Methoxy polyethylene glycol-epoetin β for the Treatment of Renal Anemia among Filipino Patients with Chronic Kidney Disease

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ABSTRACT

Introduction. Methoxy polyethylene glycol-epoetin β has been shown to be effective in the treatment of anemia among chronic kidney disease (CKD) patients on dialysis or pre-dialysis. This study evaluated the effectiveness and safety of this drug in the treatment of renal anemia among Filipino patients, demonstrating relevant clinical experiences in drug administration and dose adjustment.

Methods. This was an open-label, one-arm prospective clinical series conducted in five renal clinics in Metro Manila, which enrolled 28 (27 evaluable) CKD patients, 18 years old and above with ESA-naive renal anemia who fulfilled the eligibility criteria. All patients gave their informed consent. The protocol was approved by the Philippine Council for Research & Development–National Ethics Committee.
Methoxy polyethylene glycol-epoetin β was given as a subcutaneous injection beginning at 0.6 ug/kg body weight once every two weeks with dose adjustment (25% increments/decrements per month) to keep hemoglobin at 11 to 12 g/dL (not to exceed 13 g/dL), and then maintained once every four weeks on a dose equal to twice the previous once-every-two-weeks dose, over a 24-week study period. Data analysis was done using STATA version 10.

Results. Across the 24 weeks of methoxy polyethylene glycol-epoetin β treatment, there was a mean increase in hemoglobin of $\geq$1.0 g/dL from baseline; >60% of patients achieved hemoglobin levels $\geq$11 g/dL starting at week 8 (mean time to first target hemoglobin 5.7 weeks) with variability, no blood transfusion, and mean of 1.52$\pm$1.25 SD dose adjustments per patient. The manner of dose adjustment can be the main driver of hemoglobin variability. Common adverse events were sudden rise in blood pressure (6 patients), back pain (3), and fever (3).

Conclusion. Methoxy polyethylene glycol-epoetin β administered once monthly after an initial once every two weeks correction phase can improve hemoglobin levels at target 11 to 12 g/dL, with hemoglobin variability and safety events as expected for a CKD population.

Keywords: Methoxy polyethylene glycol-epoetin β, renal anemia

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Introduction

Methoxy polyethylene glycol-epoetin β is a chemically synthesized continuous erythropoietin receptor activator. It differs from epoetin β through integration of an amide bond between an amino group and methoxy polyethylene glycol-butanoic acid. This results in a molecular weight of ~60,000 Da.[1]

In pre-clinical studies[1], methoxy polyethylene glycol-epoetin β was a more potent stimulator of erythropoiesis than epoetin β, with substantially increased magnitude and duration of response. Once weekly and biweekly dosing regimens were equally effective in stimulating erythropoiesis, which was dose-dependent. The effect was specific to erythrocytes, not significantly affecting white blood cells and platelets.

In contrast with epoetin β, methoxy polyethylene glycol-epoetin β has a reduced affinity for the erythropoietin receptor which is characterized by a reduced association rate, a slightly faster dissociation rate, and an increased half-life (about 130 hours). These pharmacological properties allow longer (once monthly) dosing intervals.

Most regimens for the treatment of anemia of CKD require one to three administrations of erythropoiesis stimulating agents (ESAs) per week. In patients with CKD, alleviation of anemia requires life-long treatment with an ESA. Any modification extending the half-life of the protein and thereby allowing even less frequent administration, with sustained efficacy, should improve the convenience and therapeutic utility of the drug.

Methoxy polyethylene glycol-epoetin β efficacy and safety trials focused on correction[2,3] of renal anemia and

maintenance[4-7] of hemoglobin levels among ESA-treated CKD patients.

The response rates of the methoxy polyethylene glycol-epoetin β patient group during the correction and evaluation periods were 93% (p<0.0001; 95% CI=87.7–96.9)[2] and 98% (p<0.0001; 95% CI=93.8–99.3%)[3], respectively, with the lower limit of the CI well above 60% confirming that methoxy polyethylene glycol-epoetin β resulted in the correction of the anemia. In the AMICUS study,[2] the median dose at the time of hemoglobin response was 0.6 ug/kg once every two weeks IV (compared with the starting dose of 0.4 ug/kg once every two weeks IV), suggesting that 0.6 ug/kg once every two weeks is appropriate for both IV and SC routes of administration. In the ARCTOS study,[3] the median dose at the time of response was the same as the starting dose (0.6 ug/kg once every 2 weeks SC).

