WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 8, 1676-1693. Research Article ISSN 2277– 7105

COST-EFFECTIVENESS OF METHOXY POLYETHYLENE GLYCOL-EPOETIN B VERSUS EPOETIN ALFA IN THE TREATMENT OF HEMODIALYSIS PATIENTS WITH RENAL ANEMIA

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Article Received on
20 June 2016,
Revised on 10 July 2016,
Accepted on 01 August 2016
DOI: 10.20959/wjpr20169-6967

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ABSTRACT

Background: Renal anemia is the decrease in one or more of the major red blood cell measurements; concentration of hemoglobin, hematocrit, or red blood cell count. Impaired ability of the kidneys to secrete erythropoietin and consequent reduction in the erythrocytes production was the major cause of anemia. **Objective:** The aim of the study was to assess the cost-effectiveness of methoxy polyethylene glycol-epoetin β versus epoetin alfa in the treatment of hemodialysis patients with renal anemia **Methods:** A prospective single center-randomized-controlled-open labeled clinical trial with three months treatment and follow up periods was performed. Forty six Patients with renal anemia were randomly allocated to receive either MPG-EPO 100µg once every two week or epoetin alfa 4000 IU twice per week subcutaneously and were evaluated at baseline and monthly during the followed up period. Blood sample of patients groups were evaluated for Hb, PCV, Reticulocyte count, serum ferritin, iron, total iron binding capacity. Monitoring of the adverse effects of methoxy poly-ethylene glycol epoetin beta and epoetin alpha was done either by clinical examination for the objective data or by questionnaire for the subjective data. Cost analysis was done taking into account the direct drug acquisition cost only, the cost result was the difference in patients per month cost with MPG-EPO versus epoetin alfa. **Results:** Hemoglobin concentration, reticulocyte count and packed cell volume were significantly increased with MPG-EPO and epoetin alfa. Mean change of Hb was 1.53±1.04 g/dl for MPG-EPO versus 1.41±0.96 g/dl for epoetin alfa. The rise in

haematological parameters in methoxy polyethylene glycol-epoetin beta group was non significantly higher than that of epoetin alfa groups. One case of arteriovenous fistula thrombosis and local pain after S.C injection was reported in MPG-EPO arm. Other adverse events and complications include flu-like symptoms, diarrhea and blood transfusion was reported in both arms of study. There were no cases of hypertension, nasopharyngitis, upper respiratory tract infection, rash and hot flushes were reported for both MPG-EPO and epoetin alfa and no death reported during the study. The patient/month cost was 292£ for MPG-EPO and 190£ for epoetin alfa, with a difference of 102 £. **Conclusion:** Methoxy polyethylene glycol epoetin beta provided comparable effect on hematological parameter to that of epoetin alfa in patients with renal anemia. Methoxy polyethylene glycol epoetin beta had a good safety profile that comparable to epoetin alfa and it is well tolerated in renal anemia. Treatment with MPG-EPO has led to an increase of 102 £ in the patient/month cost.

KEYWORDS: methoxy polyethylene glycol-epoetin beta, end-stage renal disease, anemia, epoetin alfa, cost.

1. INTRODUCTION

Chronic kidney disease (CKD) is defined as "the presence of kidney damage, manifested by abnormal albumin excretion or decreased kidney function, quantified by measured or estimated glomerular filtration rate (GFR) <60 ml/min that persist for more than 3 months".[1] End stage renal disease (ESRD) Is the progression of chronic kidney disease to a GFR less than 15 ml/min, that needs renal replacement therapy, either transplantation or dialysis.[2] As the kidney disease progresses, anemia increases in occurrence affecting approximately all patients with stage 5 CKD.[3] Anemia in ESRD is inevitable due to decrease of erythropoietin (EPO) production. Deformities in platelet functions and white blood cell (WBC) also occur and lead to easy bruising and increased susceptibility to infection. Anemia occurs mainly due to EPO deficiency and to a lesser degree from the presence of uremic inhibitors, hemolysis, blood loss, and iron deficiency.[4] Anemia can be defined as the reduction in one or more of the major red blood cell measurements; concentration of hemoglobin (Hb), hematocrit (Hct), or red blood cell count (RBC)". Anemia defined by World Health Organization (WHO) as a hemoglobin level less than 13 g/dL, Hct is < 39% in men and post- menopausal women and Hb less than 12 g/dL, Hct is <36% in premenopausal women.[5] Anemia prevalence increased with the stage of CKD: less than 10% in stages 1 and 2, 20–40% in stage 3, 50–60% in stage 4 and more than 70% in stage 5 of CKD.[6] Erythropoietin hormone that stimulates the red

