Clinical Comparison of Renogen, a Biosimilar Epoetin-α, with the Originator, Eprex, in Chronic Kidney Disease Anemia in Indonesia: A Preliminary Study

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ABSTRAK

Latar belakang: *terapi eritropoietin sangat penting pada pasien penyakit ginjal kronik (PGK) untuk mempertahankan kadar Hb tetap optimal. Renogen adalah suatu epoetin-α biosimilar, sedangkan Eprex adalah epoetin-α inovator. Penelitian ini bertujuan membandingkan efikasi dan toleransi Renogen dengan Eprex untuk anemia akibat PGK.* ***Metode:*** *Renogen dan Eprex dibandingkan dalam studi random (2:1), tidak tersamar, selama 8 minggu, didahului dengan fase penyesuaian selama 4 minggu, pada pasien anemia akibat PGK yang menjalani hemodialisis di RSUPN Cipto Mangunkusumo, Jakarta, dari Juni 2017 sampai dengan Oktober 2018.* ***Hasil:*** *sejumlah 45 pasien (31 mendapat EPO biosimilar dan 14 menerima EPO inovator) diikutsertakan dalam studi. Pada awalnya, rerata (SD) kadar Hb berturut-turut 10,9 (0,74) g/dL dan 10,9 (0,61) g/dL dalam kelompok EPO biosimilar dan EPO inovator. Di akhir studi (8 minggu), rerata (SD) kadar Hb berturut-turut 10,5 (1,28) g/dL dan 11,0 (1,13) g/dL dalam kelompok EPO biosimilar dan EPO inovator. Proporsi pasien dengan kadar Hb yang bertahan dalam kisaran target (>10 g/dL) selama 8 minggu adalah 58,1% dalam kelompok EPO biosimilar dan 71,4% dalam kelompok EPO inovator (p=0,60; TB). Tidak ada perbedaan bermakna dalam dosis epoetin dari EPO biosimilar dan EPO inovator yang digunakan, dan tidak ada efek samping yang terkait dengan obat pada kedua kelompok.* ***Kesimpulan:*** *kadar Hb >10 g/dL dapat dipertahankan selama 8 minggu pengobatan dengan EPO inovator maupun EPO biosimilar (lebih konsisten dengan EPO inovator dan lebih berfluktuasi dengan EPO biosimilar), dengan dosis epoetin yang sama dan tidak ada efek samping yang berkaitan dengan obat.*

Kata kunci: *anemia ginjal, eritropoietin, biosimilar, hemodialisa.*

ABSTRACT

Background: *treatment of erythropoietin (EPO) is essential in chronic kidney disease (CKD) patients to maintain optimal hemoglobin (Hb) level. Renogen is a biosimilar epoetin-α, and Eprex is the originator epoetin-α. This study aimed to compare the efficacy and tolerance of Renogen with Eprex in CKD anemia.* ***Methods:*** *Renogen and Eprex were compared in a randomized (2:1), open-label study for 8 weeks, proceeded by 4 weeks adjustment (maintenance) phase, in anemic CKD patients undergoing HD in Cipto Mangunkusumo General Hospital, Jakarta, from June 2017 to October 2018.* ***Results:*** *a total of 45 patients (31 received biosimilar EPO and 14 received originator EPO) were included in the study. At baseline, mean (SD) Hb levels were*

10.9 (0.74) g/dL and 10.9 (0.61) g/dL in biosimilar and originator EPO groups, respectively. At end of study (8 weeks), mean (SD) Hb levels were 10.5 (1.28) g/dL and 11.0 (1.13) g/dL in biosimilar EPO and originator EPO groups, respectively. The proportion of patients with Hb levels maintained within the target range (>10 g/dL) during 8 weeks randomization phase were 58.1% and 71.4% in biosimilar EPO and originator EPO, respectively (p=0.60; NS). There were no significant difference in epoetin dose between the 2 groups, and there was no drug-related adverse event in either group. ***Conclusion:*** *Hb level at >10 g/dL could be maintained for 8 weeks of treatment with both originator and biosimilar EPO (more consistent with originator EPO and more fluctuations with biosimilar EPO), with similar epoetin dose and no drug-related adverse event.*

