RESEARCH ARTICLE

Clinical Effectiveness, Quality of Life and Costs of Treatment in Transfusion-Dependent Thalassemia Patients Undergoing Iron-Chelating Therapy; Deferiprone

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Abstract

A major complication of long-term blood transfusion in thalassemia patients is a serious iron overload. Excessive iron deposits in major organs and eventually results in organ damage. Deferiprone (DFP) is an effective oral iron chelator that promotes iron excretion and prevents the progression of iron accumulation assessed by serum ferritin levels. To evaluate the overall impact of DFP in transfusion-dependent thalassemia patients, this study aimed to determine the clinical effectiveness, health-related quality of life (HRQOL) and treatment costs of DFP. A cross-sectional study was conducted among 50 transfusion-dependent thalassemia patients who received DFP at Maharaj Nakorn Chiang Mai Hospital. The data of clinical effectiveness and costs of treatment were collected from the questionnaire and retrospectively reviewed over a 12-month period from medical records and hospital database. HRQOL was assessed by using the questionnaire, EQ-5D-3L (Thai version). The result showed the mean serum ferritin level (µg/L) at baseline and final level of 1367±935 and 1386±541, respectively. The mean EQ-5D-3L and VAS scores were 0.80±0.16 and 81.9±14.0, respectively. The adherence to treatment was found to be poor and the common adverse events reported were headache, back pain, arthralgia, fever, elevated liver enzyme, nausea/vomiting, abdominal pain and diarrhea. The total annual direct costs of treatment were estimated to be 54,000 Thai Baht (THB)/patient. In conclusion, DFP was effective in maintaining serum ferritin level in transfusion-dependent thalassemia patients with reasonable costs of treatment. Although patients' HRQOL assessments were favorable, adherence to treatment was poor with more adverse events reported.

Keywords: deferiprone, iron-chelating therapy, clinical effectiveness, quality of life, costs of treatment

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ประสิทธิผลทางคลินิก คุณภาพชีวิต และต้นทุนการรักษาในผู้ป่วยธาลัสซีเมียที่พึ่งพาการรับเลือดและได้รับยาขับเหล็กดีเฟอริโพรน

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บทคัดย่อ

ผู้ป่วยธาลัสซีเมียที่ต้องได้รับการเติมเลือดมาเป็นเวลานานนั้น จะส่งผลให้เกิดภาวะเหล็กเกินตามมา ธาตุเหล็กที่เกินนี้จะไปสะสมและทำให้เกิดความเสียหายต่ออวัยวะสำคัญต่างๆ ดีเฟอริโพรนเป็นยาขับเหล็กชนิดรับประทาน ซึ่งจะช่วยป้องกันการสะสมของธาตุเหล็กในร่างกายได้ ดังนั้น เพื่อประเมินผลโดยรวมของการรักษาด้วยยาดังกล่าวต่อผู้ป่วยธาลัสซีเมียที่พึ่งพาการรับเลือด งานวิจัยนี้จึงมีวัตถุประสงค์เพื่อศึกษาประสิทธิผลทางคลินิก คุณภาพชีวิตที่เกี่ยวกับสุขภาพ และต้นทุนการรักษาของยาดีเฟอริโพรน โดยทำการศึกษาแบบภาคตัดขวาง ในผู้ป่วยจำนวน 50 ราย จากโรงพยาบาลมหาราชนครเชียงใหม่ เก็บข้อมูลประสิทธิผลทางคลินิกและต้นทุนการรักษาจากการสืบค้นประวัติการรักษาย้อนหลัง 12 เดือนและจากแบบสอบถาม ทำการประเมินคุณภาพชีวิตที่เกี่ยวกับสุขภาพโดยใช้แบบสอบถาม EQ-5D-3L (ฉบับภาษาไทย) ผลจากการศึกษาพบว่าผู้ป่วยมีระดับซีรั่มเฟอริตินเฉลี่ยตั้งต้น 1367±935 µg/L และครั้งล่าสุด 1386±541 µg/L มีคะแนนเฉลี่ย EQ-5D-3L และ VAS เป็น 0.80±0.16 และ 81.9±14.0 ตามลำดับ ผู้ป่วยส่วนใหญ่รับประทานยาไม่สม่ำเสมอ เหตุการณ์ไม่พึงประสงค์ที่พบ ได้แก่ ปวดหัว ปวดหลัง ปวดข้อ และระดับเอนไซม์ตับเพิ่มขึ้น เป็นต้น ผลรวมต้นทุนทางตรงของการรักษาประมาณ 54,000 บาท/คน/ปี ผลการศึกษานี้แสดงให้เห็นว่า การใช้ยาดีเฟอริโพรนในผู้ป่วยกลุ่มนี้มีประสิทธิผลในการรักษาระดับซีรั่มเฟอริตินไม่ให้เพิ่มสูงขึ้น มีต้นทุนการรักษาที่สมเหตุสมผล ผู้ป่วยมีคุณภาพชีวิตที่เกี่ยวกับสุขภาพค่อนข้างดี อย่างไรก็ตาม ผู้ป่วยส่วนใหญ่รับประทานยาไม่สม่ำเสมอ และมีรายงานเหตุการณ์ไม่พึงประสงค์ค่อนข้างมาก

