Research Article

การประเมินความเหมาะสมของยากลุ่ม Erythropoiesis stimulating agents ในผู้ป่วยโลหิตจางจากโรคไตเรื้อรัง: การศึกษาย้อนหลัง

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บทคัดย่อ

การประเมินความเหมาะสมของยากลุ่ม Erythropoiesis stimulating agents ในผู้ป่วยโลหิตจางจากโรคไตเรื้อรัง: การศึกษาย้อนหลัง

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ภาวะโลหิตจางพบความชุกสูงในกลุ่มผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นโรคไตเรื้อรังระยะสุดท้ายซึ่งมีสาเหตุจากการสร้างฮอร์โมนอีริโธรพอยอีตินไม่เพียงพอ ยากระตุ้นการสร้างเม็ดเลือดแดง (Erythropoiesis stimulating agents, ESAs)เป็นยาพื้นฐานที่รู้จักเป็นอย่างดีที่มีความจำเป็นในการรักษาภาวะโลหิตจาง ยากระตุ้นการสร้างเม็ดเลือดแดง นั้นเป็นยาที่มูลค่ายาสูงใช้รักษาผู้ป่วยเฉพาะราย มีการรักษาโดยแพทย์เฉพาะทาง ดังนั้นการรักษาด้วยยากระตุ้นการสร้างเม็ดเลือดแดง ได้แก่ การปรับขนาดยาและการรักษาระดับฮีโมโกลบินให้อยู่ในช่วงเป้าหมายสามารถป้องกันมูลค่ายาที่สูญเสียไปและเหตุการณ์ไม่พึงประสงค์ที่รุนแรง pure red cell aplasia (PRCA) วัตถุประสงค์ของการศึกษานี้ 1. เพื่อประเมินรูปแบบการสั่งใช้ยากระตุ้นการสร้างเม็ดเลือดแดง ในผู้ป่วยที่มีภาวะโลหิตจางจากโรคไตเรื้อรังตามประเภทยา(อีโพอิติน แอลฟ่า, อีโพอิติน เบต้าและ ยาต้นแบบ, ยาชีววัตถุคล้ายคลึง), 2. เพื่อประเมินประสิทธิผลและการปรับขนาดยาในกลุ่มผู้ป่วยโรคไตเรื้อรังระยะที่4 และระยะที่5 รวมถึงติดตามอาการไม่พึงประสงค์ PRCAจากการใช้ยา 3.เพื่อรวบรวมมูลค่ายาทั้งหมดจากการรักษาและมูลค่าจากการปรับขนาดยาไม่เหมาะสม **วิธีดำเนินการวิจัย:** การศึกษานี้เป็นการศึกษาแบบย้อนหลังเชิงพรรณนาโดยข้อมูลผู้ป่วยจะถูกรวบรวมขึ้นจากการทบทวนเวชระเบียนของโรงพยาบาลราชวิถีในช่วงระหว่างเดือนมกราคม2556 – เมษายน 2559 รวมถึงประสิทธิผลและปริมาณการใช้ยา การปรับขนาดยา มูลค่ายาในการรักษา **ผลการศึกษา:** พบผู้ป่วยทั้งหมด 390 รายได้รับการวินิจฉัยว่ามีภาวะโลหิตจางจากโรคไตเรื้อรังและได้รับยากระตุ้นการสร้างเม็ดเลือดแดง มีจำนวนผู้ป่วย 201 รายที่ถูกคัดเข้าสู่การศึกษา พบผู้ป่วยจำนวน 39 รายคิดเป็นร้อยละ19.4 ที่ได้รับการวินิจฉัยเป็นโรคไตเรื้อรังระยะที่4 และจำนวน 162 รายคิดเป็นร้อยละ80.6 อยู่ในระยะที่5 โดยรวมกลุ่มผู้ป่วยทั้งก่อนได้รับการบำบัดทดแทนไตและเข้าสู่ระยะการบำบัดทดแทนไตทั้งการฟอกเลือดด้วยเครื่องไตเทียมหรือการล้างไตทางช่องท้องแบบต่อเนื่องอีกทั้งพบผู้ป่วยจำนวน 142 ราย คิดเป็นร้อยละ70.65ได้รับยาประเภทอีโพอิตินแอลฟ่าและจำนวน 59 ราย คิดเป็นร้อยละ 29.35ได้รับยาประเภทอีโพอิตินเบต้าตามลำดับ ผลการเปรียบเทียบระหว่างการใช้ยาประเภท อีโพอิตินแอลฟ่าและอีโพอิตินเบต้าต่อการรักษาระดับความเข้มข้นของฮีโมโกลบินในเลือดให้ถึงเป้าหมายในช่วง 10-11.5 g/dl พบว่ายาประเภทอีโพอิตินเบต้าสามารถรักษาระดับความเข้มข้นของฮีโมโกลบินในเลือดให้ถึงเป้าหมายดีกว่าได้รับยาประเภท อีโพอิตินแอลฟ่าอย่างมีนัยสำคัญทางสถิติ (P-value<0.05) ส่วนผู้ป่วยที่ได้รับยาชีววัตถุคล้ายคลึงอีโพอิตินแอลฟ่าสามารถรักษาระดับฮีโมโกลบินให้คงที่และถึงเป้าหมายไม่แตกต่างกันกับยาต้นแบบ (P-value>0.05) นอกจากนี้ในส่วนของมูลค่าต้นทุนทั้งหมดที่ใช้รักษาผู้ป่วยทั้งหมดเป็นจำนวนเงิน 19,077,533.97 บาท และมูลค่าที่มีการรักษาด้วยยาไม่เหมาะสมทั้งหมด 101,258.38 บาท และในการศึกษานี้ไม่พบเหตุการณ์ไม่พึงประสงค์ PRCA **สรุปผลการวิจัย:** การได้รับยากระตุ้นการสร้างเม็ดเลือดแดง ประเภทอีโพอิตินเบต้าสามารถรักษาระดับความเข้มข้นฮีโมโกลบินในเลือดให้คงที่ถึงเป้าหมายของผู้ป่วยที่มีภาวะโลหิตจางจากโรคไตเรื้อรังระยะที่4 และระยะที่5 และไม่ว่าจะเป็น ยาต้นแบบหรือ ยาชีววัตถุคล้ายคลึงของยาประเภท อีโพอิติน แอลฟ่าสามารถรักษาระดับความเข้มข้นของฮีโมโกลบินให้คงที่ได้ไม่แตกต่างกัน และหากมีการปรับขนาดยาที่เหมาะสมสามารถช่วยประหยัดมูลค่าต้นทุนค่ายาในการรักษาได้

