Preliminary Report

Hemoglobin Response and Influence on Left Ventricular Hypertrophy after 24-Week Treatment of a Biosimilar Epoetin-Alfa in Hemodialysis Patients with Anemia

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Background: *Anemia is common in end-stage renal disease (ESRD) patients and an important determinant for left ventricular hypertrophy (LVH) in dialysis patients. There are increasing numbers of biosimilar epoetin-alfa entering Thailand.*
Objective: *To conduct a prospective trial to evaluate the efficacy and safety of a biosimilar epoetin-alfa (epoetin) (Espogen™) in ESRD patients receiving chronic hemodialysis complicated by anemia and to address its impact on the left ventricular mass index (LVMI) and volume index (LVVI) in these patients.*
Material and Method: *Twenty-two hemodialysis (HD) subjects were recruited from Rajavithi and Huachiew Hospitals. Inclusion criteria were chronic HD, hemoglobin (Hb) < 10 g/dL without preceding treatment (epoetin or transfusion) for 1 month. Echocardiographic baselines were obtained. Epoetin-alfa was initially given 4,000 IU subcutaneously twice a week and titrated biweekly to keep the Hb range of 11 to 12 g/dL (titration period 12 weeks). Treatment continued until the end of 24 weeks. Records were made for conventional blood tests, blood pressure, amount of drugs needed to control blood pressure, and adverse events. Echocardiogram was repeated (on observer blinding) at the completion of the present study.*
Results: *After 24-week of epoetin therapy, the predialysis Hb level increased significantly from 8.0 ± 1.3 g/dL to 11.0 ± 1.1 g/dL ($p < 0.001$). The mean dose of epoetin at the present study entry was 143.6 ± 87.8 IU/kg/week. At the present study entry, LVH was present in 86.4% of the patients. At the completion of the present study, a decrease in LVMI was observed in 50% of the patients; however, the mean LVMI change was not significantly different. Notably, there were minimal but significant changes in LVEDD (52.8 ± 7.0 vs. 50.1 ± 6.9 mm, $p < 0.05$), LVVI (86.2 ± 25.2 vs. 75.5 ± 19.5 mL/m^2, $p < 0.05$) and when subjects were partitioned into tertiles of baseline LVMI, the LVVI change was confined to the highest tertile (103.7 ± 25.2 vs. 79.6 ± 21.9 mL/m^2, $p < 0.05$). The aortic root diameter also significantly decreased despite some increase in blood pressures but without significant change in number of antihypertensive agents. No serious adverse event was observed during the present study period.*
Conclusion: *The efficacy of anemia treatment and safety of the biosimilar epoetin-alfa was demonstrated in hemodialysis patients. Significant regression of LVVI and some reduction in LVMI were shown in this 24-week prospective trial.*

Keywords: *Erythropoietin, Epoetin, Anemia, Hemodialysis, End-stage renal disease, Left ventricular mass index, Left ventricular volume index*

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Anemia is a common feature of chronic kidney disease (CKD), and its prevalence has been shown to increase with diminishing renal function, leading to a large proportion of patients who enter for dialysis in an anemic state[1]. The major pathogenetic factor of renal anemia is inadequate production of erythropoietin from the diseased kidneys, causing an inappropriately low level of red cell production. The symptoms associated with anemia include fatigue, decreased exercise tolerance, cardiac dysfunction, and impaired cognitive function[2]. Anemia also results in an increased risk of

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development of cardiovascular disease and increased mortality[3]. Left ventricular hypertrophy (LVH) has been observed in as many as 30-45 percent of predialysis CKD patients, with a higher prevalence and more severe LVH in those with increasing lower degrees of renal function[4]. In dialysis patients, LVH is present in nearly 80% of them[5]. Moreover, it has been shown that LVH is an independent risk factor for cardiovascular mortality in patients with end-stage renal disease (ESRD)[6]. In dialysis patients, it is established that anemia has emerged as an important, independent risk factor for the development and progression of LVH, left ventricular dilatation, congestive heart failure, hospitalization, and of adverse cardiovascular outcomes, including mortality[7-9].

The management of renal anemia has been revolutionized over the last 20 years, after recombinant human erythropoietin (epoetin) was introduced into routine nephrologic practice, which replaced blood transfusions as used to be the mainstay treatment of this complication. Specific clinical guidelines have been developed to optimize the quality of anemia management for patients with CKD. As a result, many clinical practice guidelines in the management of anemia in CKD patients have been published[2,10,11]. Importantly, correction of anemia with epoetin has been associated with improvement of LVH in patients with ESRD receiving maintenance dialysis[12,13].

Because the recombinant epoetins are costly medical care and the patent of the innovator epoetin-alfa has expired. Currently, this has allowed an increasing number of biosimilar versions of epoetin-alfa to enter in the developing world, including Thailand. The authors, therefore, conducted a prospective trial to evaluate the efficacy and safety of a biosimilar epoetin-alfa in ESRD patients receiving chronic hemodialysis complicated by anemia and to address its impact on the left ventricle (LV) mass and volume in these patients.

Material and Method

Patients

Between December 2005 and May 2006, 75 chronic hemodialysis patients at Rajavithi Hospital, a supertertiary hospital of the Ministry of Public Health of Thailand, and Huachiew Hospital, a charity hospital in Bangkok, were assessed for possible eligibility. Stable end-stage renal disease adult patients ($\geq$ 18 years of age) were consecutively enrolled using the following inclusion criteria: (1) Predialysis hemoglobin less than 10.0 g/dL without preceding blood transfusion or epoetin therapy for 1 month; (2) hemodialysis started longer than 3 months; (3) receiving adequate dialysis through arteriovenous fistula or bypass graft or permanent vascular catheter; (4) having adequate iron store, serum ferritin $\geq$ 100 ng/mL and transferrin saturation (TSAT) $\geq$ 20%. The exclusion criteria were (1) patients who had evidence of infection within 1 month of the enrollment; (2) prior acute myocardial infarction, known valvular heart disease or uncontrolled hypertension; (3) medical conditions that are likely to reduce response to epoetin, including hematologic diseases, chronic inflammatory diseases, or malignancy; (4) C-reactive protein > 30 mg/L, (5) thrombocytes > 500,000/mm^3, (6) seizure within the previous year; (7) any bleeding events within the preceding month.