blood cells production by the bone marrow, being produced in the kidneys. Chronic kidney disease patients eventually present with a shortage of this hormone, that leads to an anemia.[7] The main treatment of renal anemia is to stimulate erythropoiesis by injections with erythropoiesis stimulating agents (ESAs) regularly and to ensure sufficient iron availability for proper erythropoiesis.[3] The major revolution in the treatment of renal anemia was the introduction of ESAs into clinical practice. The development of ESAs was aimed to substitute the inadequate endogenous erythropoietin production related to CKD progression.[8] Correction of renal anemia with ESAs reduces the risk of CVD, improves patient well-being, exercise tolerance, quality of life and decreases the need for blood transfusions have a major impression on patient outcomes.[9] However, due to the short half-lives of ESAs (Epoetin alpha and beta approximately seven to nine hours, darbepoetin alpha approximately 25 hours) frequent administration is necessary (two to three times for Epoetin alpha or beta and once weekly for darbepoetin alpha). Short half-life of ESAs is one of the reasons behind the fluctuations of hemoglobin (Hb) levels.[10] Dosing interval of ESAs with short half-life may contribute to the problem of Hb cycling.[11] Accordingly, agents with extended dosing interval are needed to provide stable and predictable hemoglobin responses with minimal health care professionals' intervention.[12] Methoxy polyethylene glycol epoetin beta (MPG-EPO) or continuous erythropoietin receptor activator is the first agent of a new class of longer-acting ESAs designed for correction and maintaining hemoglobin levels in patients with CKD. Contrasting shorter-acting ESAs, continuous erythropoietin receptor activator has lower affinity for erythropoietin receptors that prompts its repeated binding and further stimulation of bone marrow for red blood cell production. Long half-life of Methoxy polyethylene glycol epoetin beta (elimination half-life of 130 h) allows its administration as once every two weeks to correct anemia and once-monthly to maintain target hemoglobin levels.[13] Amongst currently available ESAs continuous erythropoietin receptor activator has the longest half-life, making it possible to achieve steady and smooth correction of Hb and stable maintenance at extended intervals.[14] In addition to, longer half-life may help in minimizing the injections frequency and number of hospital visits resulting in better compliance.[15]

The prevalence and incidence of patients with renal anemia is increasing worldwide.[16,17] Rising economic pressure on private and public consumer and increasing health care costs make current trends in anemia management essentially focus on economizing and simplifying ESA treatment, since this type of therapy still generates significant expenditures.[18] This

study was designed to assess the cost-effectiveness of methoxy polyethylene glycol-epoetin β versus epoetin alfa in the treatment of hemodialysis patients with renal anemia.

2. METHODS

2.1. Study Design

This study is a prospective single center randomized controlled open labeled clinical trial that was carried out at hemodialysis Unit, Baghdad Teaching Hospital from 1st October 2014 to 5th May 2015. Ethical Approval was obtained from the Ethics Committee by College of Pharmacy / Baghdad University and nephrology Medical Department. Subjects were assigned into two groups: **Group A:** 26 hemodialysis patients (15 males and 11 females) with renal anemia were treated with 100µg Methoxy polyethylene glycol epoetin beta S.C injection once every two weak. **Group B:** 20 hemodialysis patients (11 males and 9 females) with renal anemia were treated with Epoetin alfa 4000 IU S.C injection twice per week. When Hb level for an individual patient reached to 11g/dL, MPG-EPO can be continue as once per month using a dose equivalent to twice the previous once every two weeks dose. If the Hb level is increase and approaches 11.5g/dl for MPG-EPO and epoetin alfa, the dose reduced by approximately 25%. Treatment should be stopped when Hb level ≥11.5 g/dL.[19]

Most of the patients received 100 mg of IV iron sucrose once per weak to keep the transferrin saturation ≥ 20% and ferritin ≥ 100ng/ml. Iron therapy should be stopped when iron parameter reach celling level, serum ferritin (500-800) ng/ml and transferrin saturation ≥ 50%. Additionally, all the patients received 5 mg folic acid per day and 10µg vitamin B12 per day to prevent hyporesponsivness to treatment.