คำสำคัญ: โรคไตเรื้อรัง, โรคไตเรื้อรังระยะสุดท้าย, อีริโธรพอยอีติน, อิโพอิติน

Evaluation of the Appropriate Use of Erythropoiesis Stimulating Agents for Anaemia in Chronic Kidney Disease Patients: A Retrospective Study

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Abstract

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Anaemiais highly prevalent in end-stage renal disease (ESRD) patients. With regards to medication for this condition, erythropoiesis-stimulating agents (ESAs) have recently become known as the standard therapeutic agents for anaemia; furthermore, ESAs are one of the costly medications that are used in specific patients by specialists, so the appropriate ESAs treatment; dosage adjustment or maintaining haemoglobin(Hb) concentration within the target range could prevent value loss to all chronic kidney disease (CKD) patients and Pure Red Cell Aplasia (PRCA) adverse drug event. The objectives of this study were 1) to evaluate the ESAs usage pattern in patients with anaemia of CKD including the types of ESA (Epoetin alfa, Epoetin beta, original products and biosimilar products), 2) to assess the dosage regimen and dosage adjustment according to the recommendations in Stage 4 and Stage 5 CKD patients, as well as the efficacy and PRCA adverse drug event, and 3) to review the total cost of the ESA treatment and cost of inappropriate dosage adjustment. **Methods**: The present study is a retrospective descriptive study. Patients' data were collected from medical records or by patients' chart reviews of Rajavithi Hospital, Bangkok, Thailand between January 2013 and April 2016 included efficacy and quantity of ESA using, dosage adjustment, total cost of treatment. **Results:** A total of 390 patients was diagnosed with anaemia of CKD and received ESA therapy, 39 patients (19.4%) were diagnosed as Stage 4 and 162 patients (80.6%) had Stage 5 that included pre-dialysis or HD/CAPD cases. One hundred and forty-two patients (70.65%) received Epoetin alfa and 59 patients (29.35%) received Epoetin beta, respectively. In the comparison of the Epoetin alfa usage and Epoetin beta usage in order to achieve the target of a Hb concentration between 10.0 and 11.5 g/dL, the results showed that Epoetin beta usage could significantly achieve a higher target of the Hb concentration than Epoetin alfa usage ($P<0.05$). In addition, the patients who received epoetin alfa biosimilar had stable Hb concentration within target range which was not different from the original products (P->0.05). Therefore, this study showed that the total cost of ESAs treatment was 19,077,533.97 Thai Baht (THB) and the cost of inappropriate ESAs treatment was 101,258.38 THB. Furthermore, there were no adverse drug event of PRCAfound. **Conclusion:** Epoetin beta had a higher performance in terms of achieving the target of the Hb concentration in chronic renal anaemia patients. It was also found that both the original products or biosimilar products of Epoetin alfa could achieve the target of the Hb concentration for anaemia treatment. Thus, appropriate ESAs treatment could prevent value loss to all CKD patients.

