12-Week Clinical Effects of Erythropoietin Espogen™ in End Stage Renal Patients undergoing Hemodialysis

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Background: *Anemia is one of most common complications in end stage renal disease (ESRD) patients. Erythropoietin has been recommended for treatment of anemia in these patients.*
Objectives: *To evaluate the clinical efficacy, safety and usefulness of newly imported erythropoietin, called Espogen ™, usage in ESRD undergoing hemodialysis.*
Material and Method: *An open, non-comparative, prospective study of administered Espogen ™ was conducted in 30 ESRD patients undergoing hemodialysis for a 12 week period. Eligible criteria included hemoglobin of less than 8 g%, hematocrit of less than 25% for at least three consecutive months with a serum ferritin of more than 100 ng%. Initial dose of drug was 150 units/kg/week subcutaneously, two or three times a week and dosage was adjusted to maintain the Hb at 10-12g%.*
Results: *In 28 patients, hemoglobin and hematocrit were increased significantly from 7.1 ± 1.14 g/dl and 22.1 ± 3.24% at baseline to 10.1 ± 1.49 g/dl and 31.7 ± 4.01% at the end of the study period respectively ($p < 0.05$). Mean weekly of Espogen™ dosage was 8390 ± 2452.7 IU/week, which was 152.1 IU/kg/week. Some patients could reduce the dose at week 10. Reticulocyte increased significantly from 0.69 ± 0.58% at baseline to highest value, 1.41 ± 0.74 at 2 week and 1.30 ± 0.66 at the end of the present study. Serum vitamin B12, serum folate, and red blood cell folate were not significantly changed. However, serum ferritin decreased significantly from 840.6 ± 948.95 to 582.7 ± 990.70 ng/ml ($p < 0.05$). General condition including SF-36 score and tiredness were improved. There were no significant adverse events except mean arterial blood pressure of pre dialysis value which was statistically significant increased at the end of the present study (from 101.0 ± 17.65 at week 0 and 110.4 ± 16.8 mmHg at week 12, $p = 0.0223$).*
Conclusion: *This clinical study showed that Espogen ™ has proven effective and safe for treatment of anemia in hemodialysis patients. No serious adverse events occurred during the study period.*

Keywords: *Erythropoietin, Espogen™, Anemia, Hemodialysis, End stage renal failure*

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Renal anemia is one of the major complications of end stage renal disease. It is caused by the deficiency of iron and other nutrients, exsanguinations during hemodialysis procedure, gastrointestinal bleeding, and others causes. Additionally, inadequate erythropoietin is a critical reason. Erythropoietin (EPO) is a siaglycoprotine hormone secreted primarily by the mature kidney in response to tissue hypoxia and/or red cell mass decrease. It stimulates erythrocyte production from bone marrow[1]. The introduction of recombinant human erythropoietin (rHuEPO) therapy in 1987 offered a new way to manage the anemia, which affected more than 90% of these patients[2,3]. Several studies have show clinical efficacy of rHuEPO on anemia and several clinical aspects. Using in hemodialysis patients indicate an effective EPO level both in subcutaneous and intravenous[4], decrease of transfusion frequency, and quality of life improvement[3]. Several clinical recommendations suggest using EPO to correct anemia in these patients[5]. rHuEPO can be given either by the subcutaneous or intravenous route without any different effects[6]. However, erythropoietin treatment is still expensive, not affordable to developing

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countries if it was used extensively. The present study was conducted to evaluate the clinical efficacy, safety, and usefulness of newly imported erythropoietin, ESPOGEN™ (LG Life Science Ltd.) in the treatment of anemia of ESRD patients undergoing hemodialysis.