The four Phase III maintenance trials[4-7] indicated that the starting dose categories (60, 100, and 180 ug once a week and 120, 200, and 360 ug once every four weeks) and the dose adjustments were adequate to maintain hemoglobin concentrations. This was following conversion from a previous ESA to methoxy polyethylene glycol-epoetin β regardless of previous ESA (e.g., epoetin α, epoetin β, or darbepoetin α). At the end of the eight-week evaluation period, average hemoglobin concentration was maintained in 66% to 76% of patients in methoxy polyethylene glycol-epoetin β similar to reference treatment groups during the evaluation period within $\pm$1 g/dL of their baseline. Mean and median monthly hemoglobin concentrations in each of the treatment groups in each of the maintenance studies remained within the clinically acceptable range for the treatment of dialysis patients (11–13 g/dL) throughout the study period.

Pooled analyses[1,8] of safety data from Phase II–III studies (1,789 patients on methoxy polyethylene glycol-epoetin β and 948 epoetin α/ epoetin β/ darbepoetin α) showed comparable results between the groups for incidence of serious adverse events (AEs), severe AEs, and AEs leading to withdrawal. The death rate was low and similar between groups across clinical studies; the causes of death were varied and the events were as expected for a CKD population. No consistent pattern of individual AEs, serious AEs (SAE), or AEs leading to withdrawal was observed. Administration of methoxy polyethylene glycol-epoetin β for the treatment of anemia associated with CKD was generally well tolerated with no difference in the safety profile compared with reference ESAs. There were no newly developed detectable antibodies in patients nor was there any evidence of pure red cell anemia in patients receiving methoxy polyethylene glycol-epoetin β.

From the studies, weight, gender, race (white, black) did not affect response rates; however experiences from ethnicity sub-groups (e.g., Asian) were too small to draw relevant clinical impressions, particularly for Filipino patients who are relatively of lower weights than their Caucasian and Black counterparts.

This study evaluated effectiveness and safety of methoxy polyethylene glycol-epoetin β for the treatment of renal anemia among Filipino CKD patients, demonstrating relevant clinical experiences in drug administration and dose adjustment.

Methods

This was an open-label, one-arm prospective clinical series demonstration study which included 28 CKD patients from five renal clinics in Metro Manila, Philippines. There were eight planned study sites with about five patients per site, but three sites did not meet the deadline for study initiation.

Eligibility criteria included patients $\geq$18 years of age with asymptomatic hemoglobin <11 g/dL, ESA naive, on dialysis or not, not in acute renal failure or acute respiratory or cardiac distress, with ferritin levels $\geq$100 ug/L. Exclusion criteria were hypersensitivity to recombinant human erythropoietin, polyethelene glycol or to any constituent of the study drug formulation; administration of any investigational drug within 30 days preceding the first dose of the study drug; overt gastrointestinal bleeding or any other bleeding episode necessitating transfusion; red blood cell (RBC) transfusions within eight weeks before screening or during the screening period; history of hemoglobinopathies, hemolysis, pure red cell aplasia; active malignant disease (except melanoma of skin); chronic uncontrolled or symptomatic inflammatory disease (e.g., rheumatoid arthritis, systemic lupus erythematosus); acute infection; poorly controlled hypertension; epileptic seizure in the six months before screening; high likelihood of early withdrawal or interruption of the study (e.g., myocardial infarction, severe or unstable coronary artery disease, stroke, severe liver disease) within 12 weeks before screening; planned elective surgery during the next seven months; life expectancy less than 12 months; pregnancy or breast-feeding; women of child-bearing potential without effective contraception; uncontrolled symptomatic secondary hyperparathyroidism; platelet counts >500 x 10^9/L; failing renal graft; rapid progression of CKD; c-reactive protein (CRP) >15 mg/L (in patients not on dialysis); CRP>30 mg/L (in patients on dialysis); non-compliance with dialysis (in patients on dialysis); and immunosuppressive therapy in the 12 weeks before screening. All 28 patients enrolled in the study fulfilled the eligibility and exclusion criteria except for one who had a baseline hemoglobin of 11.5 g/dL, who was included in the safety analysis but not in the effectiveness analysis. All 28 patients were dialysis-naive.

All patients gave their written informed consent to participate in the study. The protocol was approved by the Philippine Council for Health Research & Development–

National Ethics Committee. Good clinical practice including data confidentiality was practiced.