Keywords : chronic kidney disease, end-stage renal disease, erythropoietin, epoetin

Introduction

Chronic kidney disease (CKD) is a major public health problem in Thailand, and the prevalence of CKD Stages 3 to 5 in the country was 2.9-13% (Domrongkitchaiporn *et al.*, 2005). As the end-stage renal disease (ESRD) progresses, it is necessary to provide a peritoneal dialysis (PD), haemodialysis (HD) and kidney transplant to patients who are in need because this treatment process would be able to improve their quality of life. Therefore, the target of CKD treatment is to prevent renal failure and the disease's progression to ESRD. In the case of anaemia, it usually occurs with patients who have CKD, and most patients were found to have an adverse drug event like left ventricular hypertrophy (LVH), ventricular dilation and ischemic heart disease. In addition, some patients were found to less likely have a severe adverse drug event like pure red cell aplasia (PRCA) than others. PRCA is a disorder of erythropoiesis that leads to sudden-onset, progressive and severe anaemia. In general, patients developing erythropoiesis-stimulating agent (ESA)-induced PRCA should not be treated with another ESA, From FDA safety databases include information on 59 new cases of antibody-associated PRCA, primarily associated with subcutaneous epoetin alfa (McKoy JM, 2008), the incidence rates for antibody-mediated PRCA of 0.02 to 0.03 per 10,000 patient-years among patients who received prolonged subcutaneous ESAs. These data suggest that antibody-mediated PRCA is now a rare class-related toxicity that occurs after extended periods of subcutaneous administration of EPOs to chronic kidney disease patients. Recently, ESAs have become known as a standard therapeutic agent for anaemia and have been expected to improve the quality of life, survival, and prevent the progression of CKD. The comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice (Francesco Trotta *et al.*, 2017) evaluate the comparative effectiveness and safety of biosimilars and originators of ESAs in naïve patients found that no difference between biosimilars and originators on relevant effectiveness and safety outcomes. The other study comparative risk/benefit profile of biosimilar and originator erythropoiesis-stimulating agents (ESAs) (Domenico Motola., 2018) shown that originator and biosimilar ESAs are at least equally effective and safe for the treatment of anemia due to CKD

ESAs are one of the costly medications that are used in specific patients by specialists. Consequently, it is necessary to have a proper ESAs control system for reducing the issue of costs from inappropriate ESAs usage.

Therefore, this study aimed to evaluate the ESAs usage pattern in CKD treatment including the types of ESA (Epoetin alfa and Epoetin beta, original products and biosimilar products), as well as assess the dosage regimen and dosage adjustment according to recommendations in stage 4 and stage 5 CKD patients including the efficacy and PRCA adverse drug event, and finally, to review the total cost of the ESAs treatment and the cost of inappropriate dosage adjustment.

Materials and Methods

Study population

The inclusion criteria were as follows: aged 18 years or older, stages 4 to 5 CKD patients diagnosed with anaemia and Hb concentration lower than 10.0 g/dL, which included pre-dialysis, PD and HD patients in all departments, adequate iron status[serum ferritin ≥500 ng/mL and transferrin saturation (TSAT) ≥30%), and who had continuously received the ESAs (Epoetin alfa and Epoetin beta) for 3 years 4 months, from 1 January, 2013 to 30 April, 2016, Rajavithi Hospital, Bangkok, Thailand. The exclusion criteria were as follows: patients who did not have baseline characteristics and a treatment profile, had received a kidney transplant, had not received ESAs since January 2013, active bleeding status and had enrolled for treatment in a haematology clinic.

Study design

This study was a retrospective cohort study using computerised database. The design also focussed on a descriptive approach. A data collection form was generated for the study with data referenced by the Thai National Formulary (TNF) 2010: Special Access Medicines of the National List of Essential Medicines 2015 and KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease 2012.In addition, the data form was approved by nephrologist. Furthermore, the ESAs were determined by a code depending on the type of dialysis and payment scheme: Original A 3,000IU, Original A 4,000IU, Biosimilar A1 4,000IU(HD), Biosimilar A1 4,000IU(CAPD), Biosimilar A2(Prefilled 4,000IU), Biosimilar A2 4,000IU(sss, other),

Biosimilar A1 4,000IU(Prefilled), and Biosimilar A2 4,000IU(CAPD) that were Epoetin alpha, and Original B 2,000IU and Original B 5,000IU that were Epoetin beta. Data were collected by a pharmacist in terms of the appropriate usage as defined by the KDIGO 2012 Guideline and KDOQI 2006 Guideline as follows:

1. Stage of CKD with anaemia

Some patients were diagnosed with chronic renal anaemia with aHb concentration lower than 10 g/dL and a Haematocrit concentration lower than 30 g/dL. The data of the stage 4 CKD patients who had a GFR of 15-30 mL/min/1.73 m^2 included the laboratory result (Hb concentration, Hct concentration, Scr, BUN, GFR, ferritin, and %TSAT). Moreover, the data of the stage 5 CKD patients with a HD or CAPD and whose GFR was less than 15 mL/min/1.73 m^2 included the laboratory result (Hb concentration, Hct concentration, Scr, BUN, GFR, ferritin, and %TSAT).

