalgia	1 (0.5%)
Auditory hallucination	1 (0.5%)
Seizure	1 (0.5%)
Paranoid	1 (0.5%)
Galactorrhea	1 (0.5%)
Body weight increased	1 (0.5%)
Sexual dysfunction	1 (0.5%)
Dizziness	1 (0.5%)

** Only the AE reports that relating to the RLAI treatment by investigator judgment including possible, probable and very likely

The patients experienced small changes in body weight or BMI during the study. Mean body weight and BMI at baseline and endpoint were 62.7 $\pm$ 13.8 kg and 20.5 $\pm$ 0.5 kg/m^2 and 65.5 $\pm$ 12.96 and 21 $\pm$ 0.2 kg/m^2, respectively. A mean body weight increased of 1.7 $\pm$ 0.6 kg. Little pain at the injection site was reported by the patients, and the pain ratings score decreased during the trial. The mean score on the 10-cm visual analogue scale was 3.67 $\pm$ 2.68 at the first injection and 2.74 $\pm$ 2.55 at the 7th injection, end of study visit. Neither redness nor swelling was reported at injection site.

Concomitant medications

Concomitant medications data were obtained from 66.85% of the patients during the trial with 37.4% anticholinergic drugs, 50% sedatives (*e.g.*, diazepam, lorazepam). The anticholinergic drug utilization was lower during the period of treatment, 46.9% at baseline to 37.4% at end point.

Discussion

In this 12-week study, the data demonstrated that the chronic schizophrenia patient achieved the significant clinical improvement including quality of life when their current antipsychotic therapy was switched to risperidone long-acting injection (RLAI).

The significant improvements were observed for overall psychotic symptoms (MPS total score).

Table 5. Descriptive YESS score by domain (mean $\pm$ SD)

	Parkinsonian	Akathesia	Dystonia	YESS total score
Screening	2.79 $\pm$ 2.905	0.18 $\pm$ 0.666	0.02 $\pm$ 0.155	2.99 $\pm$ 3.063
Baseline	2.47 $\pm$ 2.656	0.12 $\pm$ 0.489	0.01 $\pm$ 0.110	2.60 $\pm$ 2.705
Week 6	0.90 $\pm$ 1.550	0.12 $\pm$ 0.632	0.01 $\pm$ 0.078	1.02 $\pm$ 1.765
Week 12	0.60 $\pm$ 1.473	0.06 $\pm$ 0.299	Zero	0.65 $\pm$ 1.158

Table 6. Mean change of total YESS score, comparing between visits

	Visit							
	Week 6				Week 12			
	Parkinsonian	Akathesia	Dystonia	Total	Parkinsonian	Akathesia	Dystonia	Total
Mean change from baseline	1.571*	1.871*	0.000	1.577*	0.061	0.006	0.012	1.945*
Standard deviation (SD)	2.354	2.440	0.676	2.509	0.529	0.136	0.110	2.483
p-value	0.000	0.000	1.000	0.000	0.141	0.565	0.158	0.000

* Statistically significant

Additionally, significant improvements were observed in both positive and negative domains ($p < 0.001$).

In addition, CGI-S ratings showed a substantial increase in the number of patients rated as not ill or borderline after treatment with RLAI (5% at baseline to 53% at endpoint). The clinical improvement that has been revealed in this study is comparable with the result in previous studies with risperidone long acting injectable, as measured by CGI-S[5,8,18-20].

For the health-related quality of life in schizophrenia patients, the result is quite similar as previous studies[5]. The values for role emotional, physical functioning, general health, vitality, social functioning and mental health were significantly different from baseline ($p < 0.01$). The additional SF-36 domain that significantly different in this study is role physical that differ from Gastpar study[5] from the other 12-week treatment of RLAI, Nasrallah HA et al[15], the significantly improved domains were quite similar with this study, except bodily pain improvement.