คำสำคัญ: ดีเฟอริโพรน, ยาขับเหล็ก, ประสิทธิผลทางคลินิก, คุณภาพชีวิต, ต้นทุนการรักษา

Introduction

Thalassemia is a group of genetic blood disorders characterized by a deficiency in the synthesis of either α or β globin chain(s) during the synthesis of hemoglobin (Hb) tetramers. Abnormal Hb reduces supply of oxygen-carrying Hb within erythrocytes and leads to hemolytic anemia. The severe forms of thalassemia are β thalassemia major and β thalassemia/HbE disease. Due to ineffective erythropoiesis and severe hemolysis, these patients present with severe anemia since their childhood. They require regular blood transfusion to prolong their life as well as to improve their growth and development.[1,2] Thalassemia patients who become transfusion-dependent consequently receive excess iron from each blood transfusion. Since the body is unable to excrete the excess iron, accumulation of iron in major organs such as heart, endocrine grands and liver will result in organ damage and dysfunction.[3,4] The major cause of mortality and morbidity associated with thalassemia are a consequent of iron overload. Therefore, iron-chelating therapy (ICT) is clinically indicated to remove the excess systemic iron. Currently, there are 3 approved iron chelators available in Thailand. The first is deferoxamine (DFO) available in parenteral forms for subcutaneous or intravenous administration. In addition to prolong infusion time over 8-12 hours and frequent administration of 5-7 days per week, the cost of this drug is high and the patients' compliance is poor. To resolve these limitations, oral iron chelators are preferred. Deferasirox (DFX) is a once-daily oral iron chelator that appears to have excellent efficacy with acceptable tolerability profiles.[5] Due to its highest cost among 3 iron chelators, the use of DFX is limited in Thailand.

Deferiprone (DFP) is an effective second-line oral iron chelator with lower cost. It is given 3 times daily and required close monitoring for its adverse events; agranulocytosis, neutropenia, arthralgia and elevated liver enzymes.[5] In Thailand, the Government Pharmaceutical Organization (GPO) manufactures the generic DFP named GPO-L-One® with significant lower cost than the original DFP (Kelfer®), DFO and DFX. DFP is wildly use in thalassemia patients at Maharaj Nakorn Chiang Mai Hospital.

The study objectives were to determine the clinical effectiveness, health-related quality of life (HRQOL) and costs of DFP treatment in transfusion-dependent thalassemia patients.

Materials and Methods

Study design

A cross-sectional study was conducted among the transfusion-dependent thalassemia patients who received DFP at Maharaj Nakorn Chiang Mai Hospital. A total of 50 patients were enrolled. Their ages were ≥10 years and they could understand Thai language as well as read and write Thai. This study was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University.

Clinical effectiveness

Medical records were retrospectively reviewed over a 12-month period to evaluate the clinical effectiveness as well as the safety of DFP. For patients who

received DFP less than one year, the medical records were reviewed since the initiation of DFP treatment. Serum ferritin levels were used as clinical marker of drug effectiveness. Serum ferritin level at baseline was defined as the level obtained in the past 12 months or the level before initiation of DFP and the final level was defined as the recent available serum ferritin level. The data such as DFP and other ICT treatments, blood transfusions, DFP-related adverse events and laboratory results for toxicity monitoring (e.g. CBC, liver enzyme tests) were recorded. Adherence to DFP treatment over the previous 7-day period and adverse events over the previous 30-day period were self-reported from the questionnaire.