Material and Method

Patients

This was an open, non-comparative, prospective, "before-and-after" study at Patara-Thonburi Hemodialysis Unit and Hemodialysis Unit, Thammasat University Hospital, beween January and July 2006, among patients who had been on hemodialysis for more than 6 months with stable clinical entity for at least 3 months. Inclusion criteria included patients with Hemoglobin of less than 8g% and Hematocrit less than 25% at least three consecutive months. The last blood transfusion was not less than one month before studying. Serum ferritin level for eligible patients was more than 100 ng%.

Exclusion criteria included patients who developed active infection or inflammatory disease, taking immunosuppressive or androgen, poor control blood pressure (Diastolic pressure more than 110 mmHg and systolic pressure more than 180 mmHg), history of allergy to erythropoietin or albumin, history of convulsion. If patients had been taking other erythropoietin, previous erythropoietin was stopped at least 2 weeks before the present study.

Methods

1) Epoetin alfa dose and administration method

The Espogen™ (epoietin alfa, LG Life Science Ltd.) was used in the present study. As initial dose for dialysis patients, 150 units/kg/week was administered by subcutaneous route for hemodialysis patients. The dose was calculated to the pre-filled syringe 2,000 or 4,000 units/dose. The total dose was divided into 2 or 3 times according to hemodialysis schedule.

Dosage of EPO was adjusted according to hemoglobin change. If Hb increased more than 1.4g% within 2 weeks, the dose was reduced by 25 units/kg/week. If Hb did not increase more than 1 g% within the first 4 weeks, 50 units/kg/week would be added to the total dose of 225 units/Kg/week. If Hb reached 10g%, the dose would be adjusted to maintain Hb at 10-12g% according to researcher adjustment.

2) Methodology verify

The patients who signed the consent paper for the present study had initial blood drawn for CBC, reticulocyte count, platelet count, ferritin level, parathyroid hormone, stool occult blood, B12, Folic acid in RBC and Folate in serum. Dialysis session adequacy was evaluated as Kt/V. Eligible patients started with Espogen™ as calculated dose according to dry weight. During the follow up period, clinical evaluations included general symptoms, SF-36 score was evaluated. Blood pressure during hemodialysis session was recorded for evaluating mean arterial blood pressure. Blood was also checked for CBC, reticulocyte count every 2 weeks for the total course of 12 weeks. During 12 weeks, any adverse effects were recorded. At the end of the present study, all eligible patients were asked about their general condition, SF-36 and any adverse effects. Blood was drawn for CBC, reticulocyte count, ferritin level, PTH, B12, Folic acid in RBC and Folate in serum.

3) Efficacy and safety evaluation Methods

All data are shown as mean and standard deviation. To evaluate the efficacy of ESPOGEN™, Changes in hemoglobin, hematocrit from baseline to the end of the present study and at each time of examination were analyzed (Paired t-test, and ANOVA with repeated measures and post hoc comparisons) with a statistical significance at $p < 0.05$. For clinical significance, the number of patient that had increase hemoglobin more than 2% from the baseline was used. To evaluate safety, adverse reactions were asked at every visit for hemodialysis sessions for any related symptoms. Blood pressure was checked before during and after dialysis sessions. The pre-dialysis and immediate dialysis values were analyzed as a mean arterial blood pressure. Compare data before and after treatment was analyzed by conducting paired t-test for total measurement.

Table 1. Characteristics of patients

Male : Female	10 : 18
Mean age (year)	53.20±14.80
Mean body weight (Kg)	55.10±14.40
Mean HD session per week (times/week)	2.15±0.31
Mean Kt/V per session	2.01±0.39
Mean intact parathyroid hormone level (normal 16-62 pg/ml)	279.70±221.0
Prior erythropoietin use (number)	5
Primary diagnosis (number)	
DM	10
HT	11
CGN	4
Unknown	3

Results

Thirty hemodialysis patients were included in the present study between January and July 2006. Only 28 patients completed the present study. One patient developed bleeding per vagina due to previous underlying disease. Another patient developed pneumonia at the 8th week of study. Most of them had never received erythropoietin treatment due to financial problems.

