Original article

Cost comparison study of adding eltrombopagin combined with immunosuppressive therapy to treat severe aplastic anemia in first line setting at Khon Kaen Hospital from 2018-2020

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Abstract:

Objective: *Severe Aplastic Anemia (SAA) has a major impact on healthcare, affecting individuals at both clinical and health economic levels. Antithymocyte globulin (ATG) and cyclosporin A (CSA) are the most common treatments in first line setting. Using eltrombopag combined with ATG+CSA for six months increased patient overall response rate. To explore the potential impact of SAA prescribing patterns on healthcare costs in real life, this study analyzed the costs of adding eltrombopag combined with ATG+CSA compared with ATG+CSA by considering health outcomes and AE management.* **Materials and methods:** *A cost comparison model was developed using a 6-month response rate as the outcome input (94.0 vs. 17.4%). Direct medical and nonmedical costs of one-year care per patient were collected retrospectively from Khon Kaen Hospital from 2018-2020 and categorized as either responsive or nonresponsive to compare the costs between with and without eltrombopag in treatment using a patient perspective.* **Results:** *Data of 20 patients with SAA were included in the evaluation with 12 responsive and 8 nonresponsive. The total drug cost of ATG+CSA was estimated at 691,354 THB. Eltrombopag costs added 358,621 THB. The total direct healthcare-related costs were estimated at 193,531 THB/ year and 502,567 THB/year in responsive and nonresponsive groups, respectively. The average savings regarding direct medical and nonmedical cost was then estimated at 151,657 THB/patient/year for eltrombopag+ATG+CSA.* **Conclusion**: *Considering both relevant health outcomes and AE management, adding eltrombopag combined ATG+CSA showed a saving in overall costs/year to patients. To reduce the burden of SAA conditions, eltrombopag should be regarded as a priority to treat SAA as first line.*

Keywords : ● *Severe aplastic anemia* ● *Eltrombopag* ● *Immunosuppressive therapy* ● *Medical cost* ● *Non-medical cost*

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นิพนธ์ต้นฉบับ

Cost comparison study of adding eltrombopagin combined with immunosuppressive therapy to treat severe aplastic anemia in first line setting at Khon Kaen Hospital from 2018-2020