Health-related quality of life (HRQOL)

The HRQOL assessment were performed using the EuroQoL EQ-5D-3L (Thai version). This questionnaire consists of 2 main parts: the EQ-5D-3L descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system has 5 dimensions: 'mobility', 'self-care', 'usual activities', 'pain/discomfort' and 'anxiety/depression'. Each dimension is divided into 3 levels of perceived problems: 'no problem', 'some problems', and 'extreme problems'.[6] The EQ-5D-3L descriptive system was converted to EQ-5D-3L score using the Thai value set.[7] The EQ VAS is presented by a vertical line ranging from 0 to 100 where 0 indicate 'Worst imaginable health state' and 100 indicate 'Best imaginable health state'. The patients were asked to mark on the line to indicate their current health state.

Costs of treatment

The costs of treatment were estimated from the overall costs paid to the hospital upon followed up due to thalassemia disease with iron overload. Direct medical costs such as DFP costs and other treatment-related costs (e.g. blood transfusions, laboratory monitoring, treatment-related adverse events) were obtained from the hospital database. DFP available in the hospital were Kelfer® and GPO-L-One® which cost 37 THB/tablet and 4.50 THB/tablet, respectively. In this study, the cost of DFP was calculated as DFP (GPO-L-One®). Direct non-medical costs (e.g. costs of transportation, meals, and facilities) were obtained from the questionnaire. All costs were reported in 2013 Thai Baht (THB).

Statistical Analysis

The data were presented as frequencies, percentages, mean±standard deviation (SD), median, and range (minimum-maximum). Wilcoxon signed ranks test was used to examine the significant difference between mean serum ferritin level at baseline and final level. *P*-value of less than 0.05 was considered as statistically significant. All costs were presented as mean annual cost per patient. The data were analyzed using Microsoft Excel 2010 and SPSS statistics version 17.0 software.

Results

Demographic and Clinical characteristics

Demographic and clinical characteristics of 50 patients were summarized in Table 1. Their mean age was 21.6±8.6 years (range, 10.0-54.6), and 29 patients (58%) were female. Homozygous β-thalassemia and β-thalassemia/HbE disease were found in equal number. The majority of patients (34 patients or 68%) received blood transfusion of more than 10 units per year. Splenectomy was done in 31 cases (62%). DFP monotherapy and DFP in combination with DFO were given to 43 and 7 patients, respectively. Forty-four patients (88%) had received DFP for at least one year.

Table 1. Demographic and clinical characteristics (n=50).

Characteristics	
Age, years	
Mean±SD	21.6±8.6
Median (min-max)	19.6 (10.0-54.6)
Age range, n (%)	
10-17 years	20 (40)
≥18 years	30 (60)
Gender, n (%)	
Male	21 (42)
Female	29 (58)
Occupation, n (%)	
Student	26 (52)
Government Office	5 (10)
Trader	3 (6)
Employee	3 (6)
Business Owner	2 (4)
Office Worker	1 (2)
Farmer/Fisherman	1 (2)
None	9 (18)
Diagnosis, n (%)	
Homozygous β-thalassemia	25 (50)
β-thalassemia/HbE	25 (50)
Splenectomy, n (%)	31 (62)
Frequency of transfusions, n (%)	
unknown	5 (10)
≤10 units/year	11 (22)
11-20 units/year	25 (50)
≥21 units/year	9 (18)
Pretransfusion Hb level, g/dL	7.3±1.4
Serum ferritin level, µg/L	1386±541
Duration of DFP treatment, n (%)	
<1 year	6 (12)
≥1 year	44 (88)
Iron chelators, n (%)	
DFP	43 (86)
Combination DFP+DFO	7 (14)
Mean prescribed dose of ICT, mg/kg/day	
DFP (n=43)	45.9±14.2
Combination DFP+DFO (n=6)*	
- DFP	59.3±7.5
- DFO	12.5±4.6

* Available data were obtained from 6 patients since one patient received DFO from another hospital.