Twenty-eight hemodialyis patients (10 men and 18 women) were analyzed in the present study. The average age was 53.2 ± 14.8 years, average body weight 55.1 ± 14.4 kg. Most patients underwent twice-weekly hemodialysis with a mean Kt/V of 2.01 ± 0.39 (Table 1).

Hematological response

All 28 patients had increase in hemoglobin and hematocrit level. The number of patients who had clinical significant response, defined as more than 2% change in hemoglobin during 12-week period of study, was 22 patients (79%). A mean hemoglobin change increased significantly from 7.1 ± 1.14 g% at week 0 to 10.1 ± 1.48 at the end of study (week 12). Hematocrit also changed from 22.1 ± 3.24 at week 0 to 31.8 ± 4.01 at the end of study (week 12) ($p < 0.05$) as shown in Table 2. A change in hemoglobin and hematocrit started at week 2 in most patients and continued to rise for the period of study (as shown in Fig. 1 and 2).

Biochemical parameters

Serum ferritin showed a significant decrease from 840.6 ± 948.95 ng/ml at the beginning of the trial to 582.7 ± 990.70 at the end of the trial ($p = 0.0035$). Seven patients developed low serum ferritin (< 100 ng/ml) at the end of the present study, and most of them were less responsiveness. Serum folate level, RBC folate, Vitamin B12 did not show any statistically significant change compared between before and after treatment (Table 3).

Epoietin alfa dose

Mean of doses of Espogen ™ starting dose was 8428.5 ± 2062.51 unit/week or 153.9 ± 15.49 unit/kg/week. After treatment, two patients stopped Espogen™ at week 10 and another two patients at week 12. Another four patients could reduce the dose by 25%. The rest of them continued the same dose to maintain the desired hemoglobin and hematocrit level.

Blood pressure change

Mean arterial pressure of pre dialysis value increased statistically significant from 101.0 ± 17.65 mmHg at week 0 to 111.4 ± 14.4 mmHg at 2nd week after

Table 2. Mean change in hemoglobin and hematocrit level (n = 28*)

	At week 0	At week 12	p-value
Hemoglobin (g%)	7.1±1.14	10.1±1.49	0.00000
Hematocrit (%)	22.1±3.24	31.8±4.01	0.00000
Reticulocyte (%)	0.7±0.58	1.3±0.66	0.00127

* There were 22 patients (22/28 = 79%) who had clinical response defined as >2% change in hemoglobin during 12 weeks of study

Table 3. Showed change in blood parameter (n = 28)

	At week 2	At week 12	p-value
Serum ferritin (M 22-322 ng/mlF 10-291 ng/ml)	840.6±948.95	582.7±990.70	0.0035
Serum B12 (211-911 pg/ml)	1155.8±1416.15	1019.7±517.75	0.609
Red blood cell folate (221-1113 ng/ml)	3530.6±2733.15	4123.1±2867.38	0.237
Serum folate (5-24 ng/ml)	51.3±12.87	52.7±21.96	0.687