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บทคัดย่อ

วัตถุประสงค์ *โรคไขกระดูกฝ่อชนิดรุนแรง (Severe aplastic anemia, SAA) ส่งผลกระทบที่สำคัญต่อการดูแลผู้ป่วยทางคลินิกและต่อเศรษฐกิจ การรักษาด้วยการให้ยากดภูมิคุ้มกัน Antithymocyte globulin (ATG) ร่วมกับ cyclosporine A (CSA) เป็นการรักษาสูตรแรกที่นิยมใช้มากที่สุดในประเทศไทย การใช้ eltrombopag เป็นเวลาหกเดือนเพิ่มเข้าไปจาก ATG+CSA พบว่าจะเพิ่มอัตราการตอบสนองโดยรวมของผู้ป่วยให้สูงขึ้น เพื่อให้เข้าใจผลกระทบต่อค่าใช้จ่ายที่อาจเกิดขึ้นจากการรักษาดูแลสุขภาพผู้ป่วย SAA ในชีวิตจริงการศึกษานี้จึงเปรียบเทียบค่าใช้จ่ายในการเพิ่ม eltrombopag ร่วมกับ ATG+CSA โดยคำนึงถึงผลลัพธ์ด้านสุขภาพโดยรวมและการจัดการเหตุการณ์ไม่พึงประสงค์จากการรักษา   **แหล่งข้อมูลและวิธีการ** รูปแบบการเปรียบเทียบค่าใช้จ่ายได้รับการพัฒนาขึ้นโดยใช้อัตราการตอบสนองการรักษาที่ 6 เดือนเป็นผลลัพธ์ที่ใช้ (94.0% เทียบกับ 17.4%) ต้นทุนทางตรงทางการแพทย์และต้นทุนทางตรงที่ไม่เกี่ยวกับการแพทย์ของผู้ป่วยในหนึ่งปี รวบรวมย้อนหลังจากโรงพยาบาลขอนแก่นในระหว่างปี พ.ศ. 2561-2563 จัดกลุ่มผู้ป่วยเป็นสองกลุ่ม คือ กลุ่มที่ตอบสนองและไม่ตอบสนองต่อการรักษา เพื่อเปรียบเทียบค่าใช้จ่ายระหว่างมีกับไม่มี eltrombopag ในการรักษาโดยคำนึงถึงตัวผู้ป่วย   **ผลการศึกษา** ข้อมูลของผู้ป่วย SAA 20 คนได้ถูกรวบรวมโดยพบว่ามี 12 คนตอบสนอง และ 8 คนไม่ตอบสนองต่อการรักษา ค่ายาทั้งหมดของ ATG+CSA อยู่ที่ประมาณ 691,354 บาท ค่ายา eltrombopag อยู่ที่ 358,621 บาท ค่าใช้จ่ายทางตรงสำหรับการรักษาทั้งหมดประมาณ 193,531 บาทต่อปีในกลุ่มที่ตอบสนอง และ 502,567 บาทต่อปีในกลุ่มที่ไม่ตอบสนอง ดังนั้นการรักษาด้วย eltrombopag+ATG+CSA สามารถประหยัดค่าใช้จ่ายทางตรงในการรักษาโดยเฉลี่ยอยู่ที่ประมาณ 151,657 บาทต่อผู้ป่วยต่อปี **สรุป** เมื่อพิจารณาทั้งประสิทธิผลในการรักษาและการจัดการเหตุการณ์ไม่พึงประสงค์จากการรักษา การเพิ่ม eltrombopag ร่วมกับ ATG + CSA แสดงให้เห็นถึงการประหยัดค่าใช้จ่ายโดยรวมต่อปีให้กับผู้ป่วยและ eltrombopag ควรได้รับการพิจารณาว่าเป็นยาที่ใช้สำหรับการรักษา SAA ในสูตรแรกเพื่อลดภาระการรักษาผู้ป่วย SAA*

คำสำคัญ : ● *โรคไขกระดูกฝ่อชนิดรุนแรง* ● *Eltrombopag* ● *การรักษาด้วยยากดภูมิคุ้มกัน* ● *ต้นทุนทางตรงทางการแพทย์*
          ● *ต้นทุนทางตรงที่ไม่เกี่ยวกับการแพทย์*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2565;32:323-31.

Introduction

Although severe aplastic anemia (SAA) is considered a rare condition in Thailand, it exhibits high incidence in northeastern Thailand at approximately 5.6 per million inhabitants yearly[1] with the majority constituting acquired aplastic anemia[2,3]. Due to reduced ability of bone marrow in blood cells production, SAA has an influence on the frequent need for blood transfusion and other therapeutic procedures[4] leading it to be deemed as a high cost, management condition. Apart from allogeneic hematopoietic stem cell transplantation, immunosuppressive therapy, antithymocyte globulin (ATG) and cyclosporin A (CSA) has been recommended as a standard treatment in first line indications for patients with SAA aged 50 years and above without matched sibling donor, as indicated in the Guideline for Diagnosis and Management of Aplastic Anemia in Thailand 2020[5]. Due to the unavailability of horse ATG (hATG) in the country, rabbit ATG (rATG) has been used and listed together with CSA in the Thai National List of Essential Medicines (NLEM) which are reimbursed as the Universal healthcare for Thai citizens[6]. However, data from a randomized study[7] showed lower treatment effect estimates at 6 months of rATG(37%) compared to hATG(68%) specifically to patients with acquired aplastic anemia. Adding eltrombopag, a thrombopoietin receptor agonist, can improve patients' with SAA outcomes when treating combined with ATG+CSA (94.0%)[8] and is also recommended in the Thai Guidelines. Unfortunately, eltrombopag has not yet been listed in the NLEM and the incremental drug cost is close to the average annual household earnings in Thailand (312,221 THB in 2019)[9]. However, considering only drug costs seems insufficient for deciding which treatment regimen an individual with SAA should receive. Hence, estimating all direct healthcare-related costs among both responsive and nonresponsive patients treated with different regimens in the real-world setting is the key component to determine potential healthcare resources that are used resulting from

SAA conditions. The availability of real-world medical records of patients with SAA at Khon Kaen Hospital provides an opportunity to investigate these costs and reflects daily clinical practice more accurately. This study aimed to address the economic cost of illness of first line treatment for SAA and comparing these costs between with and without eltrombopag treatment.