The starting dose of methoxy polyethylene glycol-epoetin β solution in pre-filled syringe (PFS) was 0.6 ug/kg body weight administered subcutaneously (SC) in the arm, thigh, or abdomen once every two weeks to increase the hemoglobin to >11 g/dL. If hemoglobin concentrations, monitored at four weeks intervals, increased <1 g/dL, the dose was increased by 25%. If hemoglobin concentrations fell below the initial value and <9.0 g/dL, the dose was doubled. If hemoglobin concentrations increased by >2.0 g/dL or approaching 13 g/dL, the dose was decreased by 25%. If hemoglobin level began to decrease, up to 11 g/dL, the dose was re-started at 25% below the previously administered dose. If hemoglobin concentrations reached 11 to 13 g/dL, a once monthly maintenance dose was given using the dose equal to twice the previously administered once-every-two-weeks dose. Dose adjustment was performed only once every four weeks. Hemoglobin level was confirmed before dosing adjustment was made. Hemoglobin concentration was maintained within the range of 11 to 12 g/dL, not exceeding 13 g/dL. Dose adjustment for safety reasons was allowed at any time during the study. All patients received iron supplementation as per individual study site practice.

The study included a screening period, four physician visits, and one final follow-up visit. The primary parameters included increase in hemoglobin ≥1.0 g/dL from baseline, hemoglobin levels 11 to 13 g/dL for pre-dialysis patients, and secondary parameters of at least 60% responders (number of patients with target hemoglobin at 11 to 13 g/dL for pre-dialysis patients), time to first achievement of target hemoglobin response (11 to 13 g/dL), incidence of 500-cc-RBC units transfused during treatment period, number of patients with dose adjustments and number of dose adjustments, safety data including blood pressure (BP) over the 24-week treatment period.

Encoding of data was done using Epi-info 6. Effectiveness analysis was conducted over the intent-to-treat population; a safety analysis was done on all patients who received one dose of methoxy polyethylene glycol-epoetin β. Data analysis was done using STATA version 10. Mean and standard deviations were computed for numerical variables. Proportion was computed for categorical variables. Repeated measures analysis of variance (ANOVA) was used to determine if there were significant changes in hemoglobin levels over time (baseline through 24 weeks).

Results

There were 17 females and 11 males, with mean age of 62.4 years (median = 60; range = 28–84). All patients were ambulatory from baseline to week 24 except for one patient whose ambulatory function improved over time (at baseline, the patient was in a wheelchair for left-sided weakness; through time, the patient was able to ambulate with as-needed use of the wheelchair).

All patients were ESA-naive and dialysis-naïve at baseline. Majority (64%) had CKD for one to five years (Table 1).

Table 1. Distribution of patients according to duration of CKD (n=28)

Duration of CKD	No.	Percent
< 1 year	2	7
1-5 years	18	64
>5 years	8	29

Most common etiologies for CKD were diabetic nephropathy (75%) and hypertensive nephropathy (43%). Some patients had more than one disease etiology (Table 2).

Table 2. Distribution of patients according to etiology of CKD (n=28)

Etiology	No.	Percent
Diabetic nephropathy	22	78
Hypertensive nephropathy	12	43
Chronic pyelonephritis	1	4
Gouty nephropathy	1	4
Nephrolithiasis	1	4
Autosomal dominant polycystic kidney disease	1	4
Chronic glomerulonephritis	0	0

The baseline body weight, serum ferritin, creatinine and creatinine clearance are summarized in Table 3. Twenty-one of the 28 patients had normal CRP values.

Table 3. Baseline characteristics of patients (n=27)

Description	Mean	SD	Median	Range
Body weight (kg)	56.81	11.45	54.5	35 – 85
Serum Ferritin (ug/L)	839.01	517.74	728.3	134.5 – 2000
Creatinine(mmol/L)	256.04	156.68	229.5	47.53-662.64
Creatinine clearance (ccs/min))	29.74	24.54	21.2	8.1-113.9

Note: Pt No. 9 with baseline Hgb 11.5 was discontinued from the study as a protocol deviation (inclusion criteria<11), after one methoxy polyethylene glycol-epoetin β injection

Effectiveness of methoxy polyethylene glycol-epoetin β

The primary objective of mean change in hemoglobin concentration of ≥1 g/dL from baseline was achieved across the 24 weeks treatment period (Table 4).