Keywords: *renal anemia, erythropoietin, biosimilar, hemodialysis.*

INTRODUCTION

Anemia in chronic kidney disease (CKD) patients is due to failure of the kidneys to produce sufficient endogenous erythropoietin (epoetin or EPO) to stimulate the bone marrow to produce RBCs. CKD anemia is corrected and maintained with human recombinant erythropoietin (rHu-EPO) which is available since the early 1990s. Several erythropoiesis-stimulating agents (ESAs) are now available, including epoetin α and β, darbepoetin α and the biosimilars.

Treatment with erythropoietin is absolutely necessary in patients with CKD to maintain quality of life by increasing the hemoglobin level to reach the target of >10 g/dL. Eprex is the first rHuEPO (epoetin) in the world and has been shown to increase hemoglobin in CKD patients. Eprex, an EPO α, has been proven for its ability and safety in CKD patients. However, with respect to the price which is quite expensive, biosimilar products with the same ability are created, with an affordable price. Beiraghdar et al. concluded from their research comparing a biosimilar epoetin-α namely Pastopoetin to Eprex, that both products provided comparable results.[1] Harzallah et al.[2] conducted a study on a locally produced biosimilar epoetin α and found comparable results with the epoetin α produced by foreign laboratories. Based on this evidence, a study of a biosimilar epoetin α, Renogen, was carried out in anemic hemodialysis (HD) patients at Cipto Mangunkusumo Hospital (RSCM), Jakarta. The aim of this study was to assess the efficacy and tolerance of the biosimilar EPO (Renogen) in the management of anemia in CKD in Indonesia.

METHODS

A study on anemic CKD patients undergoing hemodialysis was conducted in Cipto Mangunkusumo Hospital, Jakarta, from June 2017 to October 2018. We compared a biosimilar epoetin α, Renogen, with the originator epoetin α, Eprex, in a randomized (2:1), open-label study for 8 weeks. The number of samples was 45; 30 subjects received Renogen and 15 subjects received Eprex. Since this was a preliminary study, sample size was not calculated, and a ratio of 2 to 1 was decided by the investigators.

This study has been approved by the Ethics Committee of Faculty of Medicine Universitas Indonesia, reference number 1102/UN2.F1/ETIK/2015.

Subjects

Anemic CKD patients on routine HD twice weekly for at least 6 months; hemoglobin level between 10-11 g/dL for a minimum of 12 weeks; a stable dose of erythropoietin IV for at least 8 weeks with a maximal weekly dose of 200 IU/kg body weight (definition of stable dose is a change in dose of less than 25% per week, without changes in injection frequency); serum ferritin >200 ng/mL or transferrin saturation >20%; male or female patients, aged between 18-75 years (female patients in post-menopausal period or using adequate contraception were acceptable); patients agreed to participate in the study (has signed the informed consent form). Excluded from the study were resistant to EPO; failed to achieve Hb target level despite an adequate level of transferrin saturation and after being given 500 IU/kg/week IV rhu-EPO for 4 months; hypersensitivity to erythropoietin; pregnancy, planning to get pregnant, or in a lactation program;

uncontrolled hypertension (>170/100 mmHg); malnutrition (serum albumin <30 g/L); patients on waiting list for kidney transplantation; under treatment of immunosuppressants (including corticosteroids) or androgens within 3 months before screening; post major surgery 3 months before screening (excluding vascular surgery); severe heart disease (MI, PCI, CABG) or severe cerebrovascular disease 6 months before screening; Heart Failure Class III/IV of NYHA classification or unstable angina; bleeding that requires transfusion within 3 months before screening or during screening period; non-renal anemia such as hemoglobinopathy, sickle cell anemia, hemolytic anemia, aplastic anemia, myelodysplastic syndrome, hematological malignancy, and myeloma; platelet count >500,000/mm^3; any history of malignancy 5 years before screening; grandmal's seizures for 6 months before screening; acute inflammatory diseases such as SLE, rheumatoid arthritis; acute or chronic active infection; SGOT/SGPT ≥3 times ULN; HIV or Hepatitis B infection; history of drug or alcohol abuse; participating in other clinical trials within 3 months prior to screening; inability to follow study instruction and procedure.