M = male
F = female
Value in ( ) was a normal range

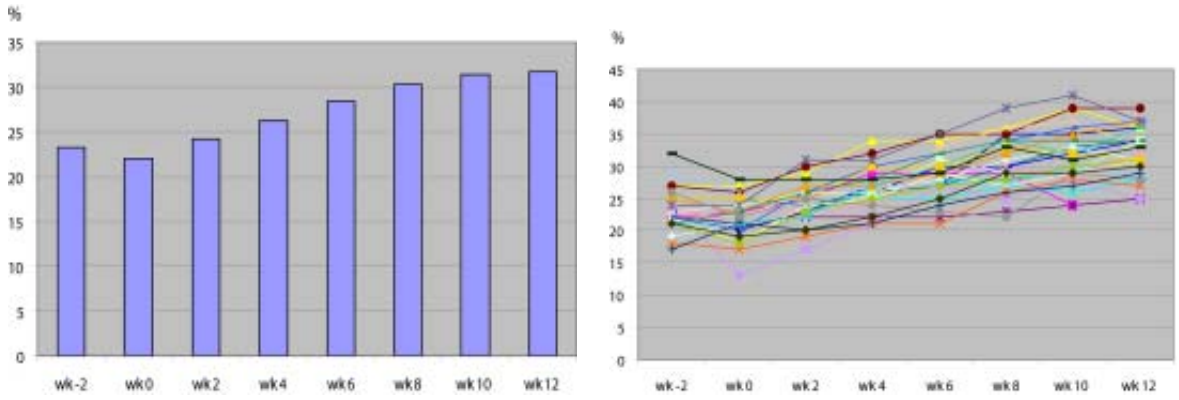

Fig. 1 Change in hematocrit level (%) during 12 week; Left panel showed mean change in all patients, Right panel showed individual change (p = 0.0000) (n = 28)

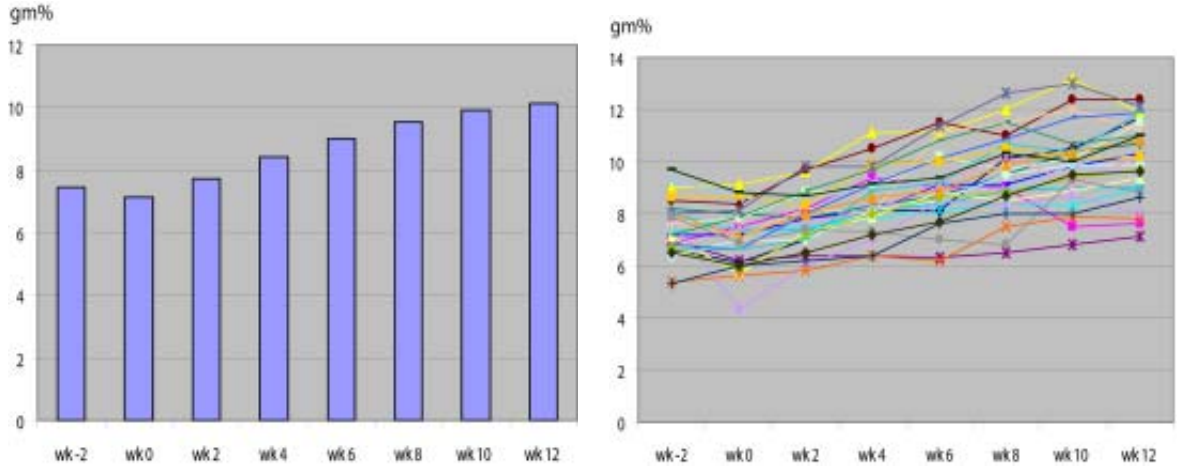

Fig. 2 Change in hemoglobin level (g%)during 12 week ; Left panel showed mean change in all patients, Right panel showed individual change (p = 0.0000) (n = 28)