Table 5 shows the overall mean hemoglobin values achieving a range of at least 11 to 12 g/dL by week 8 and up to week 24.

However, the analysis of individual patients indicates that it is not easy to maintain hemoglobin within the recommended target range. The patients can be grouped according to characteristic dose adjustment versus hemoglobin (Hb) levels, with example representative

patients shown in Figures 1 a–f: appropriate dose adjustment (ADD), lacking dose adjustment (LDA) versus low amplitude fluctuation-target haemoglobin (LATH), low amplitude-low haemoglobin (LALH), high amplitude-high haemoglobin (HAHH).

Table 4. Serial changes in haemoglobin level (g/dL) from baseline to week 24 (n=26)

Time of follow-up	Mean	SD	95% CI	p-value[a]
Week 4	1.01	0.94	0.63 – 1.39	0.4694
Week 8	1.94	1.31	1.41 – 2.47	0.0006
Week 12	2.55	1.70	1.86 – 3.24	<0.0001
Week 16	2.55	1.73	1.85 – 3.25	0.0001
Week 20	2.20	1.85	1.45 – 2.95	0.0014
Week 24	2.19	2.14	1.33 – 3.05	0.0045

[a] *One sample mean comparison t-test, with hypothesized change in hemoglobin concentration >1g/dL*

Table 5. Mean haemoglobin level (g/dL) by time of follow-up (n=26)

Time of follow up	Mean	SD	95% CI	p-value[a]	p-value[b]
Baseline	9.75	0.90	9.39 – 10.11	---	---
Week 4	10.77	1.32	10.24 – 11.30	0.0008	0.8046
Week 8	11.70	1.23	11.20 – 12.20	<0.0001	0.0041
Week 12	12.31	1.45	11.72 – 12.90	<0.0001	<0.0001
Week 16	12.31	1.36	11.76 – 12.86	<0.0001	<0.0001
Week 20	11.96	1.52	11.35 – 12.57	<0.0001	0.0017
Week 24	11.95	1.83	11.21 – 12.69	<0.0001	0.0071

[a]*Repeated measures ANOVA posthoc comparison with baseline using holm-adjusted p-values because sphericity assumption of the test was not met.*
Overall ANOVA p-value<.0001
[b] *One sample mean comparison t-test, with hypothesized hemoglobin concentration >11g/dL*

At least 60% of the patients had hemoglobin ≥11 g/dL over the 24 weeks of study treatment, but <60% of the patients achieved or maintained an 11 to 13 g/dL hemoglobin range, with wide 95% CI, due to small sample size (Table 6).

Table 6. Proportion of patients with hemoglobin level ≥11g/dL or 11-13 g/dL by time of follow-up

Time of follow-up	Hb ≥11 g/dL			Hb 11-13 g/dL		
	No.	%	95% CI	No.	%	95% CI
Week 4 (n=27)	15	55.56	35.33 – 74.52	15	55.56	35.33 – 74.52
Week 8 (n=27)	20	74.07	53.72 – 88.89	15	55.56	35.33 – 74.52
Week 12 (n=27)	21	77.78	57.74 – 91.38	13	48.15	28.67 – 68.05
Week 16 (n=26)	21	80.77	60.65 – 93.45	13	50.00	29.93 – 70.07
Week 20 (n=26)	18	69.23	48.21 – 85.67	11	42.31	23.35 – 63.08
Week 24 (n=26)	18	69.23	48.21 – 85.67	11	42.31	23.35 – 63.08

Note. One patient died, hence without data starting at week 16

None of the 28 patients had blood transfusion during the study period. The median time to first achievement of target hemoglobin level was 5.7 weeks (Figure 2).

Dose adjustments

There was a mean dose adjustment of 1.52±1.25 SD (range = 0–4) per patient. Of the 27 patients, 11 (41%) did not have dose adjustments to improve the hemoglobin level (Figures 1 d–f) in at least one dosing event; six (22%) patients had at least one dose event where no significant dose increment was done to improve low hemoglobin levels (range=7.6 to 10.5 g/dL). There were three patient-visits (3 patients) with hemoglobin 11 to 13 g/dL, eight patient-visits (8 patients) and two patient-visits (1 patient) with hemoglobin >13 g/dL, where methoxy polyethylene glycol-epoetin β dose was withheld.

Safety profile

The mean red blood cell (RBC), white blood cell (WBC) and platelet counts were without clinically significant change over the 24 weeks of treatment (Table 7).