Materials and Methods

Data collection

This study retrospectively collected the data of direct healthcare-related costs in which patients with SAA, receiving rATG and CSA as the first line treatment at Khon Kaen Hospital between 1 January 2018 and 31 December 2020 were included. All patient outcomes were classified as either responsive or nonresponsive (as defined by the *Guideline for Diagnosis and Management of Aplastic Anemia in Thailand 2020*[5]) to the treatment at 3, 6, 9 and 12 months after initiating the first dose of rATG. The overall response rate (ORR) at 12 months of each individual patient was used to determine whether a patient responded to the treatment. In the case of missing data on ORR at 12 months, the *Last Observation Carried Forward (LOCF) Approach* was used by replacing the missing value of ORR with the previously observed ORR value to define patient responsiveness. The study protocol was approved by the Ethics Committee at the participating center: Khon Kaen Hospital in November 2021.

Model structure

A cost comparison model was developed following the recommendation from the *NICE's cost comparison addendum to the guide to the methods of technology appraisal*[10]. The model compared both the costs and outcomes of adding the eltrombopag regimen with the current practice, i.e., rATG+CSA. Discount rates were not applied in this study because the time horizon was determined at one year. Details of the model are described in Figure 1.
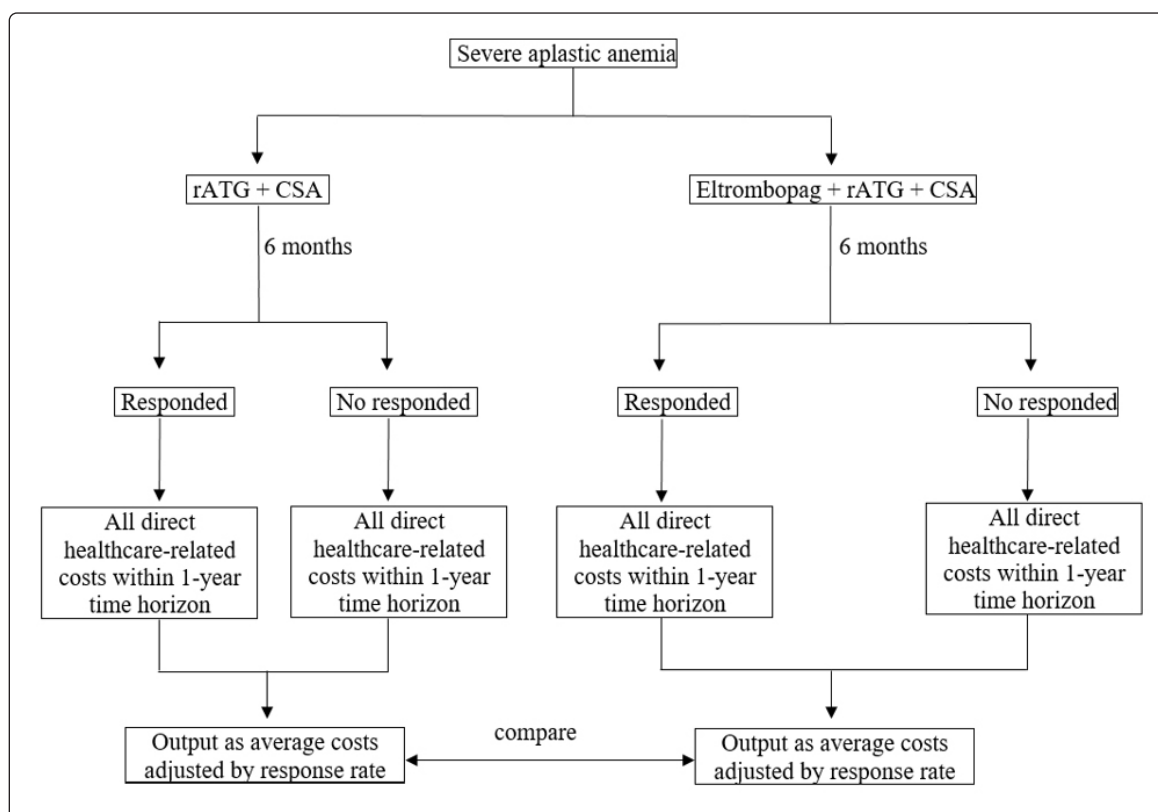
Figure 1 Cost comparison model of adding eltrombopagin combined with rATG+CSA