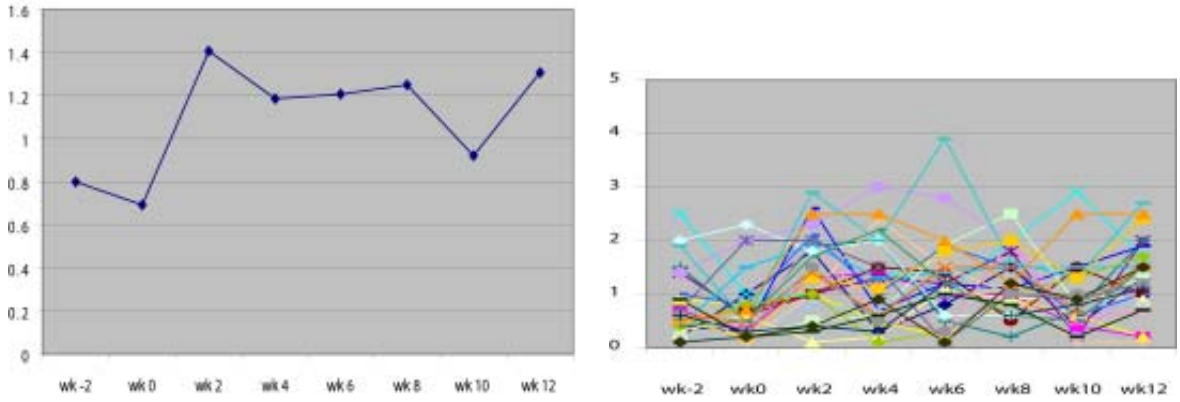

Fig. 3 A change in reticulocyte (%). Left panel: mean change in 12 week, Right panel showed individual change (p = 0.0012) (n = 28)

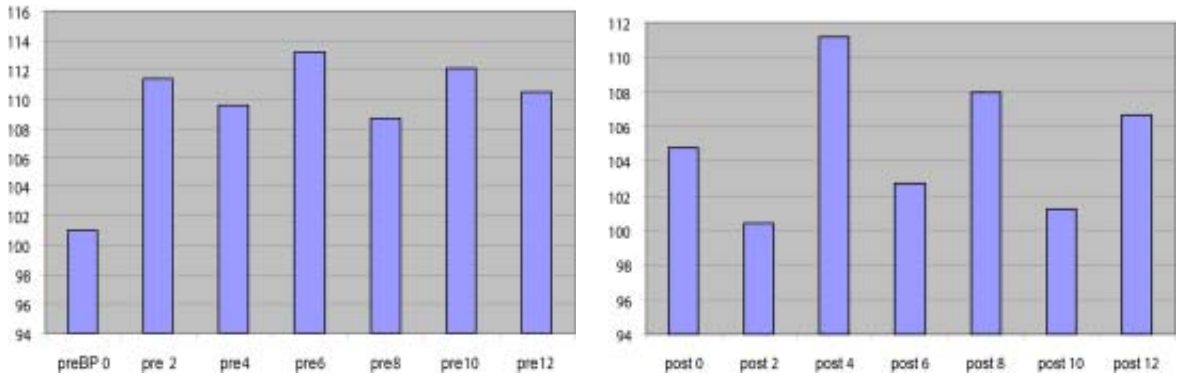

Fig. 4 Change in mean arterial blood pressure (mmHg), Left panel showed a mean of pre dialysis- mean arterial blood pressure (p = 0.0223 compare between week 0 and week 12), Right panel showed a mean of post dialysis – mean arterial pressure (p = 0.5668 compare between week 0 and week 12) (n = 28)

starting ESPOGEN™ and continued that level through the end of the present study (week 12) (110.4 ± 16.8 mmHg) (p = 0.0223). However, mean arterial pressure of post dialysis value was not statistically significantly changed compared between week 0 (104.7 ± 17.20 mmHg) and week 12 (106.6 ± 17.40 mmHg) (p = 0.5668) (Fig. 4).

Adverse events and abnormal responses

During Espogen™ administration, any adverse events such as headache, dizziness, rash etc. were not reported. Only one patient reported low grade fever that occurred after the second shot in the first week. The low grade fever subsided spontaneously the next morning without any medication. This may not be related to Espogen™ administration.

Discussion

Anemia in end stage renal disease patients is known to have a significant impact on morbidity, mortality, and quality of life (QOL). It is primarily a consequence of inadequate erythropoietin production by the kidneys. Therefore, guidelines including EPO have been issued recommending anemia treatment in CKD patients[5]. rHuEPO is rather safe and effective which can reduce the risk of cardiovascular disease and improve clinical outcomes in patients with CKD[7]. In the present study, rHuEPO, so called Espogen ™ produced by LG Life Science Ltd. was used to verify its effectiveness and safety for ESRD patients undergoing hemodialysis.