Out of the 28 patients, 16 (57%) reported adverse events (AEs) during the treatment period. There was no significant change in overall systolic blood pressure (SBP) and diastolic blood pressure (DBP) across time (Table 7). Although the more common AEs reported were sudden rise in blood pressure, back pain and fever (Table 8).

Only two of 32 (6.25%) AEs were severe (also identified as serious); 75% were mild, and 18.75% moderate in intensity. Only four of 32 (12.50%) AEs were suspected to have causal relationship with methoxy polyethylene glycol-epoetin ß (three possibly related [acneiform lesion, fever, sudden rise in BP] and one remotely [dizziness]). About half (51.52%) took medication for the AE.

Twenty-five (78.13%) of 32 adverse events were resolved without sequelae while five (15.63%) were unresolved at the end of the study (mild knee joint pains, mild BP elevation, mild gout arthropathy, severe elevated creatinine needing dialysis, mild acneiform lesion). One adverse event was resolved with sequelae (elevated creatinine requiring continuing dialysis, unrelated to methoxy polyethylene glycol-epoetin ß, reported as SAE), and another resulted in death (70-year-old patient before week 16, bled from myoma and went into fatal arrhythmia, unrelated to methoxy polyethylene glycol-epoetin β, reported as SAE; hemoglobin levels <10 g/dL).

Discussion

This study demonstrates the efficacy of methoxy polyethylene glycol-epoetin β treatment in the correction of renal anemia.

In patients[9] with renal anemia in CKD, both on dialysis and pre-dialysis, who had not previously received an ESA, methoxy polyethylene glycol-epoetin β administered IV or SC once every two weeks resulted in a steady rise in hemoglobin levels. The response rates were high (up to 97.5%) at the end of the correction period compared to up to 96.3% of the comparator ESAs (epoetin β, epoetin α,

Table 7. Mean ± SD haematology and blood pressure characteristic by time of follow-up

Characteristic	Baseline		Week 4		Week 8		Week 12		Week 16		Week 20		Week 24	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
RBC (x 10^9/L)	3.4	1	3.8	1	4.1	1	4.4	1	4.4	1	4.3	1	4.3	1
WBC (x 10^9/L)	7.5	2	6.9	1	7.3	1	7.1	2	7.1	1	7.4	2	7.5	2
Platelet (x 10^9/L)	243.0	65	243.6	60	243.1	65	229.9	60	221.8	59	237.4	75	240.4	64
SBP (mmHg)	132.3	19	129.2	21	134.2	24	130.4	19	128.1	23	127.3	20	128.8	18
DBP (mmHg)	74.2	11	75.4	9	76.2	11	76.9	8	75.4	10	76.2	11	75.4	8

darbepoetin α).[9] Extensive analysis[8] of safety events in patients with renal anemia receiving long-term treatment with methoxy polyethylene glycol-epoetin showed a safety profile consistent with that of other ESAs.

Table 8. Distribution of adverse events

Adverse Event	No.	Percent
Sudden rise in blood pressure	6	18.75
Back pain	3	9.38
Fever	3	9.38
Dizziness	2	6.25
Acute gouty attack/gouty arthropathy	2	6.25
Knee joint pain	2	6.25
Acne form lesion	1	3.13
Upper Respiratory Tract Infection	1	3.13
Acute Gastroenteritis	1	3.13
Pinpoint sensations at the sole of both feet	1	3.13
Abdominal cramps	1	3.13
Transient loss of consciousness	1	3.13
Feeling of dryness of eyes	1	3.13
Dryness of the mouth when he wakes up	1	3.13
Right lower quadrant probably secondary to obstructive lithiasis	1	3.13
Fatal arrhythmia with bleeding myoma	1	3.13
Seasonal allergy	1	3.13
Elevated creatinine needing dialysis	1	3.13
Occasional headache	1	3.13
Bipedal edema	1	3.13
Total	32	100.00

In pharmacokinetic studies of methoxy polyethylene glycol-epoetin β in CKD patients,[1,10-12] multiple dosing was found to have no effect on clearance, volume of distribution or bioavailability of the drug. The maximum serum concentrations of methoxy polyethylene glycol-epoetin β were observed 72 hours median following SC administration; the absolute bioavailability after SC administration was 62%. After administration every two weeks, the ratio of accumulation in serum was 1.12. In CKD patients, alleviation of anemia requires life-long treatment with such a drug, this time with less frequent administration and sustained efficacy.