Written informed consent was obtained from all patients and the present study protocol was reviewed and approved by the Ethical Committee of Rajavithi Hospital.

Methods

Intervention

A noncomparative, prospective, interventional study was conducted over a period of 24 weeks to observe the effects of a biosimilar epoetin-alfa on LVH in ESRD patients with anemia receiving chronic hemodialysis. At the present study entry, hemoglobin levels (g/dL), other baseline characteristics, LV mass index (LVMI) and LV volume index (LVVI) by standard echocardiographic methods were assessed[14,15].

All patients received subcutaneous injection of epoetin-alfa and oral iron supplements to maintain serum ferritin levels of $\geq$ 100 ng/mL and transferrin saturation (TSAT) of $\geq$ 20%[2]. Initially, the epoetin-alfa was given subcutaneously postdialysis twice a week at a starting dose of 4,000 IU/dose, with dose adjustments after the first 4 weeks according to the biweekly hemoglobin determinations, aiming to achieve and maintain the target hemoglobin level of 11 to 12 g/dL[2,16]. The epoetin-alfa dosages were augmented or reduced by 25% of the baseline dose if their hemoglobin levels were < 11 or > 12 g/dL, respectively. The first 12-week period was the titration phase and the remaining 12 weeks were maintenance phase.

Monitoring

All patients received twice a week hemodialysis schedule. The dialysis dose, determined by weekly sp.Kt/V urea, remained unchanged in all subjects during the present study period. The complete blood count (CBC), and reticulocyte count was monitored every

two weeks. Other laboratory parameters, including blood urea nitrogen (BUN), serum creatinine, potassium, albumin, C-reactive protein, intact-parathyroid hormone, ferritin, and % TSAT, were collected from predialysis blood samples at baseline, week 12 and week 24 of the present study. Iron overload was defined as serum ferritin in excess of 800 ng/mL[2].

Blood pressure and adverse effects

Safety was assessed by continuous monitoring and collection of adverse events throughout the present study. During the whole study period, the pre- and post-dialysis blood pressures, including intradialytic period, were closely observed and recorded. Antihypertensive medications were adjusted to keep the predialysis target blood pressure of $\leq$ 140/90 mmHg[17]. Other known adverse effects of epoetin therapy including seizure, thrombotic complications, vascular access thrombosis, flu-like symptoms or allergic rashes were also closely monitored.

Measurements

Echocardiographic studies

Two-dimensional and M-mode echocardiographic studies were performed at baseline and 24 weeks by the use of an ultrasound imaging system (Philips, Sonos 7500, Netherland), carried out when the patient had achieved dry weight, within 24 hours of a hemodialysis session, blindly by the same cardiologist, throughout the entire study. Echocardiograms were recorded at rest in the third or fourth intercostal space lateral to the left sternal border with the patient recumbent in the supine or half-sided position. Left ventricular chamber recording was obtained at the tip of the mitral valve leaflet. To characterize the left ventricular structure, measurements of interventricular septum thickness (IVST), posterior wall thickness (LVPWT), and left ventricular internal end systolic diameter (LVESD) as well as end diastolic diameter (LVEDD) were performed in accordance with the standard recommendations[18]. All parameters were determined over three cardiac cycles and subsequently mean values were calculated. Left ventricular mass (LVM), in grams, was calculated by using the formula of Devereux and Reichek as $0.00083 * [(\text{LVEDD mm} + \text{IVST mm} + \text{LVPWT mm})^3 - (\text{LVEDD mm})^3 + 0.6]$[19], Similarly, LV cavity dimensions estimated by the Penn convention were regression corrected and presented according to the standard recommendations[18]. LV volume, in milliliters, was calculated by the formula of Pombo et al as $0.001047 * (\text{LVEDD})^3$ [20]. To be able to compare among patients with varying body build both LV mass and LV volume were indexed to body surface area and were presented in grams per square meter and milliliters per square meter, respectively.

Definitions

The following definitions were used:

A) LV dilation: LV cavity volume > 90 mL/m^2[20]

B) LV hypertrophy by mass index: LVMI > 100 g/m^2 in women, > 131 g/m^2 in men. These values are the upper limits of normality among healthy participants in the Framingham Heart Study[15].

Further characterization of LVH into concentric and eccentric hypertrophy was on measurements of relative wall thickness[21].

C) Relative wall thickness (RWT), a measure of left ventricular geometry: RWT = (LVPWT + IVS.T)/LVEDD

D) Concentric LV hypertrophy: RWT $\geq$ 0.45 in the presence of LVH.

E) Eccentric LV hypertrophy: RWT < 0.45 in the presence of LVH.

F) Concentric remodeling: RWT $\geq$ 0.45 in the absence of LVH.

Study end point

The primary end point was changes from baseline in LVMI and LVVI at week 24. The other primary efficacy parameter was the median time for the hemoglobin response to epoetin therapy defined as a single hemoglobin measurement of $\geq$ 11 g/dL without the need of blood transfusion or an increase in hemoglobin $\geq$ 2 g/dL from baseline. Secondary end points included other echocardiographic variables and blood pressure changes.

Statistical analysis

Continuous variables are expressed as mean values $\pm$ standard deviation. The nonparametric Wilcoxon signed rank test was used to test the difference in mean values of study parameters before and after correction of renal anemia in hemodialysis patients or between two different time points. Pearson's Chi-square analysis or Fisher exact test when appropriate was performed to test the differences of categorical variables between the values at two different time points. Pearson correlation was used to test the correlation between two variables. A p-value of < 0.05 was considered to be statistically significant. All statistical analysis was performed by using SPSS for Windows version 13.

