Increasing The Use Of Continuous Erythropoietin Receptor Activators To Correct Anemia In Maintenance Hemodialysis Patients.

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Abstract

This article reviews the role of the Continuous Erythropoetin Receptor Activators (CERAs) in the management of anemia in the dialysis population. Despite the convenience of once per month dosage frequency instead of the twice per week conventional erythropoetin stimulators, CERAs have struggled to achieve universal acceptance. This article sheds light on the reasons and fairness of this choice.

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Introduction:

One of the main causes of anemia in the maintenance dialysis patients is the deficiency of erythropoietin (EPO). Red Blood Cells are produced in the bone marrow under the stimulatory action of EPO. EPO is a glycoprotein hormone mainly produced by the kidneys apart from a small amount produced by the liver. Hence, as the kidney function deteriorates the quantity of EPO in the body decreases resulting in a decrease in hemoglobin [1]. This deficiency can manifest as generalized weakness, fatigue, headache, dizziness or shortness of breath. Unsurprisingly this leads to a reduction in quality of life and an increase in cardiovascular mortality and morbidity [2].

Cell culture technology has enabled the mass synthesis of injectable recombinant EPO also called ESAs. The exogenous administration of ESAs to make up for its deficiency has had exceptional implications on the management of anemia in chronic kidney disease patients; making the need for recurrent blood transfusions a thing of the past. The availability of recombinant erythropoietin has not only helped avoid the complications associated with recurrent blood transfusion but has also been proven to be a more cost effective strategy [3]. The correction of anemia with recombinant EPO has been shown to improve quality of life in kidney disease patients [4].

As with all medications, ESAs are not without side effects either. The most clinically relevant ones include an increase in blood pressure, headaches and a propensity towards a thromboembolic event specifically in CKD patients having an Hb >12 g/dL. Hence a special consideration is given not to correct anemia above 12 g/dL in this population group [5].

All ESAs (both conventional and CERAs) can be administered through the subcutaneous and intravenous route. However, for the sake of convenience the NKF KDOQI guidelines recommend a subcutaneous route in the CKD population while an intravenous route in patients on hemodialysis [6]. It is noteworthy that the subcutaneous route has shown to maintain hemoglobin with a reduced average weekly dose of ESA when compared to the intravenous route [7].

ESAs have been widely synthesized and marketed since the 1980s. From a clinical standpoint these vary from each other based on the frequency of dose administration. In general, the first generation conventional ESAs are shorter acting hence require a twice to thrice per week administration frequency [8]. The first generation ESAs include:

- Epotein alfa *, Epotein beta *, Epotein omega,Epotein delta, Epotein zelta,Epotein theta

* Most commonly available.

While the second generation conventional ESAs have a relatively longer half-life hence a less frequent administration requirement. Darbepoetin, a second generation ESA is usually administered once/week to once every 2 weeks [9].

More recently an ESA with an even longer half-life (137 hours) was introduced paving the way for a new class of ESA called Continuous Erythropoietin Receptor Activators (CERAs) aiming for a once or twice per month administration schedule. CERA is a pegylated form of ESA that has been synthesized by the addition of a polymer chain into the EPO molecule. It is the integration of this large methoxy-polyethyleneglycol polymer chain into the EPO molecule that extends the duration of action of the CERA [10].

This review article attempts to weigh the pros and cons of the conventional ESAs (alpha, beta etc.) against the pegylated erythropoetins also known as CERAs.

Are Both Equally Effective?

The comparative ability of the CERAs versus conventional ESAs to maintain target hemoglobin remains the fundamental question. Canaud B. et al, through the STRIATA study have tried to address this very question. They have demonstrated a stable maintenance of hemoglobin level after the conversion to a CERA based regimen from a second generation ESA (darbapoetin) in the dialysis population [11]. While Chen N. et al, in a multi-centric randomized control addressed a comparison between once per month CERA schedule and first generation ESA (Epotein beta) and found CERA to be non-inferior to the later [12]. Additionally, a retrospective analysis of 13 trials have demonstrated an equal safety and efficacy profile between the once per month CERA regimen and conventional ESA treatment strategies [13].

Based on current data, we believe it is reasonable to infer equal efficacy between CERAs and conventional ESAs. On the other hand, certain aspects of the CERA regimen do limit its allure and practical application as discussed later.

Table 1: Demonstrates a cost benefit with a switch to CERA from conventional ESA [14].