Pharmacodynamic[1,11,12] results in healthy volunteers showed a potent, dose-dependent and long lasting erythropoietic response after both IV and SC administration of methoxy polyethylene glycol-epoetin β. The primary pharmacodynamic marker of response was reticulocyte count, which is a well accepted marker of erythropoiesis in serum. This marker showed a clear and consistent dose-dependent increase in healthy subjects. The minimum dose inducing a reticulocyte response in healthy volunteers (0.4 ug/kg SC) provided the basis for selecting the lower doses used in the Phase II studies. Consistent with the prolonged half-life, a sustained pharmacodynamic response was observed, with reticulocyte count peaking after eight to 10 days and returning to baseline after 14 to 20 days for both IV and SC routes of administration. Red blood cell parameters, such as hemoglobin, RBC count and hematocrit showed high variability. Nonetheless, a general dose-dependent increase in hemoglobin concentration was seen using doses between 0.4 and 3.2 ug/kg in healthy volunteers. The high variability emphasizes the need for individual dose adjustment based on hemoglobin levels in line with all ESAs.

The National Kidney Foundation (KDOQI) clinical practice guidelines for anemia in CKD recommends that the hemoglobin target should be maintained in the range of 11 to 12 g/dL, not exceeding 13 g/dL.[13] Fluctuation of hemoglobin levels can occur however, with difficulty in having more patients within the target hemoglobin levels.[14-18] Hemoglobin variation events had been shown to be

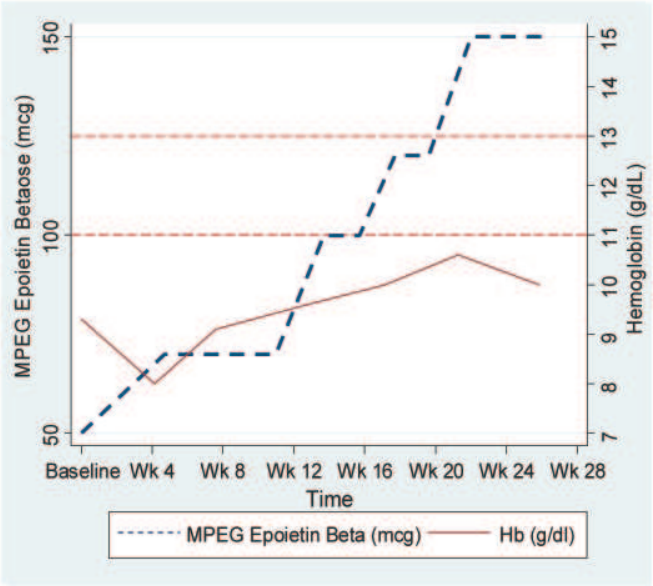

Figure 1a. Patient with appropriate dose adjustment (ADD) but with low amplitude-low haemoglobin (LALH) levels

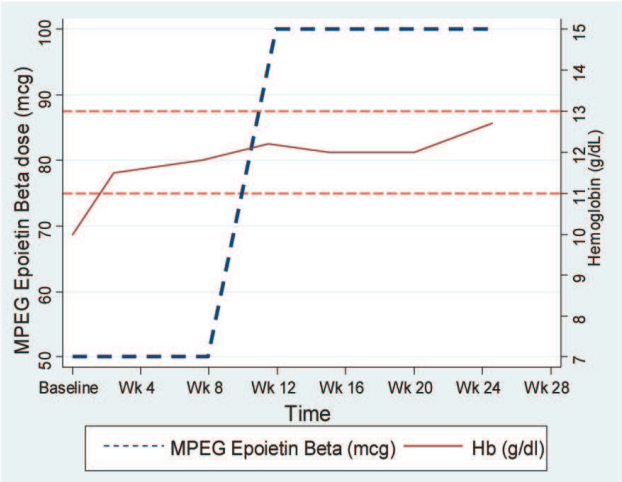

Figure 1b. Patient with appropriate dose adjustment (ADD) but with low amplitude target haemoglobin (LATH) levels