Clinical effectiveness

The mean serum ferritin level (µg/L) at baseline and final level of all patients who received DFP were 1367±935 and 1386±541, respectively. Patients who received DFP monotherapy (n=43) had similar mean serum ferritin level (µg/L) at baseline and final level of 1318±940 and 1371±529, respectively, while patients treated with combination DFP+DFO (n=7) had higher baseline serum ferritin level (µg/L) of 1670±918 and a decrease in final level to 1482±642. However, no statistically significant difference were observed between baseline and final serum ferritin levels in all groups (*P*=0.189, 0.110 and 0.866 for all patients, DFP monotherapy and combination DFP+DFO, respectively) (Figure 1).

From the questionnaire, 23 of 50 patients (46%) reported missing at least one dose during a 7-day period. A median number of the missing dose was 3 doses (range, 1-9). The adverse events occurred over a previous 30-day period were shown in table 2.

Other possible adverse events were reviewed from the medical records. Liver enzyme tests were determined in 43 patients and elevated liver enzymes were found in 7 cases (>3-fold the upper limit of normal (ULN)). Three of these patients had elevated liver enzyme due to acute febrile illness (n=2) and septicemia (n=1). Auditory examinations were conducted among 4 patients. Abnormal hearing due to noise trauma that was not related to DFP was found in one patient. Eye examinations in 8 patients showed no abnormality. Serum creatinine levels were determined in 34 patients and the results were within the normal range. Other serious adverse events such as agranulocytosis or neutropenia were not found.

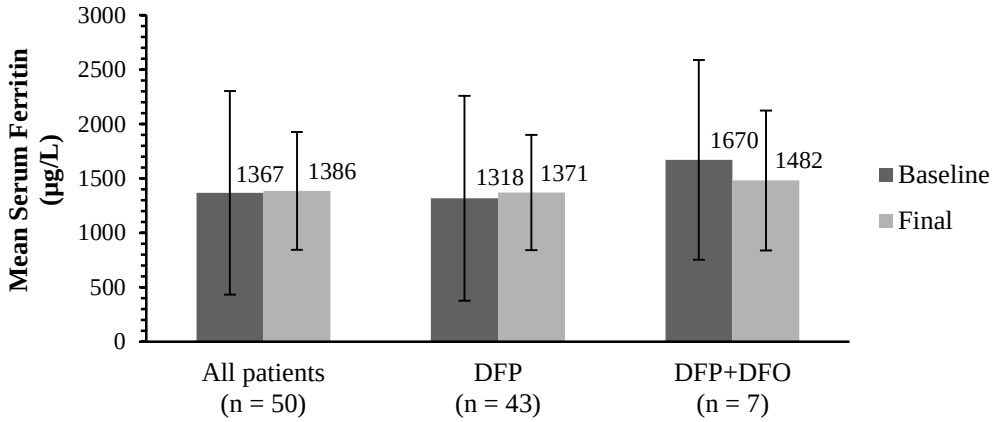

Figure 1. Mean serum ferritin levels comparison between at baseline and final.

Table 2. Adverse events (AE) in the previous 30 days.

AE	n (%)
Headache	8 (16)
Back pain	7 (14)
Arthralgia	5 (10)
Fever	3 (6)
Nausea/Vomiting	2 (4)
Abdominal pain	2 (4)
Diarrhea	2 (4)
≥1 AE*	8 (16)

* Patients who had more than one AE

Health-related quality of life (HRQOL)

The EQ-5D-3L profile was presented in Table 3. None of 50 patients reported extreme problems in any dimensions. Approximately 90% of patients reported that they had no problem in mobility, self-care, usual activities and anxiety or depression, while approximately 10% had some problems. Half of the patients reported that they had some problems with pain or discomfort. The mean EQ-5D-3L and VAS scores were 0.80±0.16 (range, 0.43-1.00) and 81.9±14.0 (range, 50-100), respectively.

Table 3. EQ-5D-3L profile.