The incidence of adverse events is quite lower (36.9%) when compared with the short-term studies, 52%-84%[6,19-22]. While the proportion of discontinuation patients due to adverse events (4.3%) was similar with the previous studies, 1-16%[6,19-22]. For movement disorders, as measured by YESS, were significantly reduced following the change from previous antipsychotic medication to RLAI with the reduction of anticholinergic prescription at the end of the study. Referring to Mazure study, the YESS rating scale was used to measure symptoms of Parkinson's disease and akathisia[16]. There are not well-established the data for this scale in the long-acting antipsychotic used patients. In the other hand, the Extrapyramidal Symptom Rating Scale (ESRS) was used in many studies[5-7,18-20]. However, the outcome from this study and other international studies that used ESRS scale are quite the same, *i.e.* the RLAI decreased the Parkinsonism symptoms significantly. Even, the extrapyramidal is the most common and concern side effect, only 5.43% of patients reported EPS in the study.

As in other long-acting risperidone short-term studies[8,19-20,22], the patients experienced weight gain. The range of mean weight gain are 0.4-2.3 kilograms, the current report is in the mentioned range (1.7 ± 0.6 kg). The similar reports for little injection-site pain were displayed in this study and Kane et al studies, the patients rated as low throughout the study and diminished from first injection to the last in all treatment groups[6]. This is contrasting with the conventional depot antipsychotic injection, *i.e.* associated with pain, bleeding, hematoma, and other injection-site reactions[23,24].

The overall common adverse events are quite low when comparing to previous studies[6,20], that reported adverse event for headache 20-25%, insomnia 15-17%, agitation 15-22%, psychosis 12% and anxiety 9%. Furthermore, while the previous studies reported the headache is the most common side effect but this study present the insomnia, agitation, vomiting and headache, respectively.

The finding that 87% of patients completed the trial is in contrast to lower completion rates regarding to Kane et al[6] and Lauriello et al[20] but comparable with Lindenmayer et al[19], Lasser RA et al[18] and Chue et al[8].

In conclusion, this data suggest that significant clinical benefits follow a switch to long-acting risperidone (RLAI), even in symptomatically chronic schizophrenia patients and mostly of schizophrenia patients had sustained improvement of positive and negative symptoms significantly. Patients' quality of life improved particularly in role physical and emotional function, social function and general health. Risperidone long acting injectable also showed a good safety and tolerability profile. No greater incidence of extrapyramidal side effect than with previous antipsychotics and anticholinergic drugs usage was lower from baseline. The patient withdrawal from the study due to adverse events was only 4.3%, weight gain less than 2 kilograms in 12 week, mildly painful at injection and fewer adverse events had been reported. These finding support the favorable clinical profile of risperidone long-acting injectable in Thai schizophrenic patients.

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การศึกษาประสิทธิภาพ และความทนต่อยาของของริสเพอริโดนชนิดออกฤทธิ์เนิ่นแบบฉีดเป็นระยะเวลา 12 สัปดาห์ ในผู้ป่วยโรคจิตเภทชาวไทยซึ่งมีอาการเรื้อรัง

สุวรรณา อรุณพงค์ไพศาล, มานิต ศรีสุรภานนท์, รณชัย คงสกนธ์, กนกวรรณ กิตติวัฒนากูล, อำไพขนิษฐ สมานวงศ์ไทย

ภูมิหลัง: *แม้ว่ายารักษาโรคจิตเภทกลุ่มใหม่ชนิดรับประทานจะมีผลการรักษาที่ดีขึ้น หากแต่การให้ความร่วมมือในการรับประทานยายังคงเป็นปัจจัยสำคัญที่ส่งผลต่อผลการรักษา ดังนั้นจึงมีการพัฒนายารักษาโรคจิตเภท ชนิดออกฤทธิ์เนิ่นแบบฉีดขึ้นเพื่อที่จะแก้ไขปัญหาเรื่องความร่วมมือในการรักษาของผู้ป่วย และยาริสเพอริโดนเป็นยารักษาโรคจิตเภทกลุ่มใหม่ชนิดแรกที่ถูกพัฒนารูปแบบการนำส่งยาเป็นแบบออกฤทธิ์เนิ่นชนิดฉีด*