Costs

This study assessed all annual direct healthcare-related costs for SAA from the perspective of two categories: direct medical costs and direct nonmedical costs.

Direct medical costs

These costs represent the costs of SAA-related medical care use (outpatient visits and inpatient admissions) including drug costs, blood transfusion costs, costs of diagnostic and laboratory charges, doctor consulting charges, nursing fees, procedures for all surgical interventions and medical supplies. Costs of eltrombopag, rATG and CSA were measured using the *Bottom-up Approach* and captured from the reference prices prepared by the Drug and Medical Supply Information Center, Ministry of Public Health[11] and the Health Standard Cost List for Health Technology Assessment in Thailand[12]. The assumption on average body weight of patients with SAA at 50 kg with 7-day duration of therapy was applied to calculate unit number of rATG daily and costs related to rATG treatment e.g., intravenous sets, medical supplies, hospital bed charges and meals etc.

For eltrombopag and CSA, the treatment length of 6 cycles (168 days) was used to determine these two drug costs. Other direct medical costs and drug costs except eltrombopag, rATG and CSA were collected and averaged from medical records of included patients with SAA at Khon Kaen Hospital.

Direct nonmedical costs

Expenditures occurred related to SAA but were not involved in the direct purchasing of medical services consisting of hospital bed charge, meals and other costs unrelated to the treatment were also included in the analysis. Direct nonmedical costs were collected and averaged from medical records of included patients with SAA at Khon Kaen Hospital.

Outcomes

Because no ORR information of adding eltrombopagin combined with ATG+CSA at 12 months was available, the ORR at 6 months from the study funded by the American National Heart, Lung, and Blood Institute 2017[8] and Asian Medical Records s in Malaysia, Taiwan, Hong Kong, and Thailand between 2006 and 2012[13] were used
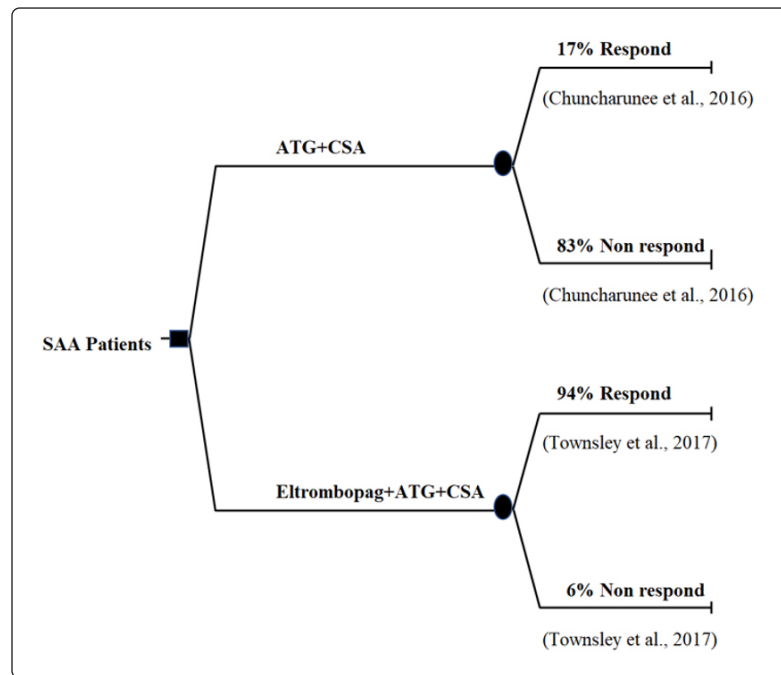
Figure 2 Decision tree model comparing outcome benefits of adding eltrombopagin combined with ATG+CSA