2. Iron storage

Adult CKD patients on ESAs therapy were monitored for serum ferritin and TSAT in which the amount of iron should sufficiently accumulate in the body. This means that the serum ferritin should be ≥500 ng/mL and the TSAT should be ≥ 30% (National list of essential medicines, 2012).

3. Dosage regimen

The Epoetin alfa or Epoetin beta dosage usually started at 20 to 50 IU/kg of the body's weight three times a week by subcutaneous (SC) administration. Higher Hb concentrations at baseline required lower initial ESA doses. The ESAs dose adjustment data were achieved and maintained the Hb concentration to be between 10-11.5 g/dL for improvements in QoL are maximized of Hb concentration in the 10-11.5 g/dl (100-115 g/l) (KDIGO, 2012) range and not to exceed 13g/dl (130g/l) indicated increased mortality at higher Hb target (KDIGO, 2012). Reduce the dose by 25% when the Hb level and Hb increasing rate keep in target. If the Hb level continues to increase, should discontinue ESAs until the Hb begin drop continuously and then start treatment that reduce the dose by approximately 25%. Increase the dose by 25% when the Hbis lower 10 g/dL and there is Hb increasing rate less than 1 g/dL after 4 weeks (the amount of iron accumulated in the body is sufficient). Do not increase the dose more often than 4 weeks.In terms of the cost of treatment, this was defined as the cost price per vial/syringe (Thai Baht) x the number of vials/syringes in all courses of treatment since 1 January, 2013 to 30 April, 2016 included the cost of inappropriate dosage adjustment. This was reported in Thai Baht and provided the total summary of each kind of medication.

Outcomes

1. Utilization pattern of ESAs in CKD treatment including the types of ESA (Epoetin alfa, Epoetin beta,original products and biosimilar products)

2. The efficacy of ESAs was evaluated based on the time to achieved target Hb level (Hb≥10 g/dl) that was number of days to achieve the Hb concentration target between Epoetin alfa, Epoetin beta, original products, biosimilar products at three months after starting the ESA administration. Maintaining a target haemoglobin concentration by epoetin alfa and epoetin beta classified by stages of CKD and dosage adjustment in stage 4 and stage 5 CKD patients

3. The PRCA adverse drug event was assessed by diagnosis record

4. Reviewed the total cost of the ESAs treatment and the cost of inappropriate dosage adjustment.

Statistical Analysis

All analyses were performed using a data analysis statistical software package SPSS version 11.5 (SPSS Inc., Chicago, IL)

1. Baseline characteristic data were expressed as frequencies and percentages.

2. The ESAs usage pattern for CKD treatment included the types of ESA (Epoetin alfa and Epoetin beta) or types of the ESAs brand were expressed as frequencies and percentages.

3. The efficacy of the ESAs was expressed as the mean ± standard deviation (SD) by using one-way ANOVA. A p value of <0.05 was considered statistically significant that compared between ND, HD and CAPD groups.

4. The total cost of the treatment and cost of inappropriate dosage adjustment were expressed as frequencies of the ESAs in term of Thai Baht

Ethics

Prior to initiation, the Ethics Committee of Khon Kaen University reviewed and approved the study. All information obtained by the researchers was handled as confidential data and identifiable only by identification numbers not linked to patient identifiers. Furthermore, all the related information was destroyed upon completion of the research.

Results

There were 390 stage 4 and stage 5 CKD patients who were diagnosed with anaemia. It was found that there were 118 patients who had not received ESAs since January 2013, 33 patients did not have available charts, 13 patients had received a kidney transplant, and 25 patients were being treated in a haematology clinic. Overall, 201 patients were enrolled into the present study.