2.2. Subject Selection

Fifty seven hemodialysis patients with renal anemia were selected randomly to participate in this study and only (46) patients completed the follow up. They were allocated to the groups explained above. The patients were instructed to continue their regular drug treatment schedule. Anemic patients in this study were diagnosed by a specialist physician based on clinical examination and laboratory test. Patients greater than 18 years of old on regular hemodialysis 2 time/ weak for at least previous 3 consecutive months. Patients with Hb concentration equal or greater than 7g/dl and less than 11g/dl with adequate iron status (serum ferritin greater than100 ng/mL and TSAT greater than 20%) were recruited in the study. Exclusion criteria included patients with Red blood cells transfusion during the previous 2 months; blood pressure >170/100; acute or chronic bleeding for example overt

gastrointestinal bleeding; chronic, symptomatic or uncontrolled inflammatory disease such as (systemic lupus erythematosus, rheumatoid arthritis); PTH > 1000 pg/mL; epileptic seizure during the previous 6months; malignancy; vitamin B12 deficiency, folic acid deficiency dignified by local lab values, erythrocyte MCV105 fL.

2.3. Clinical Laboratory and cost Evaluation

Assessment of the patient's outcome was done by measuring hemoglobin concentration (Hb), packed cell volume (PCV) and reticulocyte count. Ferrokinetic study including serum ferritin, serum iron, total iron binding capacity and transferrin saturation were done in order to maintain good iron store. All laboratory examinations were performed at baseline and months 1, 2 and 3 of the study. And monitoring of the adverse events of methoxy polyethylene glycol epoetin beta and epoetin alfa either by clinical examination for the objective data or by questionnaire for the subjective data. Blood specimen collection and laboratory analysis was done by specialized laboratory researchers who did not participate in this study. Transferrin saturation is calculated by dividing the serum iron concentration by the total iron binding capacity. The results express as a percentage by multiplying the result by 100 according to the following formula:

TSAT = (S.I /TIBC) X 100 %.[19]

Cost analysis was done taking into account the direct drug acquisition cost only, monthly cost of MPG-EPO or epoetin alfa is calculated by multiplying the cost of the one vial of each drugs by the number of injections per three month and dividing the result on three.

The cost outcome was the difference in patients per month cost with MPG-EPO versus epoetin alpha. Cost of MPG-EPO and epoetin alfa vials was obtained from the British National Formulary BNF 68.[20]

2.4. Statistical Analysis

Statistical Package for Social Sciences "SPSS version 12" for windows is used to perform the Statistics of this study. Mean± standard deviation was used to define continuous variables while numbers and frequencies was used to define discrete variable. To test the significance of association between discrete variables, chi square test was used.

Shapiro-Wilk test was used to check continuous variables normal distribution. Monthly value of each variable was compared with the baseline value of it by using (paired sample *t*-test) for

normally distributed variable and Wilcoxon-Rank test for abnormally distributed variables. Means of variables of each group also compared with the value of other groups by using Independent T test to the normally distributed variable and Mann Whitney test to the abnormally distributed variable.

3. RESULTS

The mean age of methoxy polyethylene glycol epoetin beta group did not differ significantly from epoetin alfa group (52.12 ± 16.86 years vs 53.95 ±16.51years respectively, P>0.05). Also there was no statistical significant difference in the male to female ratio among of methoxy polyethylene glycol epoetin beta group, epoetin alfa, (15:11 (58%) vs 11:9 (55%) respectively, P>0.05, Table 1). The number of patient treated with iron was comparable at the base line (22 vs18) in methoxy polyethylene glycol epoetin beta group and epoetin alfa respectively P>0.05, Table 1).