This study was conducted in 2 phases: Phase I was the adjustment (maintenance) phase for 4 weeks. Patients who have been stable on any erythropoietin previously, were changed to the originator EPO with a dose of 150-200 IU/kg BW/week, given intravenously to maintain Hb of 10-11 g/dL for 4 weeks. If during the originator EPO administration, the Hb level was >11 g/dL, the originator EPO dose was reduced, and when the Hb level was <10 g/dL, the originator EPO dose was increased. The maximum dose of the originator EPO for 4 weeks was 200 IU x 60 kg x 4 weeks = 48.000 IU.

Phase II was the randomization phase for 8 weeks. Patients were randomized into two groups, one group of patients received the originator EPO and the other group of patients received the biosimilar EPO. The maximum dose of the originator EPO or the biosimilar EPO was 200 IU x 60 kg x 8 weeks = 96.000 IU.

Other drugs given were Fe sucrose 100 mg IV once a month, and $CaCO_3$ equivalent to elemental Ca 500 mg 3 times a day with meals. Drugs that should not be used during the study was corticosteroids.

The primary endpoint was the percentage of patients with Hb level maintained within the target range (>10 g/dL) during the randomization phase. These data were analyzed using X2 statistics between the biosimilar and the originator groups.

Laboratory Tests

These tests were performed during patient screening, and at weeks 4, 8, and 12, i.e: routine hematology: leukocytes, neutrophils, lymphocytes, hemoglobin, platelets, hematocrit, MCV, MCH, MCHC, and reticulocytes; liver function tests: bilirubin, SGOT, and SGPT; kidney function tests: urea and creatinine; electrolytes: Na, K, and Cl; iron metabolism: serum iron, serum ferritin, transferrin saturation and total iron binding capacity (TIBC). ECG examination was done at screening, week 4, and week 12.

Patient Discontinuation

The patient was discontinued if any of the following occurred: at the request of the patient; HD regimen changed; Hb levels decreased ≥20% during the study compared to baseline value or <8 g/dL at 2 measurements within 1 week; uncontrolled hypertension; uncooperative patient; severe bleeding requiring blood transfusion; patients requiring surgery during the study; an emergency condition.

RESULTS

At the adjustment (maintenance) phase, there were 80 subjects participating. In the initial randomization phase, the number of subject was 47, 16 subjects in the originator EPO group and 31 subjects in the biosimilar EPO group. Before the first visit after randomization, one subject in the originator EPO group was lost to follow-up and another patient was excluded from the study because it did not meet the study requirements. Three subjects in the biosimilar EPO group were excluded during the randomization phase (during the last weeks of study or on visit 7 and 8) because the Hb level dropped >20%. But the three drop out subjects in the biosimilar EPO group were analyzed in the baseline demography data. The number of subjects who completed the study were 14 in the originator EPO group and

28 in the biosimilar EPO group (**Figure 1**). The characteristics of the study population at baseline are shown in **Table 1**.

At baseline, the median Hb in the biosimilar EPO and the originator EPO groups were 10.8 g/dL and 10.9 g/dL, respectively. At 2 weeks of randomization, the median Hb for the biosimilar EPO group was 11.2 g/dL, and for the originator EPO group was 11.3 g/dL. At 8th week of randomization, the median Hb for the biosimilar EPO and the originator EPO groups were Hb 11.0 g/dL and 10.8 g/dL, respectively. **Figure 2** showed the trend of Hb during the study. Statistical analysis (t-test) comparing Hb values at different weeks of treatment showed no significant differences between the biosimilar EPO group and the originator EPO group (**Table 2**). Proportions of subjects within Hb levels within target range (≥10 g/dL) during randomization phase were also not significantly different between the 2 groups (**Table 3**). Data on safety analysis during the study are shown in **Table 5**.