EQ-5D Dimension	Levels	n (%)
Mobility	No problem	44 (88)
	Some problems	6 (12)
	Extreme problems	0
Self-care	No problem	48 (96)
	Some problems	2 (4)
	Extreme problems	0
Usual activities	No problem	43 (86)
	Some problems	7 (14)
	Extreme problems	0
Pain/Discomfort	No problem	25 (50)
	Some problems	25 (50)
	Extreme problems	0
Anxiety/Depression	No problem	45 (90)
	Some problems	5 (10)
	Extreme problems	0
EQ-5D-3L scores		
Mean±SD		0.80±0.16
Median (range)		0.73 (0.43-1.00)
VAS scores		
Mean±SD		81.9±14.0
Median (range)		85 (50-100)

Costs of treatment

The direct costs of DFP treatment were estimated and presented in Table 4. The costs of treatment in 6 patients who received DFP less than one year were adjusted to annual costs.

The total annual direct medical costs (THB/patient) in patients treated with DFP monotherapy and treated with combination DFP+DFO were 45,716 and 69,448, respectively. Their average annual direct non-medical cost was 7,849 THB/patient. Therefore, the total annual direct costs of DFP treatment (THB/patient) were estimated to be 54,000 and 78,000 for DFP monotherapy and combination DFP+DFO, respectively. The more expenses spent in the combination treatment were due to the higher cost of DFO. The mean annual cost (THB/patient) of DFP was 5,555, while the cost of combination DFP+DFO was 29,287.

Table 4. Estimated annual costs of treatment.

Costs	Mean annual cost per patient (THB)
Direct medical costs	
Iron chelators	
DFP monotherapy (n=43)	5,555
Combination DFP+DFO (n=6)*	29,287
Other drugs	778
Laboratory tests	5,614
Blood transfusions (n=45)	31,832
Auditory examination (n=4)	188
Eye examination (n=8)	305
Medical fee	846
Other (n=4)	598
Total direct medical costs†	
DFP monotherapy	45,716
Combination DFP+DFO	69,448
Direct non-medical costs	7,849
Total direct costs of treatment	
DFP monotherapy	53,565
Combination DFP + DFO	77,297

* Available data were obtained from 6 patients since one patient received DFO from another hospital.

† Total direct medical costs were calculated from the assumption that patients had to pay for the expense of all the items mentioned above.

Discussion

This cross-sectional study was conducted among 50 transfusion-dependent thalassemia patients who regularly received DFP at Maharaj Nakorn Chiang Mai Hospital. We determined the overall impact of DFP on these patients by assessment of clinical effectiveness, HRQOL and the costs of treatment.

The clinical effectiveness end point of DFP was serum ferritin level, which represent total body iron. Serum ferritin level was a non-invasive, inexpensive and widely used indicator for monitoring the effect of iron chelators. The result showed that all 50 patients enrolled in this study had higher serum ferritin level than the target level of ≤1000 µg/L.[8] There was no statistical significant different between baseline and final serum ferritin levels. The possible reason that DFP could not reduce the final level from baseline was due to their severe anemic condition in homozygous β-thalassemia and β-thalassemia/HbE disease that required regular blood transfusion and a continuous in iron overload. In addition, the mean baseline serum ferritin level in this study was ≤2500 µg/L, complied with previous study that showed DFP can decrease a mean serum ferritin level only in patients with higher baseline level of >2500 µg/L, but no significant changes were found in patients with baseline level of ≤2500 µg/L.[9]

Patients' adherence to DFP treatment was mostly poor. Almost half of these patients reported missing at least one dose during a previous 7-day period. This might limit the clinical effectiveness of DFP in these patients.

The common adverse events were consistent with previous report such as headache, back pain, arthralgia, gastrointestinal distress, and elevated liver

enzyme.[10,11] However, the incidence of headache in this study was higher than previous report. Neither neutropenia nor agranulocytosis was observed in this study.

HRQOL were assessed using the EuroQoL EQ-5D-3L (Thai version) which is a generic instrument for HRQOL and health utility assessment. The tool is easy for self-completion and takes only a few minutes to complete the assessment. The results showed that the patients had good HRQOL. Approximately 90% of patients reported that they had no problem in mobility, self-care, usual activities and anxiety or depression. However, half of them reported some problems in pain or discomfort. The mean health utility scores were 0.80 for EQ-5D-3L and 81.9 for VAS. These score indicated that patients' current health were approximately 80% of perfect health. Previous studies in Thai patients showed that the mean health utility scores of other diseases are 0.65 (EQ-5D-3L) for patients undergoing peritoneal dialysis and 80 (VAS) for Thai HIV/AIDS patients.[12,13] Moreover, a study in Italy showed patients with β-thalassemia major undergoing ICT have the mean VAS score of 73.[14]

In this study, the costs of treatment were estimated from the overall costs that patients had to pay to the hospital since the expense of ICT could not be separated from the costs of thalassemia treatment. The total annual direct costs (THB/patient) of treatment were estimated to be 54,000 and 78,000 for patients treated with DFP monotherapy and combination DFP+DFO, respectively.