Table 1: Baseline characteristics and demographic data of patients

Parameter	Group A (26)	Group B(20)	P-Value
Age (years)	52.12 ± 16.86	53.95 ±16.51	0.514
Male: Female n (Male %)	15:11 (58%)	11:9 (55%)	0.949
CKD duration (years)	2.41 ± 1.59	2.6 ± 1.85	0.910
Dialysis duration (months)	4.96 ± 2.49	4.65 ± 2.13	0.880
DM n (%)	7 (27%)	9 (45%)	0.313
Hypertension n (%)	13 (50%)	10 (50%)	0.531
MCV (fL)	91.55±3.96	91.19±3.29	0.742
Systolic blood pressure (mmHg)	134.27±10.62	135.55±12.71	0.712
Diastolic blood pressure (mmHg)	81.08±8.11	80.8±6.36	0.901
Parathyroid hormone (pg/mL)	287.88±240.77	258.17±128.5	0.595
(Iron treatment n (%)	22:4 (85%)	18:2 (90%)	0.5908

Continuous variables presented as Mean ± Standard deviation; and discrete variables as numbers and frequencies. P value <0.05 is considered significant.

3.1. Effect of Methoxy Polyethylene Glycol Epoetin beta and Epoetin alfa on Hemoglobin Concentration (Hb)

Table 2 showed that there was a non-significant difference in Hb concentration in group A and B at baseline level (P =0.518). Moreover, there was a non-significant increase in Hb concentration after one month for both groups as compared to the baseline, but increase significantly from the baseline after two months (12.39%, 11.28%) and three months (17.24%,16.26 %) of study for group A and B respectively.

Overall there was a non-significant difference between both groups after two months (P = 0.241) and three months (P = 0.723) of the study.

Table 2: Effect of methoxy polyethylene glycol epoetin beta and epoetin alfa on Hb

Group A			Group B		P value
Baseline	**PCV%**	**P value**	**Baseline**	**PCV%**	
	After 1 month 28.93±3.99	**0.011**		**After 1 month** 28.72±4.01	**0.002**
	After 2 month 31.42±3.56	**0.000**		**After 2month** 31.07±2.78	**0.000**
26.88±3.17	**After 3month** 32.57±3.76	**0.000**	26.61±3.76	**After 3 month** 31.99±3.18	**0.000**
Change (%) after 1 month	7.66%		7.92%		0.123
Change (%) after 2 month	16.88%		16.76%		0.339
Change (%) after 3 month	21.19%		20.2%		0.64

Data expressed as Mean± SD. significant difference when ($p<0.05$), non-significant difference when ($p>0.05$).

3.2. Effect of Methoxy Polyethylene Glycol Epoetin beta and Epoetin alfa on Packed Cell Volume (PCV)

Table 3 showed that there is a no significant difference in PCV between groups (A and B) at the baseline (P = 0.594), but there was a significant increase in PCV from the baseline after one (7.66%, 7.92 %), two (16.88%, 16.76%) and three (21.19%, 20.2%) months of study for MPG-EPO and epoetin alfa treated groups respectively.

However, there was a non-significant difference between groups after one moth (P = 0.123), two months (P = 0.339) and three months (P = 0.64) of the study.

Table 3: Effect of methoxy polyethylene glycol epoetin beta and epoetin alfa on PCV

Group A			Group B		P value
Baseline	**PCV%**	**P value**	**Baseline**	**PCV%**	
	After 1 month 28.93±3.99	**0.011**		**After 1 month** 28.72±4.01	**0.002**
	After 2 month 31.42±3.56	**0.000**		**After 2month** 31.07±2.78	**0.000**
26.88±3.17	**After 3month** 32.57±3.76	**0.000**	26.61±3.76	**After 3 month** 31.99±3.18	**0.000**
Change (%) after 1 month	7.66%		7.92%		0.123

Change (%) after 2 month	16.88%	16.76%	0.339
Change (%) after 3 month	21.19%	20.2%	0.64

Data expressed as Mean± SD. significant difference when ($p<0.05$), non-significant difference when ($p>0.05$).

3.3. Effect of Methoxy Polyethylene Glycol Epoetin beta and Epoetin alfa on Reticulocyte Count

Table 4 show that there was no significant difference in reticulocyte count between group A and B at baseline. (P = 0.271).