Table 1 Baseline characteristics of the enrolled patients

Characteristic	No. patients (%) n = 20
Age distribution	
< 20 years	1 (5)
20-40 years	6 (30)
> 40 years	13 (65)
Sex	
Female	11 (55)
Responsiveness	
Yes, median age (years)	12 (60), 52
No, median age (years)	8 (40), 54

to compare the outcome benefits between the two regimens. These estimations were assigned to the decision tree model illustrated in Figure 2. Threshold analysis was also performed to confirm at which point different ORRs, adding eltrombopag to the standard treatment, would benefit patients with SAA. Outcome benefits were calculated using Microsoft Excel Spreadsheet Software 2016 and Plant-A-Tree Add-In ,Version 1.0.

Results

In this study, 20 patients with SAA were included in the analysis. Baseline characteristics are shown in Table 1. Mean patient age was 47 years (range 15-68 years). Of these patients, 12 were (60%) classified as the responsive group. The majority (92%) showed responsiveness to ORR at 12 months while only one patient (8%) was classified using ORR at three months due to loss-of-follow up. For patients were classified as the nonresponsive group (n = 8, 40%), one half were observed with ORR at 12 months. Two patients had been lost to follow-up (25%) and two patients died (25%) in the nonresponsive group. The observed numbers of patients in each group are summarized in Table 2.

Table 3 illustrates the total estimated costs of eltrombopag, rATG and CSA. The average annual direct healthcare-related costs compared between responsive

Table 2 Responsiveness of observed patients

Response	Responsive group (%)	Nonresponsive group (%)
Response at 3 months	7 (35%)	13 (65%)
Response at 6 months	9 (45%)	11 (55%)
Response at 9 months	10 (50%)	10 (50%)
Response at 12 months	12 (60%)	8 (40%)

Table 3 Estimated drug cost of eltrombopag, rATG and CSA

	Eltrombopag 25 mg tablet	rATG 25 mg sterile powder	Ciclosporin 25 mg capsule
Strength	25 mg/tablet	25 mg/vial	25 mg/capsule
Price (included 7% VAT)	712 THB/tablet	8,740 THB/vial	24 THB/capsule
Daily dose	75 mg	3 mg/kg body weight	5 mg/kg body weight
Number of units daily	3 tablets	6 vials	10 capsules
Total drug costs	358,621 THB	367,080 THB	39,917 THB
Costs related to the daily treatment, i.e., medical supplies, hospital bed charges and meals	N/A	1,350 THB	N/A
Total costs related to the treatment, i.e., medical supplies, hospital bed charges and meals	N/A	9,450 THB	N/A
Total	**358,621THB**	**377,880 THB**	**39,917 THB**
ATG+CSA*		417,797 THB	
Eltrombopag+ATG+CSA		776,418 THB	

