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PEGINESATIDE- A NOVEL ERYTHROPOIETIN MIMETIC AGENT FOR THE TREATMENT OF ANAEMIA IN CHRONIC RENAL FAILURE PATIENTS

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ABSTRACT: Anaemia associated with chronic kidney disease (CKD) affects the overall health of the patients leading to increased morbidity and mortality. Erythropoietin stimulating agents (ESAs) have been the standard of care for the treatment of such patients since last 20 years. These agents have the potential to increase mean haemoglobin levels in both pre dialysis and dialysis maintenance phases hence lowering the cardiovascular complications and all-cause mortality. After epoetin and darbepoetin, Peginesatide, a novel pegylated erythropoietin (EPO) mimetic agent has recently been approved in March, 2012. Its better stability, once a month administration and non-immunogenicity makes this a preferable ESA. This review will elucidate the available evidence on efficacy and safety of this drug after analyzing various studies conducted in patients with renal anaemia. Searches of Pubmed, Cochrane database, Medscape, Google and clinicaltrial.org were made for terms like peginesatide, CKD, ESA and renal anaemia.

INTRODUCTION: Chronic kidney disease (CKD) is a major worldwide public health problem afflicting approximately 13 % of the population in United States (US). Number of patients eventually reaching ESRD are increasing rapidly with estimated 450,000 in 2003 to 661,330 by the year 2010 [1, 2].

According to the National Kidney Foundation (NKF)of US, CKD is defined as an evidence of kidney damage based on abnormal urinalysis results / structural abnormalities or an absolute glomerular filteration rate (GFR) <60 ml/min for three or more months [3].

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Kidney disease has been graded into five stages depending upon transition from preserved GFR to end stage renal failure.

Stage 1 occurs when the GFR is ≥ 90 ml/min/1.73 m^2. Stages 2, 3, and 4 CKD are defined by a GFR of 60–89 ml/min/1.73 m^2, 30–59 ml/min/1.73 m^2, and 15–29ml/min/1.73 m^2, respectively. The final stage, Stage 5, occurs when the GFR is < 15 ml/min/1.73 m^2 or when patients require dialysis [4].

Anaemia is one of the morbid CKD associated complications with an estimated prevalence of 50% leading to profound impact on patients' health and quality of life. It increases proportionately with worsening of renal functions.1/4 th of CKD stage 1 patients, 1/2 of stage 2, 3, 4 patients and 2/3th of end stage patients needing dialysis suffer from anaemia.

In a third National Health and Nutrition Examination Survey (NHANES III) done in US, 15,000 people in general population were found to have inverse relationship between GFR <60ml/min /1.73 m^2 and prevalence of anaemia [5]. Type of anaemia generally observed in CKD patients is normochromic, normocytic and hypoproliferative as determined by absolute reticulocyte count [1].

NKF has defined anaemia as haemoglobin (Hb) concentration <12 g/dl for females and, 13.5 g/dl in males whereas European best practices guidelines for managing anaemia in CKD patients defines anaemia as Hb concentration <11.5 gm/dl in females, <13.5 gm/dl in males with age ≤70 years and <12 gm/dl in males aged >70years [6, 7]. Among various etiologies of anaemia in CKD patients(iron , folic acid and vitamin B_{12} deficiency, GIT bleeding, severe hyperparathyroidism, systemic inflammation and decrease RBC survival), most important cause is erythropoietin (EPO) deficiency [1].

EPO is a 30,400 dalton glycoprotein which is secreted by renal peritubular interstitial cells of kidneys in adults and hepatocytes in foetus [8]. Progressive tubular interstitial fibrosis in CKD patients impairs the synthesis of sufficient EPO by kidneys hence resulting in deficiency state leading to renal anaemia [1, 2].

