

Lessons learned from peginesatide in the treatment of anemia associated with chronic kidney disease in patients on dialysis

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Abstract: Peginesatide is the newest erythropoietin-stimulating agent (ESA) in the quest for the ideal treatment of anemia in chronic kidney disease (CKD) patients. Reduced frequency of administration along with a possibly lower cost as a result of simpler manufacturing techniques compared with other available agents makes peginesatide a highly desirable product in the competitive ESA market. Peginesatide is noninferior to the other ESAs, and has a good safety profile in patients on hemodialysis. The higher rates of adverse cardiovascular events reported in CKD patients not on dialysis in the recent Phase III studies require further, better planned, studies. Peginesatide had to be withdrawn from the market in the US after some reports of hypersensitivity reactions to the drug. This is a setback, but the scientific advances gained as a result of this product development can be used to develop other, newer products.

Keywords: anemia, hemodialysis, chronic kidney disease, peginesatide

Introduction

Anemia as a result of chronic kidney disease (CKD) represents a major burden of illness. If left untreated, it can lead to significant deterioration in cardiac function as well as debilitating symptoms. Before the advent of erythropoietin-stimulating agents (ESAs), frequent red cell transfusion was the only relatively safe method of correcting anemia in CKD and hemodialysis patients. ESAs have transformed the management of CKD over the past 20 years. Use of ESAs has led to elimination of anemia as a major cause of morbidity and to improved quality of life in CKD patients.¹

The first-generation ESAs were human recombinant erythropoietins (epoetin alfa and epoetin beta). Although these agents have been very effective, their frequent dosing regimen of up to three times per week can be very labor-intensive, leading to considerable burden on patients, carers, and health care staff. Pharmacologic research has been focused on finding ESA agents with a longer half-life and hence a reduced dosing frequency. This has been done by increasing the receptor affinity of the erythropoietin molecule through changes in the amino acid sequence (darbepoetin alfa) and an increase in the glycosylation pattern by addition of a pegylated moiety (continuous erythropoietin receptor agonist [CERA]).^{2,3}

The second-generation human recombinant ESAs, darbepoetin and CERA, have a longer half-life and more biological activity compared with human recombinant erythropoietin, enabling these agents to maintain target hemoglobin levels effectively with less frequent dosing. The infrequent dosing schedules of once weekly or once every 2 weeks with darbepoetin and monthly dosing with CERA offer many potential benefits to both patients and caregivers. Recombinant DNA technology and mammalian

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cell lines are used for the manufacturing of these ESAs based on endogenous erythropoietin molecules.

Peginesatide is another milestone in the quest for a longer-acting and relatively cheaper ESA. These properties make peginesatide a very desirable product for the management of anemia in CKD and hemodialysis patients. Peginesatide is a synthetic, pegylated dimeric peptide comprised of two identical 21-amino acid chains covalently bonded to a linker derived from iminodiacetic acid and β -alanine. Peginesatide is manufactured as an acetate salt. The dimeric peptide (approximate molecular weight 4,900 Da) is covalently linked to a single lysine-branched bis-(methoxypolyethylene glycol) (PEG) chain (approximate molecular weight 40,000 Da). Peginesatide has no amino acid sequence homology to erythropoietin. The empiric formula is C2031H3950N62O958S6 (free base). The total molecular weight is approximately 45,000 Da.⁴

In vitro studies show that peginesatide and human recombinant erythropoietin activate similar erythropoietin receptor-mediated pathways, leading to proliferation and differentiation of erythroid progenitor cells.⁵ In animal models, pharmacokinetic studies revealed that the volume of distribution of peginesatide is slightly smaller than the blood volume, indicating limited distribution outside the vascular compartment. In these studies, the half-life of peginesatide was dose-dependent and 1.6 times longer in a rat model of chronic renal impairment, suggestive of renal excretion of the drug. Consequently, a greater hematologic response to the peginesatide dose was also observed in the rat model of chronic renal impairment. The reported half-life of peginesatide was 22–31 hours in rats, which is significantly longer than the half-lives reported for human recombinant erythropoietin and darbepoetin alfa in rats.⁶ These findings were confirmed further by autoradiography in a pharmacokinetic profiling study in monkeys. The drug was found to be principally localized to hematopoietic sites even at 3 weeks post drug administration, and had a small volume of distribution. The peginesatide molecule was excreted primarily in urine.⁷