*The average cost of the second cycle of ATG+CSAas subsequent treatment was added in the decision tree model (Figure 3).
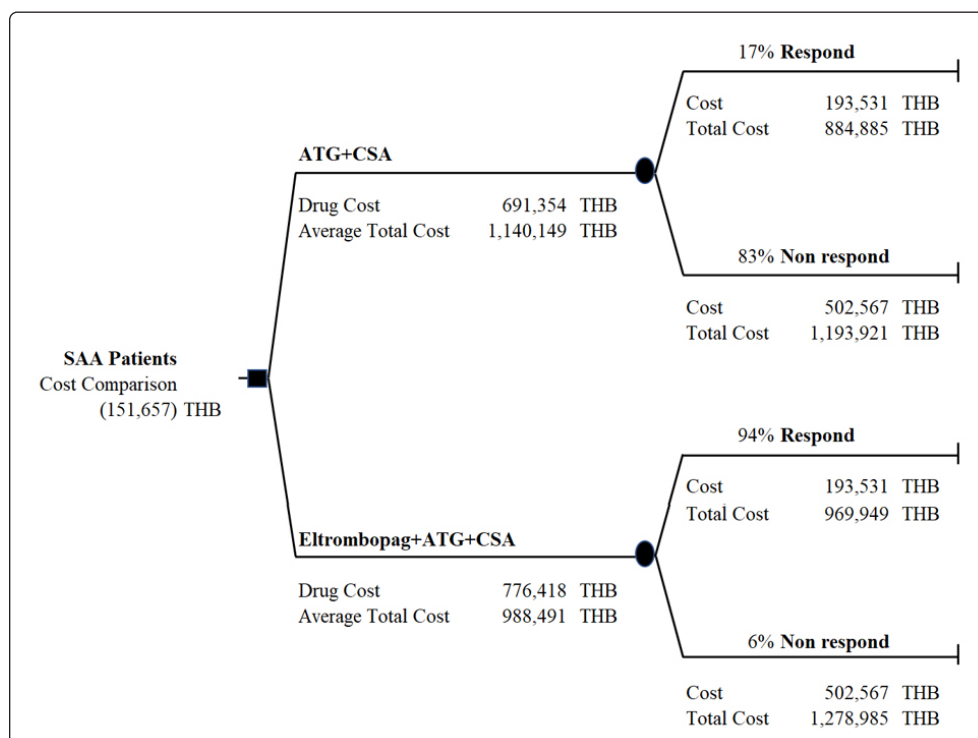

Figure 3 Decision tree model comparing annual direct healthcare-related costs adjusted with outcome benefits of adding eltrombopagin combined with ATG+CSA

Table 4 Average annual direct healthcare-related costs between responsive and nonresponsive groups as defined by ORR at 12 months

Cost	Responsive group (n = 12)	Nonresponsive group (n = 8)
Direct medical costs	184,958 THB (95.57%)	471,364 THB (93.79%)
Drug costs except eltrombopag, ATG and CSA	84,951 THB (43.90%)	130,371 THB (25.94%)
Blood transfusion costs	70,930 THB (36.65%)	243,663 THB (48.48%)
Diagnostic and laboratory charges	12,190 THB (6.30%)	43,436 THB (8.64%)
Doctor consulting charges and nursing fees	10,380 THB (5.36%)	32,896 THB (6.55%)
Costs of procedures for all surgical interventions	119 THB (0.06%)	1,185 THB (0.24%)
Costs of medical supplies	6,387 THB (3.30%)	19,812 THB (3.94%)
Direct nonmedical costs	8,573 THB (4.43%)	31,203 THB (6.21%)
Costs of hospital bed charges and meals	8,133 THB (4.20%)	30,363 THB (6.04%)
Other costs unrelated to treatment	440 THB (0.23%)	840 THB (0.17%)
Total	**193,531 THB (100%)**	**502,567 THB (100%)**

Table 5 Number of outpatient visits and inpatient admissions in responsive and nonresponsive groups over 12 months of treatment

	Responsive group (n = 12)	Nonresponsive group (n = 8)
Number of outpatient visits; median (95%CI)	8 (5-12)	4 (2-6)
Number of inpatient admissions; median (95%CI)	3 (1-10)	18 (7-22)

and nonresponsive groups are shown in Table 4. The total annual direct healthcare-related costs represented at 2.6 times higher in the nonresponsive group (502,567 THB) than those in the responsive group (193,531 THB). The highest annual cost in both responsive and non-responsive groups was incurred for blood transfusion (36.65 to 48.48%) followed by other drug costs except eltrombopag, ATG and CSA (25.94 to 43.90%).

The number of outpatient visits and inpatient admissions for one year of treatment is shown in Table 5. Both responsive and nonresponsive group were hospitalized for at least one course of ATG+CSA. Of these two groups, the latter required hospital admission for a second ATG+CSA as subsequent treatment when medically needed and receiving treatment for complications such as blood transfusion for severe thrombocytopenia and antibiotics for infections.