Results

Patients

Twenty-two stable chronic hemodialysis patients, with a mean age of 51 ± 13 years (range 24 to 78 years) and 72.7% being female, met the enrollment criteria and agreed to participate in the present study. Their baseline characteristics are presented in Table 1. Over one-third of them (36.4%) had never received epoetin therapy due to pecuniary issue. However, most patients who had previously received the epoetin therapy could not afford regular epoetin administration. Therefore, almost all the patients (95.6%) had previously received blood transfusion periodically for treatment of anemia prior to the enrollment. Most of the patients (81.8%) had the initial hemoglobin levels of 9 g/dL or less (Table 1). The major cause of ESRD was diabetic nephropathy in nearly one-third (31.8%) of the patients. The type of vascular accesses were native arteriovenous fistula in 90.9%, tunneled cuffed venous catheters were used in the remainders. Strikingly, all patients were hypertensive and received antihypertensive agents. Use of multiple antihypertensive medications was common. Only one patient (4.6%) received monotherapy. Ten patients (45.5%) received three or more antihypertensive agents. The mean number of antihypertensive agents was 2.59 ± 0.85, with 22.7% of the patients received an ACE inhibitor.

Table 1. Baseline characteristics of chronic hemodialysis patients (n = 22)

Characteristics	Value
Age (years)	51 ± 13 (range 24-78 yr)
Gender: Male / Female (%)	27.3/72.7
Body weight (kg)	59.9 ± 17.8
Diabetic nephropathy (%)	31.8
Duration of hemodialysis (months)	40.3 ± 32.7
Type of vascular access:	
AV fistula (%)	90.9
Tunneled cuffed catheter (%)	8.1
Hypertension (%)	100
Previous blood transfusion (%)	95.6
Previous epoetin therapy (%)	63.6
Blood urea nitrogen (mg/dL)	82.3 ± 20.6
Serum creatinine (mg/dL)	13.0 ± 3.2
Hemoglobin (g/dL)	8.01 ± 1.26
< 8 g/dL, n (%)	11 (50%)
> 8 to 9 g/dL, n (%)	7 (31.8)
> 9 g/dL, n (%)	4 (18.2%)
Hematocrit (vol%)	24.5 ± 3.6

± Refers to mean value plus/minus standard deviation

Clinical effects of the intervention

Efficacy of epoetin-alfa

The initiation dose of epoetin was 143.6 ± 37.8 IU/kg/week. During therapy with epoetin, the predialysis hemoglobin concentration increased significantly from 8.0 ± 1.3 g/dL at baseline to 10.5 ± 1.6 g/dL at week 12 ($p < 0.001$) and to 11.0 ± 1.1 g/dL at week 24 ($p < 0.001$). As well, the hematocrit values increase from 24.5 ± 3.6% to 31.9 ± 4.7% at week 12 ($p < 0.001$) and to 33.7 ± 3.1% at week 24 ($p < 0.001$) (Table 2). Fig. 1 and 2 show the hemoglobin (Fig. 1A) and hematocrit (Fig. 1B) results over time and the changes of epoetin dose over time (Fig. 2). By the 6th week onwards, a statistically higher hemoglobin ($p < 0.001$), compared to baseline level, was achieved through the end of the present study. The rate of increase in the hemoglobin during the first 12 weeks was 0.19 ± 0.12 g/dL/week or 0.78 ± 0.49 g/dL/month. The median time for the hemoglobin response to epoetin therapy was 10 weeks with 54.6% of patients had a hemoglobin response, and the proportion of responders further rose to 63.6% at 12 weeks. By the time of 10 weeks, the mean hemoglobin level increased to 10.3 ± 1.4 g/dL, with the mean dose of epoetin of 193.3 ± 43.2 IU/kg/week. The peak value of hemoglobin level was attained by the 18th week, and maintained at plateau values there-after. Accordingly, the peak value of epoetin dosage, 193.3 ± 43.2 IU/kg/week, was reached by the 10th week and then progressively decreased to 149.7 ± 73.3 IU/kg/week at the end of the present study (Fig. 2). The absolute reticulocyte count increased significantly from baseline since the 2nd week of treatment (32,668 ± 32,871 vs. 48,526 ± 4,516 /cu.mm, $p < 0.05$) onwards (Table 2).

Toward the end of the titration phase, during the first 12 weeks, the mean hemoglobin level and epoetin dosage were 9.1 ± 1.2 g/dL and 170.3 ± 39.5 IU/kg/week, respectively. During the maintenance phase, from weeks 12 to 24, the mean hemoglobin level and epoetin dosage were 11.0 ± 1.6 g/dL and 158.8 ± 52.3 IU/kg/week, respectively. Of the entire study period, the mean predialysis hemoglobin level was 9.9 ± 1.2 g/dL and the mean dose of epoetin was 164.5 ± 30.7 IU/kg/week (Fig. 1A, 2).

Biochemical parameters and blood pressure changes

The serum ferritin level at study entry was 1,298.1 ± 968.1 ng/mL. Thirteen patients (59%) had iron overload. After epoetin therapy, the mean serum

Table 2. Biochemical and dialysis parameters at baseline, week 12 and week 24 (n = 22)

Parameters	Baseline	Week 12	Week 24
Body weight (kg)	59.9 ± 17.8	60.4 ± 18.0	60.3 ± 17.7
Body surface area (m^2)	1.61 ± 0.26	1.62 ± 0.26	1.62 ± 0.26
Number of anti-hypertensive agents	2.59 ± 0.85	2.77 ± 0.81	2.64 ± 0.79
Using ACE inhibitor	22.7%	13.6%	13.6%
Using calcium-channel blocker	95.5%	95.5%	95.5%
Hemoglobin (g/dL)	8.0 ± 1.3	10.5 ± 1.6***	11.0 ± 1.1***
Hematocrit (vol%)	24.5 ± 3.6	31.9 ± 4.7***	33.7 ± 3.1***
Absolute reticulocyte count (per cu.mm)	32,668 ± 32, 871	56,929 ± 22,904**	48,526 ± 4,516*
TSAT (%)	45.7 ± 19.2	27.0 ± 13.6***	24.9 ± 11.8***
Serum ferritin (ng/mL)	1,298.1 ± 968.1	1,078.6 ± 1,030.3**	845.3 ± 957.5***
Serum potassium (mEq/L)	4.93 ± 0.55	5.11 ± 0.65	4.73 ± 0.63
Serum albumin (g/dL)	3.7 ± 0.5	3.8 ± 0.4*	3.6 ± 0.4
Weekly sp.Kt/V urea	3.57 ± 1.10	4.41 ± 4.80	3.57 ± 1.29
Serum intact PTH (pg/mL)	453.1 ± 489.7	268.8 ± 352.1	265.6 ± 274.4*
C-reactive protein (mg/L)	2.57 ± 2.99	2.99 ± 4.12	2.73 ± 3.98