Study	Design and setting	Patient number, type, mean age (years)	Duration (months)	Comparator ESAs and median doses	Costs
Müller and Moll[37] (MA)	Retrospective, single-center, D center; Germany	26; HD; 60 (range: 46–90)	7	Epo beta SC (43.000±30.923 IU/month), CERA IV, Q4w (139 µg/month)	22.3% cost reduction/patient/month Cost savings: €113/month and €1,356/year
Franz et al[38] (MA)	Prospective, multicenter, 34 D centers; Switzerland	184; HD, PD; 65 (range: 25–95)	6	Epo alpha, Epo beta, DA, CERA (160 µg/month)	14% cost reduction/patient/month Epo alpha, Epo beta, DA CHF 759 (~€506) versus CERA CHF 650 (~€433) (P=0.004)
Cynke et al[39] (MA)	Retrospective, single-center, D center; Switzerland	14; D; NA	15	Epo beta (16.640 IU/week) CERA (214 µg/month)	35% cost reduction/patient/month Epo beta CHF 1,340 (~€893) versus CERA CHF 848 (~€565) months 1–14 (CHF 802; ~€ 533; month 15)
Franz and Cynke[40] (MA)	Retrospective, single-center, D center; Switzerland	14; D; NA	5	Epo beta (16.640 IU/week), CERA (228 µg/month, months 1–4, 169 µg/month, month 5)	45% cost reduction/patient/month Epo beta CHF 1,251 (~€782) versus CERA CHF 921 (~€576) months 1–4 (CHF 658; ~€411; month 5)
Echarri Arrieta et al[41] (MA)	Retrospective, CEA, sensitivity analysis, single-center, hospital; Spain	38; PD; 38, 59	12	DA (137 µg/month) versus CERA (92 µg/month)	39% cost reduction/patient/year DA (€5.440) versus (€3.340) Cost savings: €2.100/patient/year

So What Limits Universal CERA Use?

Despite significant advantages (see later) and sufficient evidence demonstrating equal efficacy and safety profile of the CERAs in comparison to conventional ESAs [11-13], a few factors do limit its universal use.

The relative cost effectivity of a CERA based regimen has been a bone of contention. Furthermore; the scarce availability of tangible data to address this aspect has not made things easier either; with studies supporting and negating its cost effectivity in the same magnitude. The noteworthy studies demonstrating CERA to be more cost effective are shown in table 1 [14] while table 2 [14] shows the CERA regimen to be less cost effective. It is important to note that the majority of evidence supporting either side comes from weak single center retrospective analyses.

TABLE 2: Table demonstrates a CERA based regimen to be more expensive in comparison to conventional ESA.

Study	Design and setting	Patient number, type, mean age (years)	Duration (months)	Comparator ESAs and median doses	Costs
Silva et al[31] (MA)	CEA, Markov model, sensitivity analysis; PHS; Brazil	NA; D	48	Epo, CERA	Epo more cost-effective than CERA Costs/QALY for CERA: R $72.974 (~€25.906)
Escudero-Vilaplana et al[32] (PRJ)	CMA, multicenter, two hospitals; Spain	409; HD, PD, pre-D	NA	Epo, DA, CERA	Median costs/patient/month Epo (€103.20) versus DA (€134.40) versus CERA (€147.50)
Albero Molina et al[33] (PRJ)	Prospective, single-center, hospital; Spain	17; HD	6	Epo SC, CERA SC (160±40 µg/month, month 1–5, 200±95 µg/month, month 6)	Average costs/patient/month (months 1–5): Epo (€174.30±€85.40) versus CERA (€290.10±€69.00; +66.4%) Further increase of costs for CERA at month 6: CERA (€361.60±€169.30; +107%)
Tsai et al[34] (PRJ)	Retrospective, single-center, hospital; Taiwan	15; PD; 50.4±13.1	6	DA (1.51 µg/kg/month), CERA (1.59 µg/kg/month)	Costs for CERA are slightly higher (NS; P=0.156) Average costs/patient/month: DA NT ($4,337±$1,069; ~€105±€26) versus CERA NT ($4,775±$728; ~€115±€17.5)
Padullés-Zamora et al[35] (PRJ)	Retrospective, single-center, hospital and outpatient clinic; Spain	190; pre-D; 65 (range: 22–93)	12	Epo beta, DA, CERA (75 µg/month; range: 50–150 µg/month)	Higher costs after switching from Epo beta, but more cost effective after switching from DA Average costs/patient/month: Epo beta (€86.8) versus CERA (€135.10; P<0001); DA (€220.10) versus CERA (€148.90; P<0001)
Olmos et al[36] (MA)	Retrospective, single-center, D center; Uruguay	17; D; 70 (range: 47–85)	12	Conventional Epo (23.150 IU/month), CERA (122 µg/month)	Higher medication costs/year for conventional Epo (US $14.170; ~€10.121) versus CERA (US $15.000; ~€10.741) Lower total costs/year for conventional Epo (US $27.860; ~€19.900) versus CERA (US $16.809; ~€12.006); fewer transfusions and hospitalizations; better compliance

To take this further we can take the example of our local setting (Pakistan) where the monthly cost of 8000 iu Epotin Alpha/week regimen is Rs. 14,400(US$ 132)/month [15]. Alternatively if the same patient were to be shifted to a CERA the adequate dose would be of 150ug/month which would cost Rs. 16,100(US$148)/month [15]. Importantly these prices are of commercial packages only and bundle purchase prices would vary. Clearly a CERA based regimen is more expensive in Pakistan. Whether this difference of Rs. 1700(US$15.6)/month is significant when one takes into account its benefit is left to better judgement of the reader.