When the drug costs of eltrombopag, rATG and CSA were considered with annual direct healthcare-related costs, the total costs of patients receiving eltrombopag+rATG+ CSA and responding to the treatment (969,949 THB) were lower than for those receiving only rATG+CSA and without response (1,193,921 THB). Results of the analysis are presented in Figure 3. After analyzing the annual direct healthcare-related costs by considering outcome benefits of each regimen, the incremental cost of adding the eltrombopag regimen to the current practice, i.e., ATG+CSA, was determined (Figure 3). The average annual direct healthcare-related costs were estimated at 151,657 THB lower for each individual patient in the regimen of eltrombopag+rATG+CSA. Specifically, these costs were estimated at 1,140,149 THB/patient/year and 988,491 THB/patient/year for ATG+CSA and eltrombopag+ATG+CSA, retrospectively.

Result from threshold analysis showed that, given the cost of eltrombopag equals 358,621 THB for the total course of treatment, the incremental benefit of ORR between the two regimens should differ at least 28% to confirm the benefits of adding eltrombopag over standard treatment.

Discussion

In this cost comparison analysis, we aimed to add more information concerning the total direct health-care-related costs for the first line treatment of SAA and to highlight the importance of considering other direct medical and nonmedical costs apart from drug costs. Even though all the direct healthcare-related costs are in the same proportion among both respon-sive and nonresponsive patients with SAA, over three and one half times more expense could be observed among nonresponsive patients. Moreover, patients with SAA who were nonresponsive to treatment showed an approximately six times higher rate of inpatient admissions resulting in more healthcare resource use that could also affect efficiency of hospital infrastructure and healthcare providers. Although eltrombopag cost accounted for almost one half of the total drug costs, considering its health outcomes and AE management, this treatment option produced the highest the cost savings. The results from this study are in line with a recent cohort study investigating healthcare resource use in the USA[14]. This cohort study affirmed that eltrombopag cost could be offset by reducing direct costs. Regarding a specific health condition as SAA, blood transfusion costs have been shown in one third of total average annual direct healthcare-related costs. Considering the high incidence of transfusion-dependent patients with SAA at 85%[15], this study revealed that the costs of blood transfusion could be saved over two third for each individual patient when they responded to the treatment. To reduce the chance of these high expenses, treatment with significant higher ORR should be considered as the first option. The next focus should be on how to deliver the essential healthcare in an efficient and sustainable ways to manage SAA in the Thai context.

One of the major strengths in this study was that we captured all direct healthcare-related costs occurring in the real-world practices with one-year follow up. Hence, it would be reasonable to use the information obtained from this study as comprehensive evidence on managing SAA in Thailand and to formulate policy recommendations for standard treatment in Thai secondary and tertiary care settings. The executive level of Thai government should consider eltrombopag as the standard option of first line treatment for patients with SAA even though it may seem costly to implement but would provide potentially large economic benefits to society.

Our study encountered limitations. First, one of the key factors determining the saving cost of eltrombopag is the estimations of outcome benefits between the two regimens. This study used the ORR at six months of rATG+CSA compared with eltrombopag+hATG+CSA from two studies that had different baselines of patient characteristics. However, one related study revealed the equitable comparability of response rates between the hATG and rATG at six months (60% vs. 55%, $p = 1.0$)[16]. Hence, we believe that our assumption is comparatively acceptable. Second, addressing the economic cost of illness, indirect costs should be another main factor to consider. These costs refer to the potential resources that are lost resulting from SAA conditions, e.g., premature mortality and hospital-related absenteeism[17], which can be calculated based on the data on average earnings of patients with SAA. In this study, we did not calculate these indirect costs because most patients with SAA are elderly and are not in the working age population. Further studies should, reflect the fast pace of aging populations in Thailand and worldwide, and note these indirect costs. In addition, it would beneficial to explore more specifically on which other drugs except eltrom-bopag, ATG and CSA have contributed the greatest proportion on direct healthcare-related costs and due to what circumstances.

Conclusion

Patients with SAA receiving eltrombopag combined with immunosuppressive therapy as the first line treatment had a higher chance of saving direct healthcare-related costs. Therefore, eltrombopag should be included in

the country Universal Coverage as the standard first line treatment for patients with SAA to promote the best use of restricted Thai healthcare.

Acknowledgement

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