* p < 0.05, ** p < 0.01, *** p < 0.001 vs baseline value

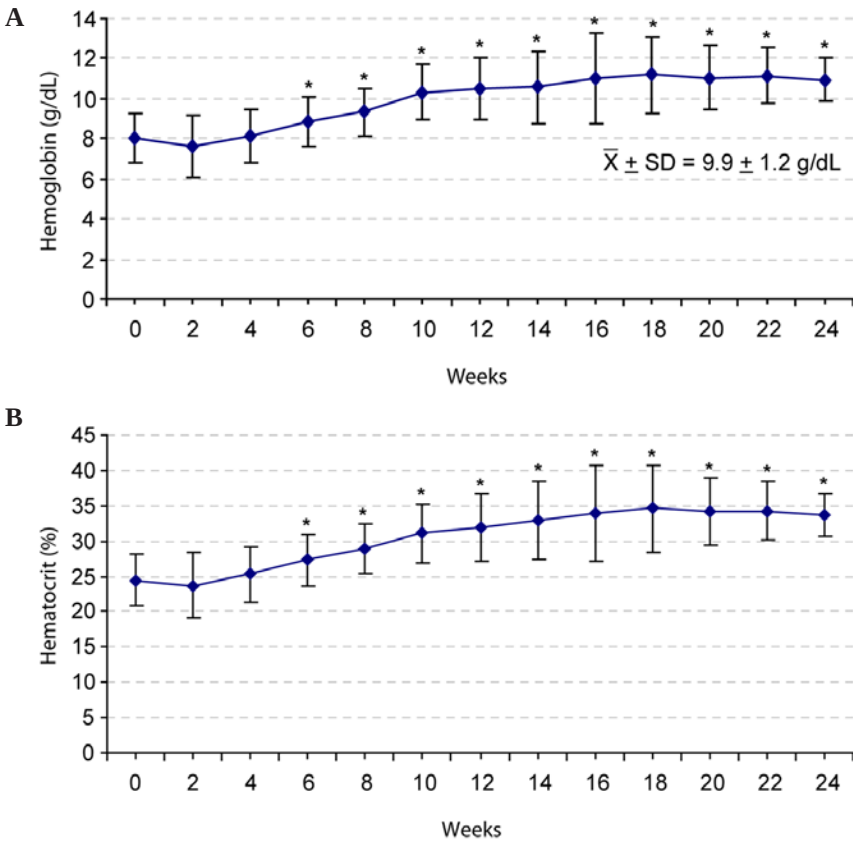

Fig. 1 Average biweekly hemoglobin (A) and hematocrit levels (B) over time in hemodialysis patients (n = 22) receiving epoetin-alfa during the 24 weeks of study (* p < 0.001vs wk 0)

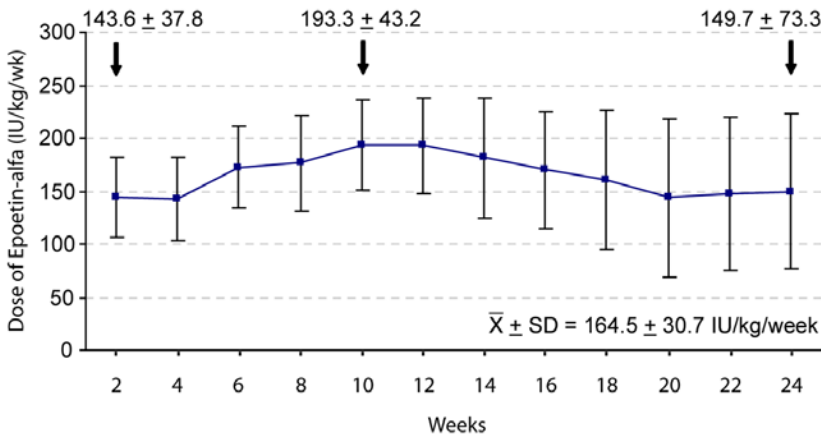

Fig. 2 Average weekly dosage of epoetin-alfa during the 24 weeks of study

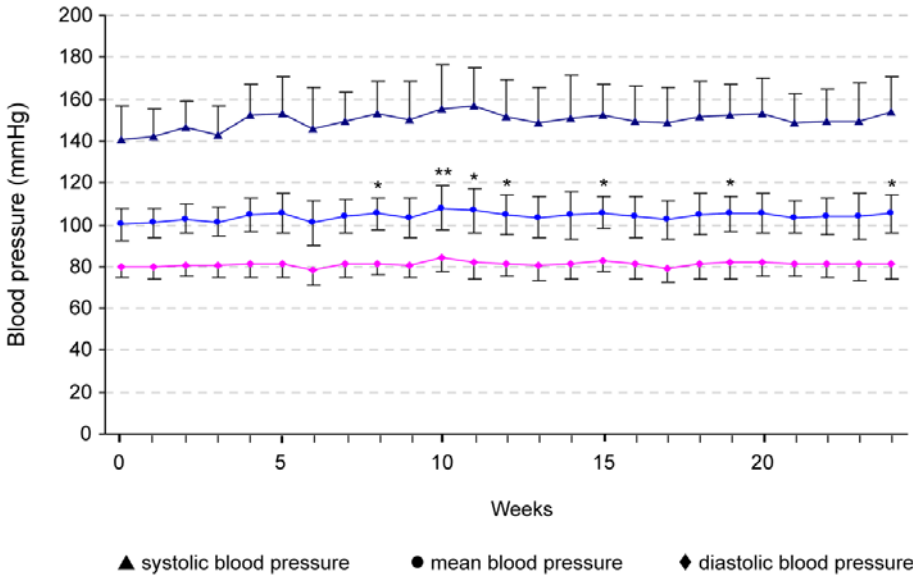

Fig. 3 Average predialysis blood pressure of hemodialysis patients during the 24 weeks of study (* $p < 0.05$ vs wk 0, ** $p < 0.01$ vs wk 0)

ferritin level decreased to 1,078.6 ± 1,030.3 ng/mL ($p = 0.013$, vs. baseline) at week 12, and 845.3 ± 957.5 ng/mL ($p < 0.001$) at week 24. This accounted for a 37.5% reduction in serum ferritin levels after 24 weeks of therapy. Other biochemical variables are shown in Table 2.