After treatment, hemoglobin and hematrocrit increased significantly from a mean baseline value of 6.85 g/dl and 21.9% to 10.1 g/dl to 31.8% at the end of the present study. The levels started rising at the 4th week of treatment. Among 28 patients who had final analysis, 22 patients (79%) showed more than 2.0 g/dl increase of Hb (good responsive group) and 6 patients (21%) showed Hb increase more than 1-2.0g/dl (less responsive group) at the end of the present trial. In these patients, serum ferritin was rather low, less than 100 ng/ml at week 12 follow up. This could confirm clinical guideline to re-check ferritin level when the patients had no response or less response to EPO therapy[8]. The good response patients were also seen in patients who prior received EPO.

The response of treatment would be seen as increase in reticulocyte response and change in hemoglobin and hematocrit. The maximum reticulocyte response was seen at the 2nd week, some at 4th week. Reticulocyte response was increased from a mean of 0.69% at the beginning to maximum 1.41% after 2nd week of treatment. This result is similar to another study[9]. After the maximum response in each patient, reticulocyte response is more varied and could not evaluate any response. This suggested that using reticulocyte count to evaluate erythropoietin response is not a good parameter after 4 weeks both in good or less responsive patients. There were no patients who were resistant to Espogen™ treatment in the present study.

Mean of doses of Espogen™ after 12 weeks was 8390 ± 2452 unit /week refer to 152 unit/kg/week to maintain hemoglobin and hematocrit level at more then 10g% and 30%. Almost half of the patients (13/28 patients) could reduce the dosage of Espogen™. Two patients stopped at week 10 and another two at week 12 of treatment.

The estimated prevalence of iron deficiency in hemodialysis patients during EPO therapy is around 43-90%. In the present study, most patients (25 in 28 patients) significantly decreased serum iron and ferritin after giving EPO. This is due to the increase of iron consumption. Some of the presented patients, despite taking oral ferrous sulfate, had low ferritin level (less than 100 ng/ml) at the end of the present study which caused a slight drop in hemoglobin and hematocrit response occurring at the final week. Absolute iron deficiency in hemodialysis patients occurs for a variety of reasons including increased erythropoiesis from the use of EPO[10]. According to the National Kidney Foundation-Kidney Disease Outcomes Qualitative (K-DOQI) anemia guidelines, therefore patients should have sufficient iron to achieve and maintain a Hb of 11-12g/dl and hematrocrit of 33-36%.and to accomplish this, the guidelines suggest administrating sufficient iron to a maintain tranferrin saturation (TSAT) of > 20% and serum ferritin > 100ng/ml[5].

After rHuEPO administration for 12 weeks, Vitamin B12, serum folate, and red blood cell folate level did not change significantly compared between before and after the present study. This is probably due to supplement with vitamin B and folic acid (5 mg/day) in addition to no restriction in the diet, which is the unit routine practice. For economic view, this means that it does not need routine check for vitamin B12, red cell folate, and serum folate in this aspect.

Not only laboratory parameter improvement, general condition and quality of life showed improvement after 12 weeks' evaluation. The functional status, appetite, well being, easily fatigued, dizziness showed significant improvement after treatment. This may relate to treatment of anemia or additional effects of erythropoietin itself[3].

Giving EPO may cause rising blood pressure[11]. The exact mechanism is still controversial, possibly related to nitric oxide, impaired endothelial function[11]. In the present study, compared mean arterial blood pressure of pre-dialytic value before and after treatment showed a statistically significant increase from 101 mmHg to 110 mmHg. However, rising in this mean arterial blood pressure occurred at the 2nd week of treatment and continued that same level through the 12th week. Thus, initial blood pressure response should be noted in cases starting EPO. The immediate post dialytic value did not show any statistically significant change compared between before treatment and at the end of 12 weeks. This adverse effect should be noted and observed for wider use.