In a Phase I study in healthy volunteers, peginesatide showed a dose-dependent increase in reticulocyte response and a rise in hemoglobin levels. The reticulocyte response peaked at 7 days and returned to baseline after 2 weeks at all doses. There was a statistically significant increase in hemoglobin from baseline at a dose of 0.1 mg/kg compared with placebo, which was sustained during the follow-up period of 42 days.⁸

Peginesatide has a half-life of approximately 3–4 weeks and the dose requirement is the same irrespective of the route

of administration. Peginesatide was licensed by the US Food and Drug Administration in March 2012 for the treatment of anemia in patients undergoing hemodialysis.

Two open-label, randomized, controlled Phase III clinical trials in CKD patients not undergoing dialysis, ie, PEARL 1 and 2 (Peginesatide for anemia in patients with chronic kidney disease not receiving dialysis)⁹ and two Phase III clinical trials in patients undergoing hemodialysis, ie, EMERALD 1 and 2 (Efficacy and safety of peginesatide for the maintenance treatment of anemia in patients with chronic renal failure who were receiving hemodialysis and were previously treated with epoetin)¹⁰ have shown that peginesatide is noninferior to standard ESAs in achieving and maintaining hemoglobin within the target range.

In the PEARL 1 and 2 studies, 983 CKD patients who had not received any ESA in the past were randomized to receive peginesatide subcutaneously once a month at a dose of 0.025 mg or 0.04 mg/kg of darbepoetin alfa at a starting dose of 0.75 μ g/kg every 2 weeks. All three patient cohorts were randomized in a 1:1:1 ratio and followed up for a median of nearly 20 months. In the PEARL 1 study, the mean difference in hemoglobin was slightly higher in the cohort receiving a higher peginesatide dose (0.03 g/dL for the lower starting dose and 0.26 g/dL for the higher starting dose) compared with the darbepoetin group. However, in the PEARL 2 study, the mean difference was 0.14 g/dL and 0.31 g/dL for the lower and higher starting dose, respectively (Table 1).⁹

In the EMERALD 1 and 2 studies, 1,608 dialysis patients were randomized to either peginesatide (mean dose 4.8–5.7 mg) or to continue with epoetin (mean weekly dose 4,625–9,000 U), aiming at a target hemoglobin range of 10–12 g/dL. The median duration of follow-up was around 16 months. In the EMERALD 1 study, the mean change in hemoglobin level during the study evaluation period was -0.24 ± 0.96 g/dL in the peginesatide group and -0.09 ± 0.92 g/dL in the epoetin group, and in the EMERALD 2 study was -0.07 ± 1.01 g/dL in the peginesatide group and -0.17 ± 1.00 g/dL in the epoetin group (Table 2).¹⁰

The composite cardiovascular safety endpoints for the groups receiving peginesatide and the groups receiving standard ESAs were similar in patients on hemodialysis (EMERALD 1 and 2). The hazard ratio for the adverse cardiovascular endpoints with peginesatide for CKD patients not receiving hemodialysis (PEARL 1 and 2) was 1.32 (95% confidence interval 0.97–1.81), and there was also an increased incidence of sudden death, unstable angina, and arrhythmia among these patients. The rate of acute kidney failure and

Table 1 Summary of peginesatide studies in non dialysis requiring CKD patients

| | PEARL 1 | | | PEARL 2 | | |
|--|----------------------------|-----------------------------|---------------------------|----------------------------|-----------------------------|---------------------------|
| | Peginesatide 0.04 mg/kg | Peginesatide 0.025 mg/kg | Darbepoetin 0.75 µg/kg | Peginesatide 0.04 mg/kg | Peginesatide 0.025 mg/kg | Darbepoetin 0.75 µg/kg |
| Patients (n) | 165 | 161 | 164 | 163 | 167 | 163 |
| Change in Hb g/dL* (mean ± SD) | 1.39 ± 0.87 | 1.64 ± 0.97 | 1.37 ± 0.86 | 1.50 ± 0.90 | 1.68 ± 0.96 | 1.35 ± 1.00 |
| Difference in Hb versus darbepoetin group, mean (97.5% CI)** | 0.03 (-0.19.6 to 0.26) | 0.26 (0.04-0.48) | | 0.14 (-0.09 to 0.36) | 0.31 (0.08 to 0.54) | |
| Transfusion (% of patients) | 6.2% | 7.3% | 4.9% | 11.4% | 10.4% | 4.9% |

Notes: *Changes in Hb levels from baseline to mean level during 12-week evaluation period; **noninferiority criteria.