Fig. 3 shows the changes of predialysis systolic, diastolic, and mean blood pressure in these patients. Only modest elevation of the mean blood pressure was observed at weeks 8, 10, 11, 12 and 15, when compared to the value at entry. However, the average numbers of antihypertensive agents used by each patient were not significantly different throughout the course of treatment; with the values at entry, week 12, and week 24 of 2.59 ± 0.85, 2.77 ± 0.81, and 2.64 ± 0.79, respectively ($p > 0.05$). The percentage of ACE inhibitors and calcium antagonists were similar during the entire period of the present study (Table 2).

Adverse effects of epoetin-alfa

There was no occurrence of arteriovenous access thrombosis during the entire course of the

present study period. Although there was one episode of fluid overloading in one patient related to excess fluid consumption after the first month of therapy and needed hospitalization, but the problem could be solved immediately by urgent dialysis. Another patient experienced severe hypertension during the 10th week; however, the blood pressure was under control after some adjustment of his antihypertensive medication. None of their hemoglobin levels was out of range during the events. Finally, one patient experienced some itching without a rash at the injection site during the 3rd week but spontaneously disappeared in a very short time after injection.

Echocardiographic findings

Overall, 19 patients (86.4%) met the criteria for echocardiographic LVH at the present study entry, which comprised concentric LVH in 10 patients (45.5%) and eccentric LVH in nine patients (40.9%). There were nine patients (40.9%) with LV dilation (LVVI > 90 mL/m^2). Table 3 shows the echocardiographic parameters compared between the baseline values and those at week 24 of the epoetin therapy. There was no change in body surface area. The changes in LVMI and LVVI in individual patients are demonstrated in Fig. 4 and 5. At the end of the present study, 50% of patients had a decrease in LVMI, and there was a trend of decrease in LVMI (152.1 $\pm$ 45.8 vs. 146.1 $\pm$ 3.6 g/m^2, p > 0.05) for the entire group (change from baseline -6.1 $\pm$ 38.3 g/m^2), with the mean percentage LVMI decrement of 0.48 $\pm$ 21.5% (Fig. 4). Notably, the LVVI decreased significantly from 86.2 $\pm$ 25.2 mL/m^2 at baseline to 75.5 $\pm$ 19.5 mL/m^2 at the end of the present study (change from baseline -10.7 $\pm$ 23.3 mL/m^2, p = 0.042). Fifteen patients (68.2%) had a decrease in LVVI, with the mean percentage LVVI decrement of 8.2 $\pm$ 26.6% for the entire group (Fig. 5). Additional analysis of LVMI by tertiles (Table 4) of baseline LVMI ($\leq$ 130, > 130 to 160, and > 160 g/m^2) showed that a significant decrement in LVVI at the end of the present study could be demonstrated only in patients with the highest tertile (103.7 $\pm$ 25.2 vs. 79.6 $\pm$ 21.9 mL/m^2, p = 0.028). Furthermore, the authors could also demonstrate a significant decrease in LVEDD (52.8 $\pm$ 7.0 vs. 50.1 $\pm$ 6.9 mm, p = 0.042), aortic root diameter (29.8 $\pm$ 3.3 vs. 26.1 $\pm$ 5.0 mm, p = 0.002). All other echocardiographic parameters did not change significantly (Table 3). Finally, there was significant correlation between the aortic root diameter and LV mass both at baseline (r^2 = 0.672, p = 0.001) and at week 24 (r^2 = 0.483, p = 0.023).

Discussion

The present study, to the authors' knowledge, is the first prospective trial in Thailand to evaluate the

Table 3. Echocardiographic parameters at baseline and week 24 (n = 22)

Parameters	Baseline	Week 24		p-value
			Change from baseline	
LVEDD (mm)	52.8 $\pm$ 7.0	50.1 $\pm$ 6.9	-2.7 $\pm$ 5.7	0.042*
LVESD (mm)	48.3 $\pm$ 24.9	50.9 $\pm$ 29.1	2.6 $\pm$ 36.3	0.141
IVST (mm)	11.1 $\pm$ 2.2	11.7 $\pm$ 2.4	0.6 $\pm$ 2.6	0.280
LVPWT (mm)	11.8 $\pm$ 2.7	12.2 $\pm$ 1.9	0.5 $\pm$ 2.0	0.424
Ejection fraction (%)	66.6 $\pm$ 10.5	66.7 $\pm$ 11.3	0.2 $\pm$ 10.6	0.948
Fractional shorting (%)	37.8 $\pm$ 8.4	37.8 $\pm$ 8.3	0.0 $\pm$ 8.0	0.961
Aortic root diameter (mm)	29.8 $\pm$ 3.3	26.1 $\pm$ 5.0	-3.6 $\pm$ 3.7	0.002*
LVMI (g/m^2)	152.1 $\pm$ 45.8	146.1 $\pm$ 3.6	-6.1 $\pm$ 38.3	0.935
LVVI (mL/m^2)	86.2 $\pm$ 25.2	75.5 $\pm$ 19.5	-10.7 $\pm$ 23.3	0.042*
LV mass/volume ratio (g/mL)	1.84 $\pm$ 0.47	2.01 $\pm$ 0.52	0.17 $\pm$ 23.3	0.236
LVH (% of patients)	86.4	90.9		0.636
LV dilation (% of patients)	40.9	22.7		0.195