After one month, there was a non-significant increase compared to the baseline (26.87%) for group A but significant increase for those in group B (49.4%). Moreover, there was a significant increase in reticulocyte count after two (75.48%, 50.36%) and three (86.83%, 89.14%) months of study for group A and B respectively. Over all there was a non-significant difference between the two groups after one (P = 0.159), two (P = 0.877) and three (P=0.990) months of the study.

Table 4: Effect of methoxy polyethylene glycol epoetin beta and epoetin alfa on reticulocyte count

Group A			**Group B**		**P value**
Baseline	**Reticulocyte count %**	**P value**	**Baseline**	**Reticulocyte count %**	
1.15±0.5	**After1 month** 1.45±1.09	0.242	1.04±0.77	**After 1 month** 1.55±0.84	**0.024**
	After 2 month 2.01±1.56	**0.009**		**After 2 month** 1.56±0.69	**0.038**
	After 3 month 2.14±1.13	**0.000**		**After 3 month** 1.96±0.84	**0.005**
Change (%) after 1month	26.87%		49.4%		0.159
Change (%) after 2 month	75.48		50.36		0.877
Change (%) after 3 month	86.83%		89.14%		0.990

Data expressed as Mean± SD. significant difference when ($p<0.05$), non-significant difference when ($p>0.05$).

3.4. Changes in Serum Ferritin in Renal Anemic Patients Treated with Methoxy Polyethylene Glycol Epoetin beta and Epoetin alfa

Table 5 showed that there was no significant difference in the baseline serum ferritin level between group A and B (P = 0.739). After one month, there was a non-significant increase in ferritin level compared to the baseline (5.03%) for group A and significant increase (11.41%) for those in group B. This increase become significant after two (10.32%, 11.9%) month and non-significant after three (13.22%, 17.27%) months of study for group A and B respectively.

Overall there was a non-significant difference between the two groups after one (P = 0.927), two (P= 0.892) and three (P = 0.392) months of study.

Table 5: Changes in serum ferritin in anemic patients treated with methoxy polyethylene glycol epoetin beta and epoetin alfa

<table>
<tr><th colspan="3">Group A</th><th colspan="2">Group B</th><th>P value</th></tr>
<tr><td rowspan="4">Baseline

509.59±289.85</td><td>Ferritin ng/ml</td><td>P value</td><td rowspan="4">Baseline

526.99±337.11</td><td>Ferritin ng/ml</td><td></td></tr>
<tr><td>After 1 month
535.2±270.57</td><td>0.290</td><td>After 1 month
587.12±324.14</td><td>0.001</td></tr>
<tr><td>After 2 month
562.18±279.67</td><td>0.049</td><td>After 2 month
589.72±302.28</td><td>0.013</td></tr>
<tr><td>After 3 month
576.99±315.58</td><td>0.092</td><td>After 3 month
618±248.42</td><td>0.184</td></tr>
<tr><td>Change (%)
after 1 month</td><td colspan="2">5.03%</td><td colspan="2">11.41 %</td><td>0.927</td></tr>
<tr><td>Change (%)
after 2 month</td><td colspan="2">10.32%</td><td colspan="2">11.9%</td><td>0.892</td></tr>
<tr><td>Change (%)
after 3 month</td><td colspan="2">13.22%</td><td colspan="2">17.27%</td><td>0.392</td></tr>
</table>

Data expressed as Mean± SD. significant difference when ($p<0.05$), non-significant difference when ($p>0.05$).

3.5. Changes in Transferrin Saturation in Renal Anemic Patients Treated Methoxy Polyethylene Glycol Epoetin beta and Epoetin alfa

Table 6 showed that there was non-significant difference in TSAT level in group A and B at baseline level (P = 0.129). After one month there was a non-significant decrease in TSAT level compared to the baseline (-4.4%) for group A and non- significant increase (1.55%) for those in group B. Moreover, there was a non- significant increase in TSAT level after two (0.20%, 8.39%) and three (3.39%, 16.84%) months of study for both MPG-EPO and epoetin alfa treated groups respectively.

Overall there was no significant difference between the two groups after one (P = 0.591), two (P= 0.244) and three (P =0.41) months of study.