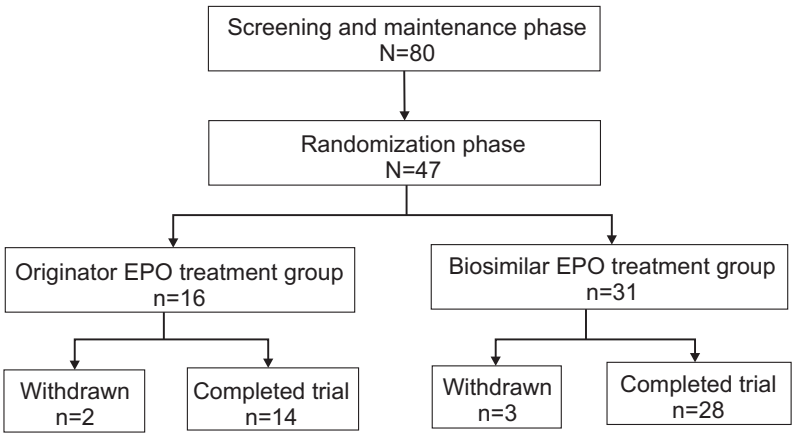

Figure 1. Flowchart of subjects included in the study.

Table 1. Demographics and other baseline characteristics of subjects enrolled in the study

Variables	The Originator EPO (N = 14)	The Biosimilar EPO (N = 31)
Male, n (%)	6 (42.9%)	16 (51.6%)
Age (years), mean (SD)	46.6 (12.90)	45.6 (12.57)
Body weight (kg), mean (SD)	57.8 (13.37)	57.4 (10.91)
Comorbidities (%)		
- Diabetes mellitus	-	3 (9.6%)
- Hypertension	4 (28.6%)	19 (59.4%)
- Heart disease	1 (1.7%)	3 (9.6%)
- Stroke	1 (1.7%)	-
- Hyperthyroid	1 (7.1%)	-
- Hepatitis C	1 (7.1%)	2 (6.5%)
- Lupus	1 (1.7%)	-
Systolic blood pressure (mmHg), mean (SD)	130.4 (19.51)	140.5 (18.29)
Diastolic blood pressure (mmHg), mean (SD)	75.9 (9.69)	78.0 (14.00)
Hemoglobin (g/dL), mean (SD)	10.9 (0.61)	10.9 (0.74)
Serum iron (μg/dL), mean (SD)	60.9 (23.51)	59.1 (19.24)
Ferritin serum (ng/dL), mean (SD)	338.7 (315.61)	595.2 (696.11)
Total iron binding capacity (μg/dL), mean (SD)	229.2 (49.12)	209.2 (38.00)
Transferrin saturation (%), mean (SD)	26.2 (6.59%)	28.7 (9.50%)

Table 2. Hemoglobin levels every two weeks of treatment with the biosimilar EPO and the originator EPO

Hemoglobin (g/dL)	Baseline	Randomization Phase			
		2 weeks	4 weeks	6 weeks	8 weeks
THE BIOSIMILAR EPO	n = 31	n = 31	n = 31	n = 31	n = 28
Mean (SD)	10.9 (0.74)	11.3 (1.21)	11.1 (1.09)	11.0 (1.60)	10.5 (1.28)
Median	10.8	11.2	11.2	11.2	11.0
Range	10.0 – 12.7	8.8 – 15.2	9.2 – 14.9	7.4 – 15.4	6.9 – 12.0
THE ORIGINATOR EPO	n = 14	n = 14	n = 14	n = 14	n = 14
Mean (SD)	10.9 (0.61)	11.2 (0.96)	11.3 (1.33)	11.5 (0.98)	11.0 (1.13)
Median	10.9	11.3	11.4	11.6	10.8
Range	10.0 – 12.0	9.7 – 12.7	9.6 – 14.9	9.2 – 12.7	9.4 – 13.1
Statistic test *	t = 0.160	t = 0.358	t = 0.581	t = 1.204	t = 1.166
p value	0.87 (NS)	0.72 (NS)	0.57 (NS)	0.24 (NS)	0.25 (NS)