Table 1. Demographic data

Patients' characteristics	N = 201(%)
Gender	
Male	87 (43.3)
Female	114 (56.7)
Age (years)	
Under 30 years	5 (2.5)
30-40 years	12 (6)
41-50 years	13 (6.5)
51-60 years	31 (15.4)
60 years +	140 (69.7)
Payment Scheme	
CSMBS[a]	116 (57.7)
SSS[b]	21 (10.4)
UCS[c]	63 (31.3)
Other	1 (0.5)
CKD Stage	
IV	39 (19.4)
V	162 (80.6)
Renal Replacement therapy (RRT)	
HD	81 (40.3)
CAPD	62 (30.8)
Underlying Disease	
Diabetes Mellitus	126 (62.7)
Hypertension	97 (48.3)
Dyslipidemia	42 (20.9)
Iron Storage at the Initial Phase	
Serum ferritin $\geq$ 500 ng/mL	201(100.0)
TSAT $\geq$ 30%	201(100.0)

[a]CSMBS (Civil Servant Medical Benefit Scheme)

[b]SSS (Social Security Scheme)

[c]UCS *(Universal Coverage* Scheme)

Table 2. Number of patients receiving ESAs classified by the brand name

Type of ESAs	Drug Name	No. of patients (%) (N=201)
Epoetin alpha	**Original brand**	
	Original A 3,000IU	7 (3.5%)
	Original A 4,000IU	44(21.9 %)
	Generic brand	
	Biosimilar A1 4,000IU(HD)	2 (1.0%)
	Biosimilar A1 4,000IU(CAPD)	10 (5.0%)
	Biosimilar A1 4,000IU(Prefilled)	16 (8.0%)
	Biosimilar A2 4,000IU(sss, other)	20 (10%)
	Biosimilar A2 (Prefilled 4,000IU)	16 (8.0%)
	Biosimilar A2 4,000IU(CAPD)	26 (12.9%)
Epoetin Beta[a]	**Original brand**	
	Original B 2,000IU	5 (2.5%)
	Original B 5,000IU	55 (27.4%)

[a] Shown as only the original brand as there was no local brand.

Table 3. The mean days of the achieved target (Hb≥10 g/dl) classified by the type of ESAs

Type of ESAs	Mean days to achieve the target (Hb>10 g/dl) (±SD)	Mean days difference to achieve the target		
		Epoetin beta (N=60)		
		ND[a]	HD[b]	CAPD[c]
Epoetin alpha (N=141)	550.3 (±SD 194.9)	-171 (P=0.04)*	-204 (P=0.02)*	-288 (P=0.02)*
Epoetin beta (N=60)	672 (±SD 255.7)	-	-	-

* The mean difference was found to be significant at a level of 0.05.

[a] ND (Non-dialysis)

[b] HD (Hemodialysis)

[c] CAPD (Continuous Ambulatory Peritoneal Dialysis)

Table 4. The mean days of the achieved target (Hb≥10 g/dl) classified by the trade name

ESAs	Mean days of the achieved target* (Hb>10 g/dl)			Mean days of the lower target (Hb<10 g/dl)		
Epoetin Alpha	ND	HD	CAPD	ND	HD	CAPD
Original A 3,000IU (N=7)	450	252	-	630	180	-
Original A 4,000IU (N=44)	567	657	576	405	423	477
Biosimilar A2(Prefilled 4,000IU) (N=16)	524	495	567	258	675	477
Biosimilar A2 4,000IU(sss,other) Biosimilar A2 4,000IU(CAPD) (N=46)	-	540	720	135	630	450
Biosimilar A1 4,000IU(Prefilled) (N=16)	297	288	522	468	540	648
Biosimilar A1 4,000IU(HD) Biosimilar A1 4,000IU(CAPD) (N=12)	-	540	531	-	135	639
Epoetin Beta						
Original B 2,000IU (N=5)	180	540	990	630	360	180
Original B 5,000IU (N=55)	774	792	756	423	369	414

* The achieved target each time of the follow up of every three months.

1. Patients' Characteristics

The demographic data are shown in Table 1. The inclusion criteria were as follows: aged 18 years or older; however, most of the patients were older than 60 years and there were 114 female patients (56.7%). Thirty-nine patients (19.4%) were diagnosed with stage 4 anaemia chronic kidney disease and 162 patients (80.6%) had stage 5. In addition, it was found that 81 patients (40.3%) had received HD, 62 patients (30.8%) had received CAPD, and others were in pre-dialysis stage. All patients had continuously received ESAs since January 2013 to April 2016, and the serum iron was ≥ 500 ng/mL and the TSAT was ≥30% of all patients in the initial phase. For treatment, the physician selected ESAs depending on the payment scheme in which it was found that most patients were under the Civil Servant Medical Benefit Scheme (CSMBS).