The limitations of this study were small sample size and the data were retrospectively collected from medical records and hospital database. There may be some confounding factors and some missing data. However, the findings from this study can lead to further study such as a health utility score that can be used in the pharmacoeconomic evaluation.

Conclusion

Deferiprone was effective to maintain serum ferritin level in thalassemia patients with iron overload from regular blood transfusion. Adverse events frequently occurred and required monitoring. Patients' adherence to treatment was quite poor. However, most of patients appeared to have good HRQOL. The estimated total annual costs of treatment (THB/patient) were approximately 54,000 and 78,000 for patients treated with DFP monotherapy and combination DFP+DFO, respectively.

Acknowledgements

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References

1. Rund D, Rachmilewitz E. β-Thalassemia. N Engl J Med. 2005;353(11):1135-46.
2. Cappellini MD, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A. Guidelines for the clinical management of thalassaemia. 2nd rev ed. Nicosia: Thalassaemia International Federation; 2008.
3. Anderson GJ. Mechanisms of iron loading and toxicity. Am J Hematol. 2007;82(S12):1128-31.
4. Andrews NC. Disorders of Iron Metabolism. N Engl J Med. 1999;341(26): 1986-95.
5. Poggiali E, Cassinerio E, Zanaboni L, Cappellini MD. An update on iron chelation therapy. Blood Transfus. 2012;10(4):411-22.
6. Oemar M, Oppe M. EQ-5D-3L User Guide: Basic information on how to use the EQ-5D-3L instrument version 5.0 [Internet]. Rotterdam: EuroQol Group; 2013 [cited 2015 Feb 20]. Available from: http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-3L_UserGuide_2013_v5.0_October_2013.pdf.
7. Tongsiri S. The Thai population-based preference scores for EQ-5D health states [Doctoral dissertation]. London: University of London; 2009.
8. Vichinsky E, Levine L, Bhatia S, Bojanowski J, Coates T, Foote D, et al. Standards of Care Guidelines for Thalassemia 2012 [Internet]. California: Children's Hospital & Research Center Oakland; 2012 [cited 2013 Aug 26]. Available from: http://thalassemia.com/documents/SOCGuidelines2012.pdf.
9. Cohen AR, Galanello R, Piga A, Dipalma A, Vullo C, Tricta F. Safety profile of the oral iron chelator deferiprone: a multicentre study. Br J Haematol. 2000;108(2):305-12.
10. Cohen AR, Galanello R, Piga A, De Sanctis V, Tricta F. Safety and effectiveness of long-term therapy with the oral iron chelator deferiprone. Blood. 2003;102(5):1583-7.
11. Viprakasit V, Nuchprayoon I, Chuansumrit A, Torcharus K, Pongtanakul B, Laothamatas J, et al. Deferiprone (GPO-L-ONE®) monotherapy reduces iron overload in transfusion-dependent thalassemias: 1-year results from a multicenter prospective, single arm, open label, dose escalating phase III pediatric study (GPO-L-ONE; A001) from Thailand. Am J Hematol. 2013;88(4):251-60.
12. Sakthong P, Kasemsup V. Health Utility Measured with EQ-5D in Thai Patients Undergoing Peritoneal Dialysis. Value Health.15(1):S79-S84.
13. Sakthong P, Schommer JC, Gross CR, Prasithsirikul W, Sakulbumrungsil R. Health Utilities in Patients with HIV/AIDS in Thailand. Value Health. 2009;12(2):377-84.
14. Scalone L, Mantovani LG, Krol M, Rofail D, Ravera S, Bisconte MG, et al. Costs, quality of life, treatment satisfaction and compliance in patients with beta-thalassemia major undergoing iron chelation therapy: the ITHACA study. Curr Med Res Opin. 2008;24(7):1905-17.