*t-test (t); NS = Not significantly different

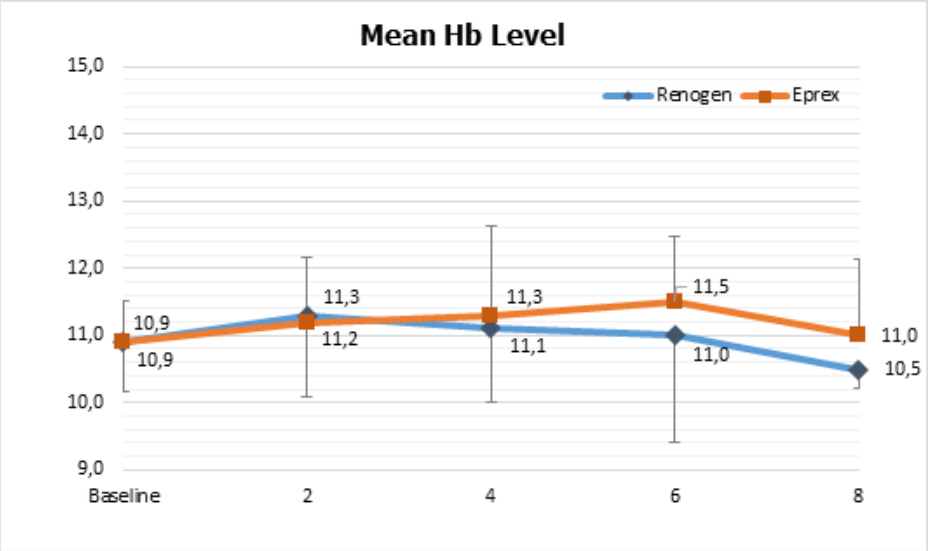

Figure 2. Mean Hb levels during 8 weeks of treatment with the originator EPO and the biosimilar EPO.

Table 3. Proportion of subjects (in the biosimilar EPO and the originator EPO groups) with Hb levels maintained within the target range (>10 g/dL) during the randomization phase

Group	Number (%) of subjects with Hb levels		
	Success* (Hb ≥ 10 g/dL)	Failure** (Hb < 10 g/dL)	Total
The biosimilar EPO	18 (58.1%)	13 (41.9%)	31 (100 %)
The originator EPO	10 (71.4%)	4 (28.6%)	14 (100%)
Total	28 (62.2%)	17 (37.8%)	45 (100%)
Statistical test:			
X2 test		0.275	
p value		0.6 (NS)	

* Hb was consistent at >10 g/dL at each visit (every 2 weeks) during 8 weeks of treatment
**Hb was dropped below 10 g/dL at >1 visit during 8 weeks of treatment

Table 4. Epoetin doses (IU) of the biosimilar EPO and the originator EPO at each visit during 8 weeks of treatment

Drugs	Baseline	Randomization Phase		
		2 weeks	4 weeks	6 weeks
THE BIOSIMILAR EPO	n = 31	n = 31	n = 31	n = 31
- Mean	4645.2	4774.2	4516.1	4516.1
- Median	4000	4000	4000	4000
- Range	4000 - 6000	4000 - 6000	4000 - 6000	4000 - 6000
THE ORIGINATOR EPO	n = 14	n = 14	n = 14	n = 14
- Mean	4857.1	4571.4	4285.7	4428.6
- Median	4000	4000	4000	4000
- Range	4000 - 6000	4000 - 6000	4000 - 6000	4000 - 6000
Mann-Whitney U				
- test (Z)	0.680	0.508	0.851	0.313
- p value	p = 0.50 (NS)	p = 0.61 (NS)	p = 0.40 (NS)	p = 0.75 (NS)

Table 5. Subjects with adverse event and serious adverse event during 8 weeks' treatment of the biosimilar EPO and the originator EPO

Description	The biosimilar EPO (n = 32)	The originator EPO (n = 15)
Subjects for safety analysis	32 (100%)	15 (100%)
Total subject with AE	-	-
Total subject with SAE	1 (3%)	-
Serious adverse event list		
Herpes (non drug-related)	1 (3%)	-

The erythropoietin doses were not significantly different between the biosimilar EPO and the originator EPO groups throughout the study (**Table 4**).