2. Medication used

There were 141 patients (70.1%) who received Epoetin alfa and 60 patients (29.9%) who received Epoetin beta, respectively. All patients were administered by a subcutaneous route. The physician selected ESAs depending on the payment scheme that comprised the CSMBS, Social Security Scheme (SSS) and Universal Coverage (UCS). The ESAs original product were Original A 3,000IU (7 patients, 3.5%), Original A 4,000IU (44 patients, 21.9%), Original B 2,000IU (5 patients, 2.5%), and Original B 5,000IU (55 patients, 27.4%). The other patients received the ESAs biosimilar product of Biosimilar A1 4,000IU(HD) (2 patients,1.0%), Biosimilar A1 4,000IU(CAPD) (10 patients, 5.0%), Biosimilar A2(Prefilled 4,000IU) (16 patients, 8.0%), Biosimilar A2 4,000IU(sss,other) (20 patients, 10%), Biosimilar A1 4,000IU(Prefilled syringe) (16 patients, 8.0%) and Biosimilar A2 4,000IU(CAPD) (26 patients,12.9%) (Table 2).

3. Number of days to achieve the Hb concentration target (Hb≥10 g/dl)

This study showed the appropriate maintained individual patient's Hb concentration in the target range between 10.0 and 11.5. g/dL. This was based on the mean days of patients who achieved the target each time of the follow up. It was found that Epoetin beta had a total of 672 mean days (±SD 255.7), which could achieve a higher target (Hb≥10 g/dl) than Epoetin alfa that only had 550.3 days (±SD 194.9) in ND-patients (P=0.04), HD patients (P=0.02) and CAPD patients (P=0.02), respectively (Table 3). Moreover, the number of mean days to achieve the target of the Original A 4,000IU was 657 days for HD and 576 days for CAPD, but biosimilar A2(Prefilled 4,000IU) and biosimilar A2 4,000IU (sss,other) could only achieve 567 days and 720 days for CAPD, respectively.

In addition, the biosimilar A1 4,000IU (Prefilled) could not achieve the target of the Hb concentration to be greater than 10g/dL in both HD and CAPD, but biosimilar A1 4,000IU (HD) and biosimilar A1 4,000IU (CAPD) achieved the target only for HD. It was also found that Epoetin beta could achieve the target of the Hb concentration to be greater than 10g/dL in both HD and CAPD (Table 4).

4. Maintaining a target haemoglobin concentration by Epoetinalfa and Epoetin beta classified by stages of CKD

In this study, it was found that 74 patients who received Epoetin alfa still had more Hb concentration lower than 10 g/dL, 11 patients in stage 4 and 63 patients in stage 5, respectively. Reasons for maintained Hb concentration that was lower than 10 g/dL such as, non-compliance, non-responsiveness that had signs of an iron deficiency, appropriately treated before the dosage adjustment. These patients received a dosage adjustment according to the recommendations of the KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease 2012. and the National List of Essential Medicines of Thailand, which recommended to increase the dose by 25% when the Hb was lower than 10 g/dL or the Hb increased its rate to be less than 1 g/dL after four weeks, which was the period of time that the amount of iron accumulated in the body should be sufficient. However, the dose should not be increased more than four weeks. In addition, for patients who acquired ESA hyporesponsiveness, if after treatment with a stable dosage they required an increase of up to 50% in ESA beyond the dose at which they had been stable, then in an effort to maintain a stable Hb concentration, it was suggested to limit the increased Hb concentration to 11.5 g/dL but not to exceed 13 g/dL, as this would result in adverse outcomes but there were no PRCA adverse drug events found in study.

On the other hand, there were 60 patients who received Epoetin beta and could maintain a greater Hb concentration between 10-11.5 g/dL of the target. Eleven patients had stage 4 CKD and 35 patients had stage 5. In addition, there were six patients who received Epoetin alfa and three patients who received Epoetin beta with aHb concentration above 13 g/dL. All of these patients had their dosage decreased if the Hb level continued to increase; thus, the ESAs would be discontinued until the Hb began to continuously drop and then treatment would be restarted with a dose reduction by approximately 25% (Table 5).

5. Total costs and cost of dosage adjustment in the treatment of anaemia chronic kidney disease

The total cost of ESAs treatment for anaemia chronic kidney disease was 19,077,533.97 Thai Baht in which there were 116 CSMBS patients (57.7%) who received ESAs. Among these patients, the total cost was approximately 17,673,542.03 Thai Baht. In addition, there were 21 SSS patients (10.4%) and 63 UCS patients (31.3%) that received ESAs, in which the total cost for treatment was about 247,064.10 Thai Baht and 1,271,139.67 Thai Baht, respectively (Table 6). The appropriate ESAs dosage adjustment should be the patient's Hb within a range of ±1.0 g/dL of the reference range of Hb level at the last visit, and the dosage should not be adjusted to increase the Hb concentration to exceed 1 g/dL per two weeks, as this could result in cardiovascular disease. From Table 6, the cost of inappropriate dosage adjustment was 101,258.38 Thai Baht of the total cost of the treatment course. Furthermore, it was found that the cost of the inappropriate dosage adjustment of the original A2 was 25,680 Thai Baht and Original B1 was 47,174.16 Thai Baht that cost higher than other forms of medication (Figure 1).