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพ และความทนต่อยาของของริสเพอริโดนชนิดออกฤทธิ์เนิ่นแบบฉีด เป็นระยะเวลา 12 สัปดาห์ ในผู้ป่วยโรคจิตเภทชาวไทยซึ่งมีอาการเรื้อรัง*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาแบบเปิด ชนิดขาเดียว ไม่มีการสุ่ม ทำในศูนย์การศึกษาจำนวน 5 แห่งในประเทศไทย โดยมุ่งการศึกษาในผู้ป่วยซึ่งเป็นโรคจิตเภทตามเกณฑ์ของ DSM-IV ผู้ป่วยได้รับริสเพอริโดน แบบออกฤทธิ์เนิ่น ชนิดฉีดขนาด 25, 37.5 หรือ 50 มิลลิกรัม ทุก ๆ 2 สัปดาห์ การประเมินประสิทธิภาพของการรักษาใช้มาตรวัด ดังต่อไปนี้คือ Manchester Psychiatric Rating Scale (MPS), CGI-S, และ SF-36 โดยประเมินที่ค่าพื้นฐานสัปดาห์ที่ 6, สัปดาห์ที่ 12 หรือ เมื่อสิ้นสุดการศึกษา นอกจากนี้ยังมีการประเมินความทนต่อยา โดยใช้มาตรวัดคือ Yale Extrapyramidal Symptoms Rating Scale (YESS) ประเมินความเจ็บปวดบริเวณที่ฉีดยาโดยใช้ Visual analogue scale บันทึกน้ำหนักตัวของผู้ป่วย และเหตุการณ์ไม่พึงประสงค์ที่เกิดขึ้นระหว่างดำเนินโครงการ*

ผลการศึกษา: *จากข้อมูลผู้ป่วยที่เข้าร่วมการศึกษาจำนวน 184 ราย มีจำนวนผู้ป่วยที่เข้าร่วมการศึกษาจนเสร็จสมบูรณ์ จำนวน 160 คน (ร้อยละ 87) โดยที่ยาริสเพอริโดนแบบออกฤทธิ์เนิ่นชนิดฉีดสามารถปรับปรุงคะแนน MPS positive จากค่ามาตรฐานเฉลี่ย 4.4 $\pm$ 3.7 เป็น 1.6 $\pm$ 2.6 ที่จุดยุติอย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) อีกทั้งยังสามารถลดคะแนน MPS negative จากค่ามาตรฐานเฉลี่ย 3.06 $\pm$ 2.68 เป็น 0.93 $\pm$ 1.61 อย่างมีนัยสำคัญทางสถิติเช่นกัน ($p < 0.001$) นอกจากนั้นคะแนนการประเมิน CGI-S มีการปรับปรุงอย่างมีนัยสำคัญทางสถิติ ($p < 0.001$) เมื่อเทียบระหว่างสัดส่วนของประชากรที่ถูกประเมินว่า "ไม่มีความเจ็บป่วยเลย" หรือ "มีความเจ็บป่วยเล็กน้อย" จากค่าพื้นฐานเฉลี่ยร้อยละ 5.9 เป็นร้อยละ 53.2 ที่จุดยุติ ส่วนผลการประเมินคุณภาพชีวิตโดยใช้แบบทดสอบชนิดย่อ 36 ข้อ (SF-36) พบว่ามีการปรับปรุงอย่างมีนัยสำคัญทางสถิติในทุก ๆ ส่วนของแบบสอบถาม ส่วนการประเมินด้านความผิดปกติของการเคลื่อนไหวโดยใช้ YESS scale พบว่าลดลงอย่างมีนัยสำคัญทางสถิติเมื่อเปลี่ยนมาใช้ยาริสเพอริโดนแบบออกฤทธิ์เนิ่นชนิดฉีด และไม่พบการเพิ่มขึ้นของน้ำหนักอย่างมีนัยสำคัญทางสถิติระหว่างการศึกษา*

สรุป: *การศึกษาแบบครั้งนี้แสดงให้เห็นว่าริสเพอริโดนชนิดฉีดออกฤทธิ์เนิ่น ทำให้ทำให้อาการของผู้ป่วยโรคจิตเภท และความผิดปกติของการเคลื่อนไหวดีขึ้น และแสดงให้เห็นว่าผู้ป่วยทนต่อยาได้ดี และให้ความร่วมมือในการรักษาด้วยวิธีนี้*