Impact of Anaemia: Anaemia of CKD is not just confined to symptoms like fatigue, dyspnoea, reduced exercise tolerance, decreased cognitive functions but can lead to cardiovascular complications (left ventricular hypertrophy, left ventricular systolic dysfunction, congestive heart failure and coronary artery disease) and stroke. These cardiovascular complications further worsen renal functioning. Hence this vicious cycle of 'Cardio-renal syndrome' leads to progressive deterioration of patients' health, increased hospitalization and ultimately overall mortality [9, 10].

Due to progressive increase in anaemia with gradual worsening of renal functions, early diagnosis and accurate continuous management throughout CKD continuum is the most challenging task. Proactive multimodel treatment strategy is essential for management of morbid anemia with CKD to improve outcome in such patients.

Management of Anaemia in CKD: Queries have surrounded the issue of deciding target haemoglobin which is the first and foremost strategy for anaemia management. Two randomized controlled trials - Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin (CREATE) demonstrated that Hb > 13 g/dl carries risk but no superior efficacy as compared to ≤12gm/dl [11, 12, 13].

Intensive ESA treatment has been found to be associated with increased mortality risk in patients with hematocrit > 36% or higher in a study done by Brookhart [14]. Kidney Disease Outcomes Quality Initiative (KDOQI) in 2007 suggested that safer strategy is partial correction of anemia by setting target Hb to 11-12 to reduce the incidence of thromboembolism [15].

Conventional management of anemia involves intravenous iron therapy, red blood transfusions and erythropoiesis stimulating agents (ESAs) [2, 10]. ESA have been found to be the mainstay of treatment, if used judiciously with frequent dose adjustments according to target Hb, rate of change of Hb and the clinical condition of patient [16].

Since last 20 years, clinical use of ESAs has dramatically improved the management of anaemia associated with CKD, particularly in those who are undergoing dialysis ,transfusion dependent, iron overloaded and severely debilitated due to very low Hb (6-7gm/dl) ,with continuous development and research going on in this direction [17].

In addition to the efficacy and safety of ESAs, great impact on economic status of anaemia treatment has been witnessed with ESA use, as mean total cost savings of $411 per patient per month in US had been observed in a study reflecting reduced inpatient and emergency department visits and costs, lower inpatient mortality and longer time to dialysis [18]. Evoluting from first generation recombinant human ESA – Epoetin α, second generation ESA – darbepoetin and third generation ESA - Continuous erythropoietin receptor activator (CERA) have been developed and studied. Progressive generations differ chemically in having more sialic acid residues which make them more stable and longer acting leading to less frequent administration.

Epoetin α needs 1-3 weekly injections, darbepoetin needs once weekly /2 weekly and CERA once every two weeks injections. Focusing on the search of an ESA with still longer action, less frequent administration and temperature resistance, screening of thousands of peptide molecules having affinity for EPO receptors finally ended up with the discovery of new potent EPO mimetic agent- Peginesatide. This novel non immunogenic ESA has recently being developed with similar efficacy, safety, more stability and longer $t_{1/2}$ as compared to conventional ESA [19-22]. It is the first FDA approved (March 2012) and marketed unique ESA which can be given once a month by intravenous or subcutaneous route.

Peginesatide: Peginesatide is a synthetic, dimeric peptide of molecular weight 5000amu conjugated to a 40 kDa PEG (polyethylene glycol) moiety which has amino acid sequence different from other already existing ESA [23]. Difference in chemistry escapes it from enzymatic degradation hence makes this novel agent longer acting ($t_{1/2}$ - 47.9 hours) .Peg moiety gives it stability and increased plasma persistence due to decreased renal clearance translating in less frequent administration and hence sustained action. Difference in structure also provides the advantages of non-immunogenicity and no cross reactivity with EPO which otherwise is a problem with conventional ESAs as anti EPO antibodies formed can halt red blood cell production and worsen anemia [24].

It has been synthesized by traditional solid-phase synthesis followed by single site-specific conjugation to PEG. Simple manufacturing process as compared to genetic engineering and cell cultures for recombinant ESAs is another advantage of this novel agent [25]. Most important difference which makes it a better option amongst ESAs is once a month administration which seems to make treatment more economical, comfortable and safe for the patient hence increasing treatment adherence, saving time and decreasing work load of health care providers [26].