In addition, pure red cell aplasia[12] has not been found in the present study due to the short period of study and few patients to evaluate. Although antibodies against erythropoietin were not studied in the present study, a previous study showed that antibodies against erythropoietin were never detected during Espogen™ treatment[9].

Adverse effects including rash, nausea, vomiting, and dizziness did not show in the presented patients. Only one patients reported low grade fever at the second shot in the first week, which resolved spontaneously the next morning. This could not conclude this relation to drug administration. From a previous study, the adverse events occurring during treatment with Espogen™ were usually mild in intensity and transients in nature even in a high dose study (10000 unit shot)[13].

In summary, based on the results above, it was demonstrated that this new erythropoietin, marketed in Thailand, Espogen™, is considered an effective drug for treating anemia in ESRD patients undergoing hemodialysis as formerly EPO marketed in Thailand. Adverse effects were not shown in the present study. However, there were only 28 patients included in the present study. Long-term side-effects should be evaluated for longer time of treatment.

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การศึกษาผลของยา Erythropoietin ทางคลินิกระยะเวลา 12 สัปดาห์ในผู้ป่วยไตวายเรื้อรังที่ได้รับการฟอกเลือด

ศุภชัย ฐิติอาชากุล, อดิศว์ ทัศณรงค์

ภาวะซีดในผู้ป่วยไตวายเรื้อรังระยะสุดท้ายโดยเฉพาะอย่างยิ่งในผู้ป่วยที่ทำการฟอกเลือด เป็นภาวะที่พบได้บ่อย และปัจจุบันเป็นที่ยอมรับกันทั่วไปในการใช้ยาฮอร์โมนอีรีย์โธรปอยอีตีนในการรักษา ซึ่ง ESPOGEN™ เป็นยาตัวใหม่ที่นำเข้ามาใช้ในประเทศไทย ผู้ศึกษาต้องการศึกษาผลของยาในผู้ป่วยคนไทยที่ได้รับการฟอกเลือด โดยทำการศึกษาในผู้ป่วยที่ทำการฟอกเลือดอย่างน้อย 6 เดือน และมีอาการคงที่อย่างน้อย 3 เดือน ร่วมกับภาวะซีด จากการศึกษาในผู้ป่วย 28 ราย พบว่า ค่าฮีโมโกลบินเพิ่มจาก 7.1 ± 1.14 กรัม % เป็น 10.1 ± 1.49 กรัม % และความเข้มข้นเลือด เพิ่มจาก 22.1 ± 3.24% เป็น31.7 ± 4.01% ที่ 12 สัปดาห์ หลังจบการศึกษา ($p < 0.05$) โดยขนาดยาเฉลี่ย 8390 ± 2452.7 ยูนิตต่อสัปดาห์ หรือ 152.1 ยูนิตต่อน้ำหนักตัว 1 กิโลกรัมต่อสัปดาห์ โดยที่ไม่มีการเปลี่ยนแปลงของค่าวิตามินบี 12 ในซีรัม, โฟเลท ในเม็ดเลือดแดงและซีรัม แต่พบการลดลงของค่า serum ferritin อย่างมีนัยสำคัญร่วมกับผู้ป่วยมีอาการทั่วไปดีขึ้น ผลข้างเคียงที่อาจพบได้ คือมีการเพิ่มของค่าเฉลี่ยความดันโลหิตก่อนการฟอกเลือดเมื่อเปรียบเทียบระหว่างก่อนการรักษาและหลังการรักษา โดยที่ไม่พบผลข้างเคียงอื่น ๆ

***สรุป**: การใช้ยา ESPOGEN™ ได้ผลดีในเพิ่มความเข้มข้นของเลือดและช่วยให้ผู้ป่วยอาการดีขึ้น โดยไม่พบผลข้างเคียงที่ร้ายแรง แต่ควรระวังการเปลี่ยนแปลงความดันโลหิตก่อนการฟอกเลือดเมื่อให้การรักษาด้วยยานี้*