Another potential factor that impairs universal prescription of CERAs is the comparative inability of the physician to control the drug response. With significant evidence indicating a strong relation between over-correction of anemia (Hb >12 g/dL) and thrombotic events [16], a once per month regimen leaves the physician with an inability to offer much if the hemoglobin goes above 12 g/dL half way through the month. Clearly this is not a problem with conventional ESAs which are administered twice per week. It is ironic that the biggest strength of the once/month CERA regimen can also be considered its weakness.

So Why Not Stick With Conventional ESAs?

Even though conventional ESAs are cheaper and provide a sense of control over hemoglobin increments, CERAs have significant advantages that can potentially tip the balance in its favor. Firstly, the degree of convenience attached to a once per month CERA regimen can never be underemphasized. Additionally, this regimen subjects the patient to a single needle prick every month in comparison to eight pricks (twice/week) in case of the conventional ESAs. This reduction in the number needle pricks helps improve

drug compliance. It can be argued that conventional ESAs can be administered intravenously with hemodialysis thus can be equally convenient. As mentioned earlier, it is important to note that an intravenous route in comparison to the subcutaneous route requires a larger dose hence potentially making conventional ESAs less cost effective [17].

A reduced dose frequency means less workload on the dialysis staff. It is easy to overlook the amount of time and work devoted to ESA administration starting from procurement, storage, preparation, injection to disposal of syringes and record keeping. Schiller et al, demonstrated an approximately 80% reduction in nursing ESA administration time after the patients were converted from a conventional ESA to CERAs [18]. This saved time can be better served with enhanced monitoring and nursing care. Additionally this strategy has also demonstrated a project cost saving of approximately 35%-58% [19]. Hence it is imperative that when we take into account this hidden cost when doing a comparative cost analysis.

On a global scale the impact of increased non-biodegradable waste materials should be taken into consideration. Obviously the impact of 8 syringes, plastic packings, cardboard boxes, rubber based syringe tops and printing in place of a single syringe would prove detrimental. This is without shedding light on the process of storage and disposal of this extra waste material.

Local Experience:

We studied the retrospective data of 10 maintenance hemodialysis patients who were switched from conventional ESA to CERAs in October 2015 at our local dialysis center. We analyzed the changes in hemoglobin on a monthly basis over a 6 month period. At the end of 6 months, 3 patients were excluded from the analysis due to a gastrointestinal bleed and in-hospital admission due to sepsis. All the patients were being dialyzed thrice per week through an arterio-venous fistula and had been receiving Epotein alpha 4000 iu subcutaneously twice per week on dialysis. On switching over to CERA the dose administered was 150 ug administered once per month.

After ensuring adequate iron and vitamin B12 levels and acceptable parathyroid control over the 6 month period the following findings were noted in our 7 patients (Figure 1). All patients were able to maintain their hemoglobin above 10 g/dL at the end of the six month period although 2 patients (patient 2 & 4) experienced an increase of greater than 1.5g/dL taking their hemoglobin well above 12g/dL hence CERA administration had to be stopped after the first dose. No significant untoward event was observed in all cases.

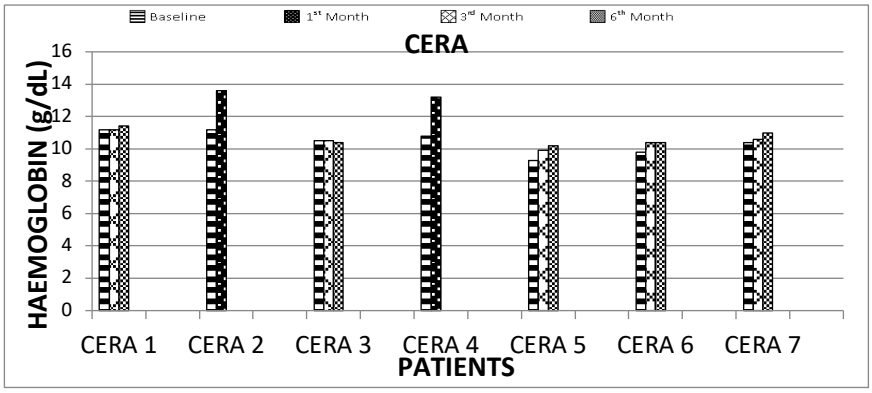

Figure 1: Demonstrates adequate maintenance of hemoglobin after shifting from conventional ESAs to CERAs. Patient 2 & 4 over-shot the target hemoglobin after the first dose of CERA hence discontinued.

Despite significant limitations, our findings are in line with the current literature showing CERAs to be equally effective and safe whilst providing substantial convenience apart from other advantages mentioned earlier. On the other hand the sudden rise in hemoglobin above target value (>12 g/dL) in 2 of our patients does give a sense of insecurity even though no adverse event occurred.

Conclusion:

CERAs have come a long way in delivering equal efficacy and safety profile. The convenience of a once per month injection and all its attached perks (less workload for the staff, more earth friendly etc.) should not be underplayed. Critics may bring up cost comparisons but it is essential to highlight the hidden costs attached with conventional ESAs which may make CERAs equal if not more cost effective.

Disclosure:

None declared

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