Table 5. Hb concentration at three months after starting the ESA administration

Stage of CKD	ESAs type	Hb concentration	N = 201 (%)
Stage 4 (N=39)	Epoetin alpha	< 10 g/dL	11 (5.5)
		10–12 g/dL	8 (3.9)
		> 13 g/dL	3 (1.5)
Stage 5 (N=162)		< 10 g/dL	63 (31.3)
		10–12 g/dL	52 (25.9)
		> 13 g/dL	3 (1.5)
Stage 4 (N=39)	Epoetin beta	< 10 g/dL	4 (1.9)
		10–12 g/dL	11 (5.5)
		> 13 g/dL	2 (0.1)
Stage 5 (N=162)		< 10 g/dL	8 (3.9)
		10–12 g/dL	35 (17.4)
		> 13 g/dL	1 (0.5)

Table 6. The cost of inappropriate ESA usage for during the three year study period

Trade name	Total cost of ESA treatment course (THB)	Cost of inappropriate ESA usage (THB)
Original A1	339,511.00	4,066
Original A2	7,139,040.00	25,680
Biosimilar A1	93,749.12	0
Biosimilar A2	310,068.88	3,483.92
Biosimilar A5	143,711.70	197.95
Biosimilar A3	271,710.45	2,648.25
Biosimilar A4	482,364.56	316.72
Biosimilar A6	504,851.68	17,102.88
Original B1	494,928.50	588.5
Original B2	9,297,598.08	47,174.16
Total cost (THB)	19,077,533.97	101,258.38

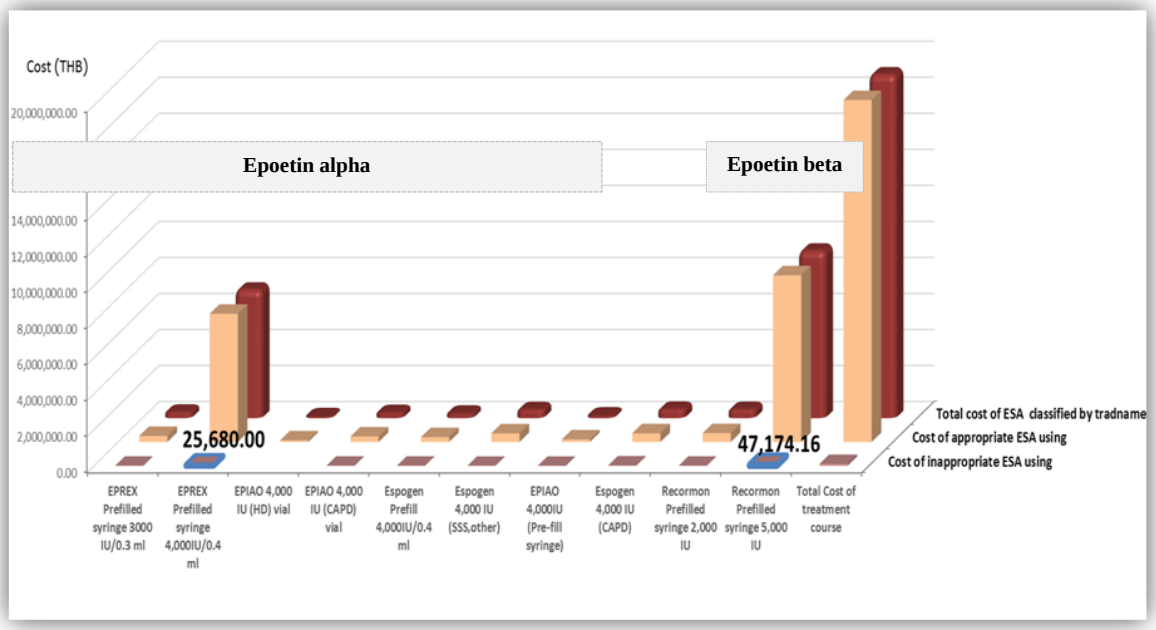

Figure 1. The total cost of ESAs treatment and cost of inappropriate dosage adjustment.