Table 6: Changes in TSAT in renal anemic patients treated with methoxy polyethylene glycol epoetin beta and epoetin alfa

Group A			Group B		P value
Baseline	TSAT %	P value	Baseline	TSAT %	
34.54±12.24	**After 1 month** 33.02±8.57	0.949	30.28±11.04	**After 1 month** 30.75±11.44	0.732
	After 2 month 34.61±12.52	0.979		**After 2 month** 32.82±11.2	0.313
	After 3 month 35.71±13.33	0.476		**After 3 month** 35.38±11.89	0.112
Change (%) after 1 month	-4.4%		1.55 %		0.591
Change (%) after 2 month	0.20%		8.39%		0.244
Change (%) after 3 month	3.39 %		16.84%		0.41

Data expressed as Mean± SD. significant difference when ($p<0.05$), non-significant difference when ($p>0.05$).

Regarding iron parameter; no patient had shown serum ferritin level < 100 ng/ml in both MPG-EPO and epoetin alfa group throughout the three month study period while (1 vs 2 patients P=0.402), (2 vs 3 patients P=0.429) and (5 vs 2 patients P=0.387) showed TSAT < 20% after one, two and three months respectively for MPG-EPO and epoetin alfa respectively but with no significant difference between the two groups.

3.6. Complication and Adverse Effects of Methoxy Polyethylene Glycol Epoetin beta and Epoetin alfa

The most common adverse event in methoxy polyethylene glycol epoetin beta and epoetin alfa was flu- like symptoms (3.8% vs 10% respectively) and diarrhea (7.7% vs 5% respectively). Fistula thrombosis and local pain or tissue reaction to S.C injection (3.8%) were reported in methoxy polyethylene glycol epoetin beta arm only. Additionally three patient (11.5%) need for blood transfusion during the study in methoxy polyethylene glycol epoetin beta group while two patient (10%) need for blood transfusion in epoetin alfa group

There was no clinically significant difference between methoxy polyethylene glycol epoetin beta and epoetin alfa regrding complication and adverse effect (P>0.05). There were no hypertension and no deaths reported during the study.

Table 7. Most common complication and adverse effect

Complication	Methoxy polyethylene glycol epoetin beta (n=26)	Epoetin alfa (n=20)
Fistula thrombosis	1 (3.8%)	0 (0%)
Local pain or tissue reaction to S.C injection	1 (3.8%)	0 (0%)
Flu-like symptoms	1 (3.8%)	2 (10%)
Diarrhea	2 (7.7%)	1 (5%)
Blood transfusion	3(11.5%)	2 (10%)

Data presented as number of reported cases and percent's.

There were no cases of hypertension, nasopharyngitis, upper respiratory tract infection, rash and hot flushes were reported for both MPG-EPO and epoetin alfa and no death reported during the study.

3.8. Cost Difference between Methoxy Polyethylene Glycol Epoetin beta and Epoetin alfa

Cost of MPG-EPO vial (100µg) is 146£ and its cost throughout the three months study period is 876£ per patient (patient/month cost is 292£) while cost of epoetin alfa vial (4000 IU) is 22£ and its cost throughout the three months study period is 572£ per patient (patient/month cost is 190£).Cost difference between the two drug is 102 £.

By asking the patients if they are willing to pay an extra 102 £ per month and injected just two time and converted to one time when Hb≥11 g/dl with MPG-EPO instead of being injected eight time with epoetin alfa, 3 of 46 patient stated that they would be willing to pay and 43 stated that they would not. And by asking the patients since the government supply both drugs would you prefer to treated with MPG-EPO or epoetin alfa, all patients prefer to treat by MPG-EPO.