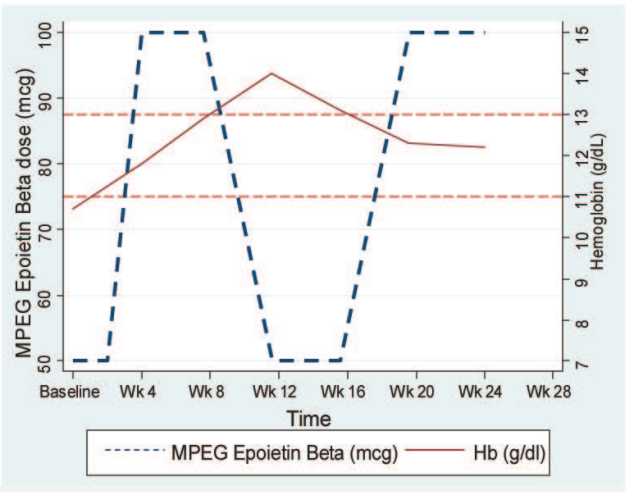

Figure 1c. Patient with appropriate dose adjustment (ADD) and with high amplitude-high haemoglobin (HAHH) levels

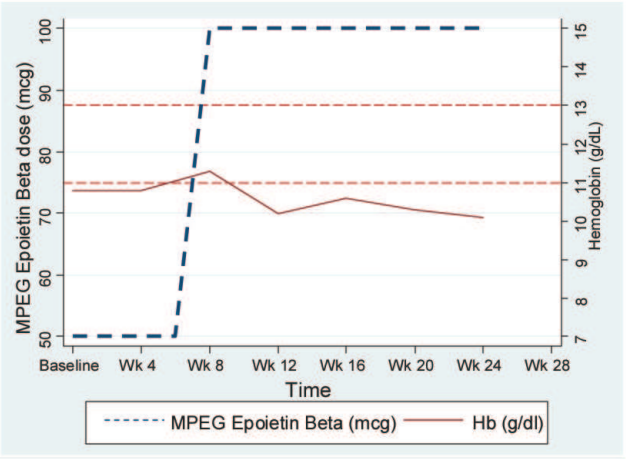

Figure 1d. Patient with lacking dose adjustment (LDA) and with low amplitude-low haemoglobin (LALH) levels

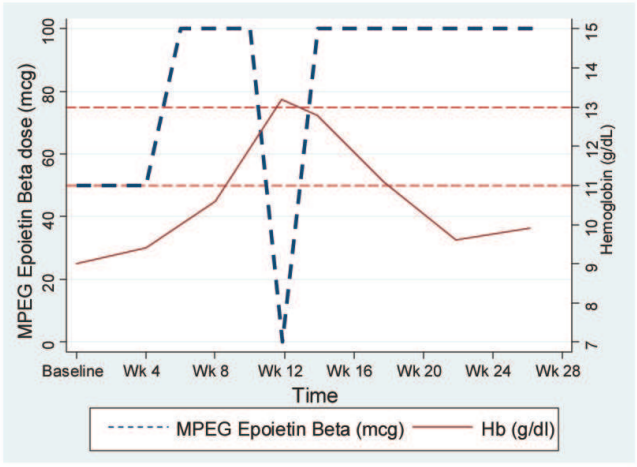

Figure 1e. Patient with lacking dose adjustment (LDA), with erratic fluctuations of haemoglobin

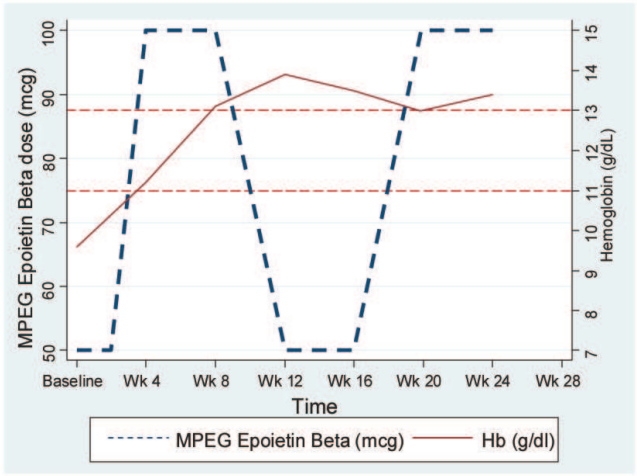

Figure 1f. Patient with lacking dose adjustment (LDA) but with high amplitude-high haemoglobin (HAHH) levels