DISCUSSION

Our study showed that the biosimilar EPO was statistically equivalent to the originator EPO in terms of Hb response on treatment. The biosimilar EPO, Renogen, is extracted from Chinese hamster ovary (CHO) cell cultures into which the human erythropoietin gene has been introduced by recombinant DNA technology. Renogen, a 165 amino acid glycoprotein, has a molecular weight of about 34KD. It has the same physiological functions as natural human erythropoietin, and can stimulate the differentiation and multiplication of committed erythropoietic progenitors in the bone marrow.[3] The use of rHuEPO has obviated the need for blood transfusion in CKD patients, thereby reducing the adverse events commonly associated with such conventional therapies.[4-7] In our study, the treatment of biosimilar EPO to CKD patients undergoing hemodialysis was effective in maintaining the hemoglobin levels within the recommended hemoglobin target for HD patients, although the Hb level can be maintained more consistently in the originator EPO group.

In a multicenter, prospective study on 24 cadaveric kidney transplant patients, Baltar et al.[8] administered rHuEPO to patients with chronic allograft nephropathy at a subcutaneous dose of 2000 IU/kg once a week. Approximately 48% of patients were reported to reach target levels of Hb (11 g/dL) after 4 months of treatment.8 In the present study, mean Hb level increased and more than 50% of patients reached normal Hb values after 8 weeks of erythropoietin therapy (58.1% and 71.4% in the biosimilar EPO and the originator EPO groups, respectively), with no significant difference in dose between the two groups (median dose of epoetin was 4000

IU twice weekly in both groups). The real-world effectiveness and safety of a biosimilar epoetin alfa (HX575) in HD patients was also assessed in a large prospective, observational study for up to 24 months follow up in 114 centers in 10 European countries.[9] The study confirmed the real-world effectiveness and safety profile of IV biosimilar HX575. They found that at baseline, mean (SD) baseline Hb was 11.09 (1.14) g/dL with HX575 dose of 106.5 (78.7) IU/kg/week; at month 24, Hb was 11.25 (1.19) g/dL with HX575 dose of 113.0 (102.5) IU/ kg/week. Variations in mean HX575 dose and Hb over the study were not statistically significant.[9]

The biosimilar EPO was well tolerated and its safety profile was comparable to the originator EPO in terms of the frequency of adverse events. We have only one serious adverse event that was not drug-related (i.e. Herpes, 1/32, 3%) in the biosimilar EPO group. This result was similar to the results of a large observational prospective multicenter study by Stoppa et al. in 2018.[10] They found no difference between the two cohorts of users (originator versus biosimilar epoetin α) with regard to any kind of adverse events, even after adjusting for confounding factors: 1.0 (95% confidence interval [CI] 0.7–1.3) for any outcome; 1.1 (95% CI 0.7–1.8) for problems related to dialysis device; 0.9 (95% CI 0.6–1.5) for cardio- and cerebrovascular conditions; 0.9 (95% CI 0.6–1.5) for infections.[8,10] Study by London et al.[9] also reported the safety of HX575 (a biosimiar epoetin α) was comparable to the reference epoetin α. They found 140 patients (6.7%) experienced ≥ 1 adverse events; of these, 19 events (16 patients, 0.8%) were related to HX575 treatment, 148 events (108 patients, 5.2%) were reported as serious, including 12 events in 11 patients (0.5%) stated to be treatment related. No cases of anti-epoetin antibodies or pure red cell aplasia were reported.[9]

To our knowledge, this study was the first randomized controlled study on a biosimilar epoetin α in Indonesia. The limitation of this study was the small number of patients participated in the study. A large study with the same design will be expected to confirm the results of the present study.

CONCLUSION

The mean Hb level could be maintained at >10 g/dL every 2 weeks for 8 weeks of treatment with both the originator EPO and the biosimilar EPO, more consistent (stable) with the originator EPO, and more fluctuating with the biosimilar EPO. Epoietin dose did not differ significantly between the two groups. There was no drug-related adverse event in either group.

CONFLICT OF INTEREST

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