$\pm$ refers to mean value plus/minus standard deviation

LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVPWT, left ventricular posterior wall thickness; LVMI, left ventricular mass index; LVVI, left ventricular volume index; LVH, left ventricular hypertrophy

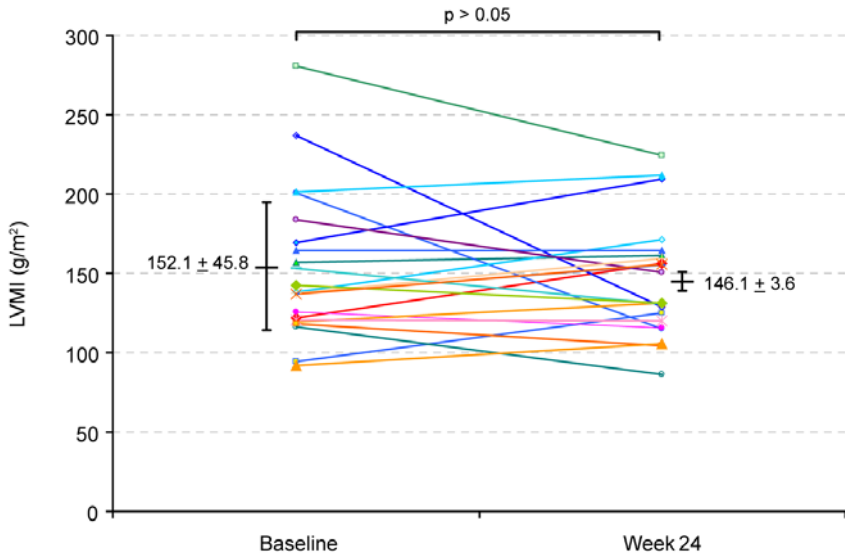

Fig. 4 Effect of partial anemia correction after 24-week therapy with an epoetin-alfa on left ventricular mass index (LVMI), comparing between data at baseline and week 24. The figure depicts individual data points of the evolution of LVMI in each patient

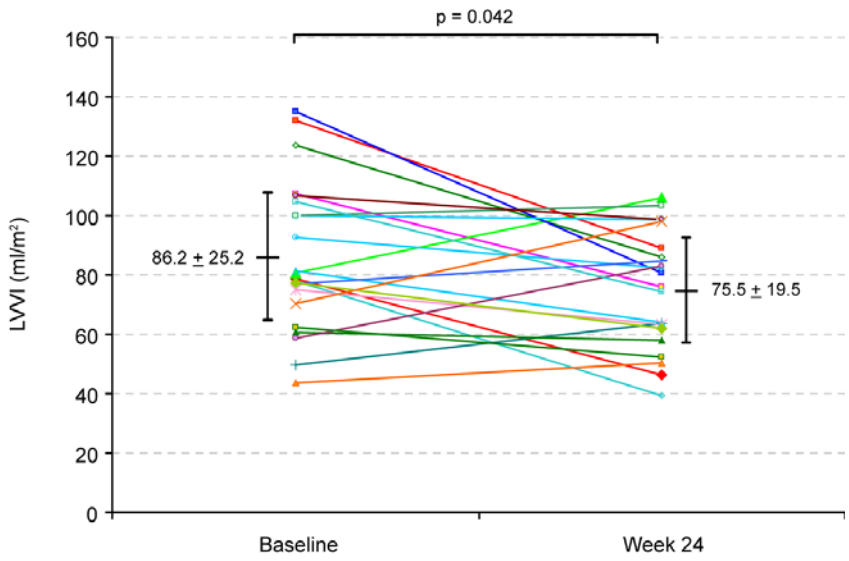

Fig. 5 Effect of partial anemia correction after 24-week therapy with an epoetin-alfa on left ventricular volume index (LVVI), comparing between data at baseline and week 24, The figure depicts individual data points of the evolution of LVVI in each patient

efficacy of a biosimilar epoetin-alfa on echocardiographic parameters in chronic hemodialysis patients with anemia. There is currently a very strong interest in biosimilar compounds, primarily because the recombinant epoetins are costly medical care and they are necessary for the treatment of anemia in CKD patients, which has exerted a tremendous value to improve quality of life and outcomes in these patients. Therefore, there is considerable interest in developing biosimilar agents that would have the same efficacy and safety

Table 4. Changes of LVMI and LVVI according to tertiles of baseline LVMI

	Tertiles by baseline LVMI (g/m^2)		
	≤ 130	> 130 to 160	> 160
LVMI			
Baseline	113.2 ± 13.0	143.0 ± 8.4	205.3 ± 41.1
End of study	118.0 ± 20.9	152.1 ± 15.4	172.2 ± 43.6
LVVI			
Baseline	75.1 ± 27.8	81.3 ± 16.1	103.7 ± 25.2
End of study	62.0 ± 13.5	86.7 ± 15.4	79.6 ± 21.9*

* p = 0.028 vs baseline

profile but be much less expensive. Accordingly, due to the patent expiry of the innovator epoetin-alfa, the biosimilar or generic version of epoetin-alfa are allowed to eventually enter in the developing world. In Thailand, biosimilar versions of epoetin-alfa have been available to nephrologists for many years, at the time of the present study; there were at least three forms of biosimilar epoetin-alfa available. One important issue is that biosimilar products may differ widely in compositions, and do not always meet self-declared specifications and exhibit batch-to-batch variation[22]. Recently, Singh AK systemically evaluated the quality of 36 batches from 16 different brands of biosimilar epoetins, including Espogen™ from Thailand[23]. It was found that many of the samples tested did not meet all EU specifications for epoetin-alfa, and with variation in vivo potency when compared to the innovator epoetin-alfa. In addition, the contamination with endotoxin and the presence of excess aggregates were a concern as both can increase the risk of patient safety. Notably, the biosimilar epoetin that was tested in this trial did meet almost all the EU specifications.