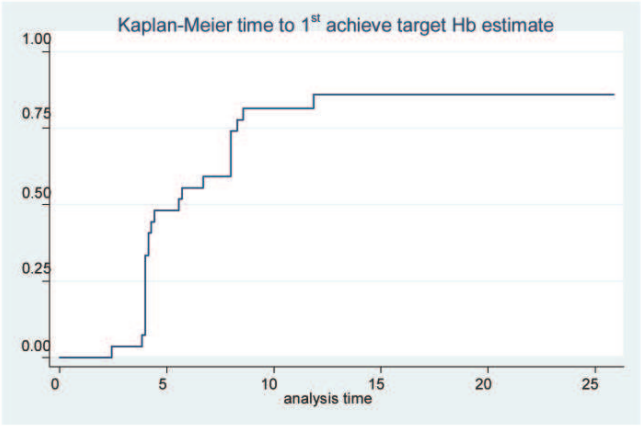

Figure 2. Kaplan-Meier Curve of first time to achieve target haemoglobin level (11-13 g/dL)

associated with clinical events or changes of ESA doses, and occurred less frequently in patients treated with long-acting ESA;[14] hemoglobin fluctuation has been shown to be associated with provider practices.[17] Ebben JP et al.[17] described hemoglobin fluctuations as consistently low (<11g/dL) as low amplitude fluctuation with low hemoglobin (LA-LH), consistently within target range (11 to 12.5 g/dL) as low amplitude fluctuation-target hemoglobin level (LA-TH), and consistently high (≥12.5 g/dL) as high amplitude fluctuation-high haemoglobin (HA-HH); 90% of the time, there was some degree of flux at any point in time. LA-LH group was shown to have the highest proportion of hospitalization and high numbers of co-morbid conditions. Patients with LA-LH levels have to be ascertained early on, for early intervention towards possible improvement as per clinical practice.

At the initial use of methoxy polyethylene glycol-epoetin β, the dose is started at 0.6 ug/kg body weight administered SC once every two weeks to increase the haemoglobin to >11 g/dL and maintained at 11 to 13 g/dL, going by dose adjustment guidelines. For hemoglobin correction, monitor hemoglobin at four weeks intervals: if hemoglobin increases <1 g/dL, the dose is increased by 25%; if it falls below the initial value and is <9.0 g/dL, the dose is doubled; if it increases by >2.0 g/dL or is approaching 13 g/dL, the dose is decreased by 25%; if it begins to decrease to 11 g/dL, re-start at a dose 25% below the previously administered dose. To maintain hemoglobin at 11 to 12 g/dL (not to exceed 13 g/dL), give methoxy polyethylene glycol-epoetin β once monthly using the dose equal to twice the once-every-two-weeks dose which corrected the hemoglobin concentration. Since iron deficiency may cause a reduced response to erythropoietin and erythropoiesis induced by treatment may lead to a depletion of iron stores, patients should receive iron supplementation as per clinical practice.

The hemoglobin level must be confirmed before the corresponding dosing adjustment is made. After the initial dose at 0.6 ug/kg body weight dose, the next calculated adjusted dose will depend on the immediate previously administered dose, and herein comes the experienced clinical eye of the attending physician.

Dose adjustment for safety reasons will take priority, and the dose can be interrupted. After a dose interruption, a hemoglobin decrease of ~0.35 g/dL per week is expected.[1]

The manner of dose adjustment is a main driver of hemoglobin variability, as shown by a cohort study which assessed such variability under daily practice conditions with the use of short-acting ESAs.[14] The cohort study indicated that only 3.8% of 420 patients maintained target hemoglobin between 11 to 13 g/dL during the one-year follow-up, confirming that maintaining stable hemoglobin within current guidelines was difficult, despite selection of patients.

The Philippine market carries methoxy polyethylene glycol-epoetin β solution 50 ug, 100 ug, and 200 ug dose strengths per PFS, with the 30 ug dose soon to be marketed. Dose adjustment should take into consideration the available dosage strengths of the drug and the co-morbidities present in the patient in addition to the prior and current hemoglobin levels and the corresponding prior methoxy polyethylene glycol-epoetin β dose.

This study achieved a mean change of hemoglobin at ≥1 g/dL at week 4 and maintained to week 24, >60% of patients with hemoglobin levels ≥11 g/dL starting at week 8 (mean time to first target hemoglobin 5.7 weeks), with no blood transfusion, with mean 1.52±1.25 SD dose adjustments per patient.

Methoxy polyethylene glycol-epoetin β administered once monthly after an initial once every two weeks correction phase beginning at 0.6 ug/kg body weight dose can improve hemoglobin levels at target 11 to 12 g/dL, with hemoglobin variability and safety events as expected for a CKD population.

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