4. DISCUSSION

Current ESA therapy for hemodialysis patients with chronic renal anemia requires close monitoring and frequent dose adjustments. Therefore, a modification allowing less frequent administration, with sustained efficacy, should improve the convenience and therapeutic benefits of ESA therapy.[21] Erythropoiesis-stimulating therapy maintains the mass of red blood cell and increasing Hb by enhancing the survival, proliferation and differentiation of erythrocyte progenitors.[22]

The current study demonstrates that both methoxy polyethylene glycol epoetin beta and epoetin alfa increased hemoglobin concentration, PCV and reticulocyte count significantly but with no significant difference between the effects of both drugs. Mean change of Hb was 1.53±1.04 g/dl for MPG-EPO versus 1.41±0.96 g/dl for epoetin alfa. MPG-EPO produced a slightly higher percent of increase in Hb relative to pretreatment than that produced by epoetin alfa (17.24%) versus (16.26%) respectively. At the end of the study, there were a greater proportion of patients with hemoglobin ≥11 g/dl in MPG-EPO group than in the epoetin alfa group (31% vs. 20%) respectively. The mean change in PCV was 5.7±3.1% for MPG-EPO versus 5.3±2.9% for epoetin alfa. Effect of MPG-EPO on Hb and PCV in this study is agreed with Vankar et al who also observed that Hb and PCV was increase significantly. Mean Hb rise of 2.58 g/dl from baseline (9.10 versus 11.68 g/dl) was accompanied with an increase in the PCV value of 6.5% (27.4 versus 33.9%) after 24 weeks study period.[23] On the other hand, Jain et al revealed that MPG-EPO had significant effect on Hb concentration and PCV as evident by increase of Hb and PCV. Average rise from the baseline of 1.85g/dl, 5.73% for Hb and PCV respectively (147). Other study show that MPG-EPO once every two weeks was effective for the correction of anemia in CKD patients on dialysis with a significant rise in mean hemoglobin from baseline to the end of 4months treatment period by 2.08 ± 1.29 g/dL.[24]

In the epoetin alfa arm, Benz et al studied the effectiveness of epoetin alfa for initiation of treatment of CKD anemia given as once every two weeks and found a significant increase in Hb and PCV with mean change of 1.9 ± 1.0 g/dl for Hb and 6.8±3.1% for PCV from the baseline.[25] Aggarwal et al report that there was a statistically significant increase in mean hemoglobin concentration and PCV even with low dose of rHuEPO from 6.48 ± 0.39 to 8.70 ± 0.60 g/dl for Hb and from 18.8 ± 1.61 to 27.8 ± 2.8% for PCV.[26]

Reticulocytes are normally released from the bone marrow 18 to 36 hours before their final maturation into erythrocytes; they provide a real-time assessment of the functional state of erythropoiesis.[27] Reticulocytes count in this study was increase significantly for both MPG-EPO and epoetin alfa. Mean change in reticulocytes count was 1.06±1.2 for MPG-EPO and 0.92±1.13 for epoetin alfa. The result is consistence with the result of Forni et al who state that methoxy polyethylene glycol epoetin beta increase mean absolute reticulocyte count significantly from 34147± 12823 cells/µl at base line to 69891± 18153cells/µl after six month of therapy and induced a more sustained reticulocytes response over time.[28] In the epoetin

alfa arm, the findings in agree with Aggarwal et al who found a statistically significant rise in mean % reticulocyte count with rHuEPO from 0.39 ± 0.14 at base line to 2.30 ± 0.72 at the end of study.[26]

According to the results of this study, there was a non-significant difference between the effect of MPG-EPO and epoetin alfa on hematological parameter. Similar results were found in the AMICUS and Al-Ali et al studies. AMICUS study concluded that Intravenous MPG-EPO once every two weeks may be as effective and safe as three times weekly epoetin for correcting of anemia in dialysis patients with mean change in hemoglobin concentration from baseline to the end of study was 2.70 ± 1.45 g/dL with MPG-EPO and 2.56 ± 1.31 g/dL with epoetin and proportion of patients with hemoglobin ≥11 g/dl were 93.3% with MPG-EPO and 91.3% with epoetin.[29] Al-Ali et al. study also indicates that Mean Hb concentrations were almost similar with non-significant differences between the epoetin and MPG-EPO both at the baseline and throughout the study.[30] Study of AMICUS showed better outcome compared to this study, this may attributed to longer duration of study (24 week) and higher base line hemoglobin level 9.58 g/dl for MPG-EPO and 9.63 for epoetin compared to this three month duration study with base line Hb level of 8.87 g/dl for MPG-EPO and 8.7 g/dl for epoetin alfa.