Mechanism of Action: Peginesatide though not chemically related to EPO binds to and activates EPO receptors (HuEPOr) just like natural EPO leading to regulation of bone marrow erythroid cell proliferation, differentiation and survival. At molecular levels action is mediated by receptor dimerization, Janus kinase (JAK2) activation, autophosphorylation of tyrosine residues and phosphorylation of several signalling proteins [8, 23].

Preclinical and Clinical Studies of Peginesatide: Regarding pharmacokinetics of peginesatide in preclinical studies, $t_{1/2}$ has been demonstrated to be in the range of 30.7-92 hours in rats and monkeys [27]. Area under curve and maximum concentration was seen to be greater by intravenous than subcutaneous route in a rodent study projecting better bioavailability by intravenous route but this difference was not observed clinically [24, 28].

Peginesatide studies in animals demonstrated dose dependent increase in RBC counts, haemoglobin and hematocrit (Hct) levels with sustained circulatory persistence. Pronounced and sustained polycythemia, bone marrow hypercellularity and extramedullary hyperplasia were also observed with peginesatide administration in animals. Toxicity observed with the study drug was found to be associated with exaggerated pharmacology and secondary effects [27-9].

The immune responses, which are observed in the repeat dose toxicity studies conducted with the currently marketed ESA, were not observed with peginesatide [28]. Antibodies to peginesatide were not found to cross-react with EPO and vice versa. Hence this new drug was able to correct antibody induced anaemia in rat pure red cell aplasia in a rat study [30]. It was also found to be non-mutagenic/clastogenic in genotoxicity testing studies in transgenic mouse [31].

Peri/post natal safety in animals was observed in a study which demonstrated negligible foetal exposue with no effect on development, functioning, mating and fertility end points in F1 generation after administration of peginesatide in pregnant rats. No effect was observed on lactation, partiruation and mating behaviour of F0 generation. Slight decrease in 2-4 days post-partum viability and low birth weight in F1 progeny was associated with exaggerated polycythemia [32]. Hence, results of this study can be extrapolated to confirm safety of this novel agent clinically also in pre/post natal phases.

A Phase I double blind, placebo controlled trial of peginesatide was carried out in 28 healthy volunteers to test the safety and pharmacodynamics of the single intravenous dose of study drug. The trial results demonstrated dose dependent increase in reticulocytes. 0.1mg/kg dose was associated with significant increase in Hb than baseline as compared to placebo (1.36±0.39 versus 0.39± 0.38; $p<0.001$) which was sustained for more than one month.

Also it was found to be well tolerated with mild adverse effects like headache, nausea, abdominal pain and dizziness [33]. A phase 2, multicenter, open label, sequential dose finding study of peginesatide was conducted in 139 non dialysis CKD patients with anaemia. Patients were assigned to eight cohorts depending upon starting dose, dosing frequency and route of administration. Across all the cohorts, 96% of patients achieved Hb response (increase of ≥1gm/dl from baseline or hb≥11gm/dl at any time) .Mean increase in Hb at the end was 1.4gm/dl with a dose response relationship. Final outcome of the study (final median range 0.019-0.044mg/kg once a month) confirmed that once a month peginestaide can be started with dose of 0.025-0.04mg/kg for further exploratory phase 3 studies [34].

An open-label, single-group trial enrolled 14 patients with CKD who had pure red-cell aplasia or hypoplasia due to anti EPO antibodies. Peginesatide was administered by subcutaneous injection at an initial dose of 0.05 mg/kg every 4 weeks. Results of this study demonstrated significant increase in Hb from 9.0 g/dl before treatment to 11.4 g /dl at the time of the last administration. Transfusion requirement diminished in 13 out of 14 patients in 12 weeks after first dose with 10 fold increase in peak reticulocyte count and mild to moderate adverse effects in majority of patients .Anti EPO antibodies also declined over the course of the study and became undetectable in six patients [35].