Most of the presented patients (81.8%) had the initial hemoglobin level of 9 g/dL or less due to lacking the opportunity to receive epoetin therapy, therefore, this lead to tremendous exposure to repeated blood transfusions and causing a very high baseline level of serum ferritin with iron overload in 59% of patients. Although the recent recommendation for hemoglobin levels in dialysis patients treated with epoetin should be maintained at or above 11 g/dL and should not be routinely maintained above 13 g/dL[24]. However, the target hemoglobin in the present study was assigned to limit between 11-12 g/dL, due to the potential disadvantage of high hemoglobin level from the previous study of Besarab et al[25] which reported a higher rate of vascular access thrombosis and a trend toward greater mortality in patients with higher hematocrit than those in the low hematocrit target. Several studies have been suggesting that lack of beneficial and potential harm may be associated when intentionally targeting the hemoglobin to > 13 g/dL have emerged. Recently, this has been demonstrated by the CHOIR[26] and CREATE[27] studies, which examined the potential benefit of normalization of hemoglobin in predialysis CKD patients with anemia, failed to demonstrate better changes in LV mass and other cardiovascular outcomes between patients who were randomly assigned to a complete or partial correction of their hemoglobin levels. Finally, the KDOQI clinical practice recommendation clearly addressed that the hemoglobin target should generally be in the range of 11 to 12 g/dL in dialysis and nondialysis in CKD patients receiving erythropoietin stimulating agent therapy[28].

The starting dose of epoetin for hemodialysis patients with adequate iron stores and without underlying active inflammation should be 50 to 100 IU/kg/dose given intravenously or subcutaneously three times weekly at each dialysis session, an acceptable response should occur within three months. Because of the relatively greater efficacy associated with subcutaneous versus intravenous administration, subcutaneous administration of epoetin for the treatment of anemia in hemodialysis patients has been recommended in the previous K/DOQI anemia guidelines[2]. In the present study the authors started with a dose of epoetin-alfa 4,000 IU/dose subcutaneously twice a week for every patient, averaged 143.6 ± 87.8 IU/kg/week, which was still within the range of recommended dose. After epoetin therapy, the rate of hemoglobin increase was 0.78 ± 0.49 g/dL/month during the first 12 weeks and

the authors could achieve the median time for the hemoglobin response to epoetin therapy by the 10th week, which is within the usual acceptable response period. The mean hemoglobin levels could be maintained at 11 g/dL or higher since the 16th week onwards throughout the end of the present study. The mean dosage of epoetin at the end of the present study remained very close to the starting dose. Clinical experience with epoetin shows that the dosage required to achieve similar hemoglobin levels varies among patients. However, common causes blunting the response to epoetin therapy had been monitored and controlled in the present study. The C-reactive protein levels did not demonstrate the possibility of underlying microinflammatory state. Although there was a 37.5% reduction in the mean serum ferritin levels at the end of the present study compared with the baseline level, the final serum ferritin level still represented an adequate iron stores. On the other hand, this supported the previous study by Eschbach et al who noted the beneficial effect of epoetin therapy in treating iron overload status in hemodialysis patients who previously received repeated blood transfusions[29].

The impact of epoetin therapy on blood pressure was of interest. Hypertension may complicate therapy, particularly if the hemoglobin is raised quickly. The hypertensive effects of epoetin appear to be confined to patients with renal failure. Patients with more severe anemia before epoetin therapy may be at greater risk of hypertension and its complication[30]. The interval between commencement of epoetin therapy and increase in blood pressure may vary from 2 to 16 weeks. Several factors have been identified that may contribute to the hypertensive response. These include a high dose of epoetin, rapid increase in hemoglobin, direct vasoconstrictive effect, diminished response to nitric oxide, marked increase in cytosolic calcium levels, enhanced responsiveness to norepinephrine, increased plasma endothelin levels, and increase in whole body viscosity[31,32]. In the present study, increase in blood pressure was not a problem in most patients, the peak predialysis mean blood pressure change, which occurred at the 10th week, was controllable after some antihypertensive adjustment without significant increase in the average number of antihypertensive agents being used.

In patients with CKD, LV mass increases progressively as renal function deteriorates[4]. Prospective studies have consistently demonstrated that LVH is common in patients with ESRD with the prevalence of 70-80% and that it entails a gloomy prognosis. In addition, progressive LV dilation with compensatory hypertrophy appears to be the characteristic evolution of cardiomyopathy in dialysis patients[33]. The presence of LVH is associated with increases in the incidence of heart failure, ventricular arrhythmias, death following myocardial infarction, decreased LV ejection fraction, sudden cardiac death, aortic root dilation, and a cerebrovascular event. Anemia has been identified as a risk factor for development of LVH and heart failure in dialysis patients[34]. Potential mechanisms that may explain the relationship between anemia and the development of LVH include the effects of reduced oxygen delivery to the myocardium, anemia-related increased cardiac output and reduced systemic vascular resistance, the role of increased oxidative stress, and finally, activation of the sympathetic nervous system[35,36].

Epoetin therapy and partial correction of severe anemia have been associated with some improvement in LVH, although correction of anemia with epoetin does not lead to significant regression of established LVH or LV dilation beyond that seen with partial correction[37]. In elderly anemic patients treated with epoetin, the high cardiac output gradually falls over a period of one year and is accompanied by a 25% reduction in left ventricular mass[12]. On the contrary, a prospective Canadian study reported that normalization of the hemoglobin, after a 48-week trial of epoetin therapy, did not lead to echocardiographic evidence of regression of LVH or LV dilatation[38]. In addition to the direct beneficial effect of anemia correction on the heart, recently it has been discovering many extra-hematopoietic functions of erythropoietin[39]. Furthermore, a growing body of evidence also indicates that this hormone has tissue-protective effects and prevents tissue damage during ischemia and inflammation. These findings may further exert the beneficial effects of epoetin therapy on cardiac status in these patients.