Discussion

In this study, most of the patients with anaemia chronic kidney disease were female or aged 60 years or older, and more than half of the total number of patients who enrolled in the present study were under the CSMBS payment scheme. All patients were diagnosed having anaemiastage 4 and stage 5 CKD with aHb concentration of <10g/dL and had received an ESAs, but the majority had Stage 5 CKD. All CKD patients on ESAs therapy were monitored for serum ferritin ≥500 ng/mL and TSAT ≥30% according to the recommendations of the KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease 2012, which was different from the K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anaemia in Chronic Kidney Disease 2006 that indicated serum ferritin ≥100 ng/mL and TSAT ≥ 20.The ESAs selected by the physician depended on the individual patient's payment scheme. There were 116 (57.7%) CSMBS patients who were diagnosed with anaemia chronic kidney disease, so there were more patients receiving original ESAs than the biosimilar brand of ESAs. As such, Original A 3,000IU, Original A 4,000IU (Epoetin alpha), Original B 2,000IU and Original B 5,000IU (Epoetin beta) were commonly used in this group of patients. In the hospital, there were several brands of ESAs that were an alternative for the physician to select for therapy.

In terms of mean days achieve target of the Hb concentration each time of the follow up between January 2013 and April 2016, the mean days to achieve target Hb (Hb≥10 g/dl) of ESAs were classified by the type and brand name of the ESAs according to the KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease 2012. The mean days to achieve target Hb of Epoetin beta had more efficacy than Epoetin alfa in this study, as there was only Original B 2,000IU and Original B 5,000IU; a brand name of Epoetin beta while Epoetin alfa had several brand names. The efficacy assessment in the non-dialysis and dialysis patients showed a difference. In the case of haemodialysis, it was found that the mean days of both Biosimilar A2 (Prefilled 4,000IU), Biosimilar A2 4,000IU(sss,other) and Biosimilar A2 4,000IU(CAPD) could achieve the target less than other brands of Epoetin alfa except Biosimilar A1 4,000IU(HD) and Biosimilar A1 4,000(CAPD) that had efficacy in HD patients. Thus, it is possible that there were more HD patients in this study. The efficacy assessment was similar to the study conducted (Lissy, 2011) in which the comparison of the pharmacokinetic and pharmacodynamic profiles of the EPREX® brand and

Epogen® brand in the U.S. had shown an equivalent pharmacodynamic response that achieved the target with all compared Epoetin alfa products. It was found that the bioequivalence, equivalent potency and efficacy were demonstrated for Epogen® as well as Eprex® of the study, and there were similar pharmacokinetic and pharmacodynamic profiles of Epogen® and Erypo®/Eprex®. Similarly, with this retrospective study, there were two biosimilar products of epoetin alfa, in which it was found that the efficacy of the original brand of Epoetin alfa and biosimilar product of Epoetin alfa had no significant difference. In this study, the comparison of the mean days between the original product and biosimilar product found that the biosimilar product could achieve a higher target (Hb≥10 g/dl) than the original product, which showed no significant difference in the HD and CAPD patients; therefore, it was possible that there were two biosimilar product of Epoetin alfa while there was only one original product of Epoetin beta. In addition, the original brand of the Epoetin alfa had two strengths as an Original A 3,000IU and Original A 4,000IU, which was one of the reasons that made the difference of efficacy between the original product and biosimilar product. In this study, there were no PRCA adverse drug events found during 3 years from ESA usage.

In this study, the calculation of the cost was only the cost of the drug without direct and indirect cost of treatment. Thus, it may not represent the actual cost-effectiveness. In terms of the appropriate dosage adjustment, increases in the Hb concentrations should not exceed 1 g/dL per four weeks according to the KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease 2012 that suggested an increase in the Hb concentrations of 1.0 to 2.0 g/dl (10 to 20 g/l) per month. This is consistent with the findings in the ESA trials (Palmer, 2012) of CKD associated anaemia where the mean initial rates of the Hb concentration increases were 0.7 to 2.5 g/dl (7to25g/l) in the first four weeks. However, a rise in the Hb greater than 2.0 g/dl (20 g/l) over a four-week period should be avoided. In terms of the cost of an inappropriate dosage adjustment, the adjustment to increase the Hb concentration to exceed 1 g/dL per two weeks or within four weeks was calculated and presented as Thai Baht per vial or the syringe of the ESAs. In this study, it was shown that the ESAs treatment of chronic renal anaemia patients was divided by the payment scheme due to the differences in the use of the ESA brand. Because there were mainly CSMBS patients who were diagnosed with chronic renal anaemia; therefore, there were more original ESA brand treatment costs that included the inappropriate cost from the dosage adjustment.

Conclusion

Epoetin beta had a higher performance in terms of achieving the target of the Hb concentration in chronic renal anaemia patients on pre-dialysis and dialysis. Both the original or biosimilar products of Epoetin alfa could achieve the target of the Hb concentration for anaemia treatment. In addition, appropriate ESAs treatment for maintaining the Hb concentration could prevent value loss due to the inappropriate treatment provided to all CKD patients; moreover, no subjects developed anti-erythropoietin antibodies upon administration of the study's medication.

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