Abbreviations: CI, confidence interval; Hb, hemoglobin; SD, standard deviation; CKD, chronic kidney disease.

back pain of unknown mechanism was also twice as high in patients receiving peginesatide in the PEARL studies. The change in residual renal function has not been reported for patients in the EMERALD studies.

There is no clear explanation for these adverse events in the patients recruited in the PEARL studies. In both these studies, there were more patients randomized to the peginesatide treatment group who were older, diabetic, and with a previous history of cardiovascular events compared with the darbepoetin group. Although the chance factor cannot be ruled out, a stepwise multivariate analysis adjusting for these baseline variables still produced a hazard ratio for the composite safety endpoint of 1.20 (95% confidence interval 0.87–1.64).⁹ A high ESA dose is unlikely to have been the cause of these adverse effects, considering that a much higher dose of peginesatide was used in patients on hemodialysis, and these patients are at a greater risk of developing cardiovascular complications than those who are not on dialysis. The two comparator drugs, epoetin and darbepoetin, have a similar cardiovascular safety profile,¹¹ hence the different comparator drugs are unlikely to be a factor contributing towards these unexpected cardiovascular events in the PEARL studies. More work is required to understand the potential adverse effects of peginesatide in experimental CKD models before further clinical trials can be undertaken.

Experimental models have shown the immunogenicity of peginesatide to be low. Because peginesatide has no sequential similarity to the erythropoietin molecule, the antibodies against peginesatide do not cross-react with antibodies against erythropoietin. Peginesatide has been used to treat patients with pure red cell aplasia.¹² To date, no case of pure red cell aplasia associated with peginesatide has been reported.

Since peginesatide was introduced in the US, the Food and Drug Administration has received 13 case reports of anaphylactic reactions secondary to administration of peginesatide, three of which resulted in death. In February 2013, the drug manufacturer voluntarily recalled the drug.

Now the question arises, where do we go from here? Or, as Locatelli and Del Vecchio mention in their recent review article, “Is peginesatide like a shooting star?”¹³ Although voluntary recall of the drug following reports of hypersensitivity reactions has been a disappointing outcome, this significant scientific development cannot be undermined. Simpler production methods as a result of nondependence on recombinant DNA techniques and mammalian cell lines has led to reduced costs. This is welcome news when use of ESAs for CKD is a financial strain on the health care system. A reduced dose frequency can only improve patient compliance, as well as save time on the part of health care

Table 2 Summary of peginesatide studies dialysis requiring CKD patients

| | EMERALD 1 | | EMERALD 2 | |
|---|---------------------------|---------------|-------------------------|---------------|
| | Peginesatide group | Epoetin group | Peginesatide group | Epoetin group |
| Patients (n) | 445 | 248 | 488 | 237 |
| Change in Hb, g/dL* (mean ± SD) | -0.24 ± 0.96 | -0.09 ± 0.92 | -0.07 ± 1.01 | -0.17 ± 1.00 |
| Difference in Hb versus epoetin group, mean (95% CI)** | -0.15 (-0.30 to -0.01) | | 0.10 (-0.05 to 0.26) | |
| Transfusion (% of patients) | 10.3% | 8.6% | 7.7% | 9.9% |

Notes: *Changes in Hb levels from baseline to mean level during the 12-week evaluation period; **noninferiority criteria.

Abbreviations: CI, confidence interval; Hb, hemoglobin; SD, standard deviation; CKD, chronic kidney disease.

staff which could be used to focus more on patient care. The techniques developed during the experimental phase of the development of peginesatide could be used for screening several other peptides for the erythropoietin receptors and various other related receptors. In our opinion, peginesatide is a new sunrise which will lighten up the CKD anemia management field with new knowledge and better treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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