In the present study, although the mean hemoglobin level that could be achieved at the end of the study was just at the lower end of the assigned target hemoglobin range of 11 to 12 g/dL, the authors were able to demonstrate that even partial correction of anemia in hemodialysis patients after 24 weeks of therapy with a biosimilar epoetin-alfa. There was a significant regression of left ventricular volume ($8.2 \pm$ 26.6% reduction in LVVI), a significant reduction in LV end-diastolic diameter and the aortic root diameter, and a trend towards the reduction of LVMI was observed, especially in the highest tertile of basal LVMI. It is of interest that the aortic root diameter was also decreased

significantly despite some increase in blood pressures but without significant change in number of antihypertensive agents. Several factors may affect the aortic root diameter including age, hypertension, and left ventricular hypertrophy. A previous study[40] has also shown that LV mass was significantly related to aortic root diameter as seen in the present study. The authors suggest that epoetin therapy, which has a positive impact on the LV mass and volume, would also, indirectly, exert its effect on the change of aortic root diameter. Therefore, it is too early to rule out later effect on regression of LVMI and there is a high possibility that a significant reduction in LVMI could also be demonstrated if the study period was extended longer to one year, with the expectancy to see better cardiovascular functions, better quality of life and the overall survival in these patients.

Conclusion

LVH is an independent determinant of survival in patients with ESRD, and anemia is one determinant of hypertrophy in such patients. The correction of anemia in these patients by a biosimilar version of epoetin-alfa results in the elimination of blood transfusion, reduction in iron overload, and improved echocardiographic parameters with a significant regression in LV volume. The authors do realize that it is impossible to demonstrate bioequivalence without a comparator. However, it was not designed to demonstrate comparability of biosimilar epoetin product with the innovator epoetin-alfa in the present study. Therefore, long-term comparative studies are still needed to adequately monitor safety and the impact on cardiovascular outcomes.

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การตอบสนองของระดับฮีโมโกลบินและผลต่อขนาดของหัวใจห้องล่างซ้ายในผู้ป่วยไตวายเรื้อรังที่ได้รับการฟอกเลือดจากการรักษาด้วยยา epoetin-alfa เป็นเวลา 24 สัปดาห์

ประเสริฐ ธนกิจจารุ, นภา ศิริวิวัฒนากุล

***ภูมิหลัง**: ภาวะโลหิตจางเป็นอาการแสดงที่พบได้บ่อยในผู้ป่วยโรคไตวายเรื้อรังระยะสุดท้าย และเป็นสาเหตุสำคัญของการหนาตัวของผนังห้องล่างซ้ายของหัวใจในผู้ป่วยที่ได้รับการฟอกเลือด*

***วัตถุประสงค์**: ผู้นิพนธ์ต้องการศึกษาถึงประสิทธิผลและความปลอดภัยของยา biosimilar epoetin-alfa ตัวหนึ่งในด้านการรักษาภาวะโลหิตจางและผลดีต่อการเปลี่ยนแปลงของหัวใจด้วยการตรวจ echocardiography*

***วัสดุและวิธีการ**: ได้ศึกษาในผู้ป่วยที่ได้รับการฟอกเลือดอย่างสม่ำเสมอจำนวน 22 ราย ที่มีระดับฮีโมโกลบินต่ำกว่า 10 กรัม/ดล. ผู้ป่วยทุกรายได้รับยา epoetin-alfa ในขนาดเริ่มต้น 4,000 ยูนิต เข้าใต้ผิวหนัง 2 ครั้งต่อสัปดาห์ และปรับขนาดยาเพื่อให้ได้ระดับฮีโมโกลบินเป้าหมาย 11-12 กรัม/ดล.*

***ผลการศึกษา**: ภายหลังการรักษานาน 24 สัปดาห์ พบว่าระดับฮีโมโกลบินเพิ่มขึ้นจาก 8.0 $\pm$ 1.3 กรัม/ดล. เป็น 11.0 $\pm$ 1.1 กรัม/ดล. ($p < 0.001$) เมื่อสิ้นสุดการศึกษา ความดันโลหิตเฉลี่ยก่อนการฟอกเลือดเริ่มสูงขึ้นเล็กน้อยหลังการรักษา 8 สัปดาห์ ซึ่งสามารถควบคุมได้ง่าย และไม่พบความแตกต่างของจำนวนชนิดยาลดความดันโลหิตที่ใช้ตลอดการศึกษา ผลการตรวจหัวใจด้วย echocardiography พบว่าดัชนีมวลกล้ามเนื้อหัวใจห้องล่างซ้ายมีขนาดลดลงในร้อยละ 50 ของผู้ป่วย แต่ลดลงเพียงเล็กน้อย (152.1 $\pm$ 45.8 ลดเหลือ 146.1 $\pm$ 36.0 กรัม/ตร.เมตร) ส่วนดัชนีปริมาตรของหัวใจห้องล่างซ้ายมีขนาดเล็กลงอย่างมีนัยสำคัญทางสถิติ (86.2 $\pm$ 25.2 ลดเหลือ 75.5 $\pm$ 19.5 มล./ตร.เมตร, $p = 0.042$). โดยการเปลี่ยนแปลงนี้เห็นได้ชัดเจนเฉพาะในกลุ่มผู้ป่วยที่มีขนาดของหัวใจโตสุดเมื่อแบ่งผู้ป่วยออกเป็น 3 กลุ่มตามขนาดของดัชนีมวลกล้ามเนื้อหัวใจห้องล่างซ้าย นอกจากนี้ยังพบว่าเส้นผ่าศูนย์กลางของขั้วหลอดเลือดแดง aorta ก็มีขนาดเล็กลงด้วย และไม่พบภาวะแทรกซ้อนหรือผลข้างเคียงของยาที่สำคัญตลอดการศึกษา*

***สรุป**: การศึกษานี้ได้แสดงถึงประสิทธิผลและความปลอดภัยของยา epoetin-alfa ในการรักษาภาวะโลหิตจางในผู้ป่วยไตวายเรื้อรังที่ได้รับการฟอกเลือด และสามารถส่งผลให้ปริมาตรของหัวใจห้องล่างซ้ายมีขนาดเล็กลงได้ภายหลังการรักษาเป็นเวลา 24 สัปดาห์*