The extracorporeal process of hemodialysis promotes constant blood and thus iron loss with such patients and subsequent iron deficiency. Untreated iron deficiency or reduced iron stores are the main cause of ESA treatment hypo responsiveness. Supplemental iron is widely used in CKD patients to treat iron deficiency and avoid its development in patients treated with ESA.[19]

The number of patient who received iron supplementation at beginning of study was comparable in the two treated groups (22 vs 18) in MPG-EPO and epoetin alfa respectively. The serum ferritin and TSAT at baseline and throughout the study treatment were also comparable among the two groups. However, at the end of the study there was a non-significant increase in levels of serum ferritin and transferrin saturation percent when compared with the baseline values in the two groups. During the study, no patient had shown serum ferritin level < 100 ng/ml in both MPG-EPO and epoetin alfa group while (1vs 2 P=0.402), (2 vs 3 P=0.429) and (5 vs 2 P=0.387) patients showed TSAT < 20% after one, two and three months respectively for MPG-EPO and epoetin alfa respectively but with no significant difference between the two groups. Reason behind this decrease in TSAT is iron

deficiency that result from gastrointestinal blood loss for some patient and incompliance with IV iron supplementation for the other. In the present study both drugs groups maintain good and comparable iron store (ferritin and transferrin saturation). So we exclude effect of iron deficiency on patient's response to the treatment.

In the current study, monthly cost of MPG-EPO was higher than that of epoetin alfa (292£ vs 190£) for MPG-EPO and epoetin alfa respectively. Cost difference between the two drugs is 102 £. Three of 46 patients are willing to pay an extra 102 £ per month to be treated with MPG-EPO instead of epoetin while 43 will not. All of the patients preferred to be treated with MPG-EPO instead of epoetin alfa when the drugs are supplied by the government due to its less frequent of administration that make them more compline with treatment.

Similar findings to the current study were found in many studies. Silva et al used a MPG-EPO and conventional EPO to evaluate the impact of a switch to MPG-EPO in Brazilian patients on dialysis and found that for the public health system, treatment with conventional EPO was more cost effective.[31] On the other hand, Padullés-Zamora et al who perform a retrospective observational study in patient’s not on dialysis and found a significant rise in costs after switching from EPO beta to MPG-EPO.[32] Additionally, Fernández et al conclude that MPG-EPO was as effective as conventional epoetin for the maintenance of hemoglobin levels after 24 weeks of follow-up and conversion to MPG-EPO has led to an increase of 10.3€ the patient per month cost.[33] Several studies demonstrating definite cost reduction with MPG-EPO compared to conventional ESA treatment. Muller and Moll demonstrate a 22.3% reduction in the cost of patient per month after switching from Epo beta to MPG-EPO.[34] On the other hand, Cynke et al shows in his retrospective, single center study that there are 35% reduction in the cost of patient per month after switching from Epo beta to MPG-EPO.[35] Difference from current study may attributed to differences in study design as in these study MPG-EPO is given as once monthly dose aim to maintain Hb with target range so it may need lower dose compare to the present study which is aimed to correct anemia with twice monthly dose of MPG-EPO. Furthermore, the dose in both of these studies is calculated based on patient body weight which may have impact in cost reduction for some patients.

Despite of higher cost differences between MPG-EPO and epoetin alfa but longer half-life of MPG-EPO allow less frequent administration and may reduce the load of anemia management for both patients and physicians and enables CKD patients to receive an ESA

based on monthly visits to the outpatient nephrology clinic. Additionally, Patients received monthly treatment of MPG-EPO may show a greater compliance to therapy, together with a positive impact on the patient's clinical status and the health care provider's health-related costs.[36]

In conclusion, methoxy polyethylene glycol-epoetin beta every two week effectively corrected renal anemia and was well tolerated and it is efficacy comparable to twice weekly epoetin alfa for anemia correcting in hemodialysis patients. and the treatment with MPG-EPO has led to an increase of 102£ in the patient per month cost. This less frequent dosing schedule of methoxy polyethylene glycol-epoetin beta may offer clinicians and patients a simplified anemia management as compared to traditional erythropoietin (epoetin alfa). However, future longer clinical trials are required with longer follow up periods to confirm the long term benefit of methoxy polyethylene glycol epoetin beta.

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