Four major phase III trials were done involving nondialysis (PEARL 1 and 2) and dialysis patients(EMERALD 1 and 2) to compare efficacy and tolerability of peginesatide once a month injection with epoetin 1-3 times a week or darbepoetin once every two weeks. PEARL 1 and EMERALD1 studies were done in US whereas PEARL 2 and EMERALD 2 studies were done in Europe and US [25, 36, 37]. The median duration of follow-up for patients on study drug in the four trials was 1.3 years. Results of these mega trials were found sufficiently convincing by regulatory authorities to approve this new drug with once a month administration for management of anemia in CKD patients on dialysis [**Table 1, Table 2**].

TABLE 1: RESULTS OF PEARL 1 AND PEARL 2 STUDIES [38, 40]

	PEARL1 (group1/group2/group3)	PEARL2 (group1/group2/group3)
Mean change in Hb from baseline(gm/dl) Treatment difference(CI)	1.39/1.64/1.37, 0.03(-0.19, 0.26) and 0.26(0.04, 0.48). Pre-specified criterion for non-inferiority was met by peginesatide in both groups.	1.50/1.68/1.35, 0.14(-0.09, 0.36) and 0.31 (0.08, 0.54). Pre-specified criterion for non-inferiority was met by peginesatide in both groups.
Proportion of patients who received blood transfusions (%)	6.2/7.3/4.9 No statistically significant difference	11.4/10.4/4.9. Statistically significant difference in group 1 and group 3
Proportion of patients with a mean Hb in target range during evaluation period (%)	93/94/94 No statistically significant difference	91/93/95 No statistically significant difference
Mean Hb during evaluation period (gm/dl)	11.5/11.6/11.5 No statistically significant difference	11.6/11.7/11.4 No statistically significant difference
Proportion of patients with serious adverse events (%)	48/46/43 No statistically significant difference	52/49/43 No statistically significant difference

TABLE 2: RESULTS OF EMERALD 1 AND EMERALD 2 STUDIES [39, 40]

	EMERALD1 Group 1/group 2	EMERALD 2 Group 1/group 2
Mean change in Hb from baseline(gm/dl)	-0.24/-0.09	-0.07/-0.17
Treatment difference(CI)	-0.15(-0.29,-0.01) pre-specified criterion for non-inferiority was met by peginesatide	0.10(-0.05,0.26) Pre-specified criterion for non-inferiority was met by peginesatide
Proportion of patients who received blood transfusions (%)	10.3/8.6 No statistically significant difference	7.6/9.9 No statistically significant difference
Proportion of patients with a mean Hb in target range during evaluation period (%)	63/71.7 Statistically significant difference	63.5/65.9 No statistically significant difference
Mean Hb during evaluation period (gm/dl)	11.1/11.3 No statistically significant difference	11.1/11.1 No statistically significant difference
Proportion of patients with serious adverse events (%)	58/63 No statistically significant difference	49/52 No statistically significant difference

Study Details of PEARL and EMERALD: PEARL 1(490)and PEARL 2(493) studies were interventional, randomized, open label, parallel group safety/ efficacy studies done in patients with chronic renal failure not on dialysis and not on ESA. Patients were randomized to three groups (1:1:1). Group 1 was given peginesatide subcutaneous once a month with a starting dose of 0.025 mg/ kg. Starting dose of peginesatide was fixed at 0.04 mg/kg in group 2 and group 3 was given darbepoetin subcutaneous every 2 weeks with a starting dose of 0.75 mcg /kg for ≥52 weeks. Doses of all the drug groups were titrated to achieve target Hb to 11-12 gm/dl. Primary outcome measure was mean change in Hb from baseline to 25-36 weeks. Secondary outcome measures were proportion of patients who received RBC transfusion/achieved Hb response above baseline (0 to 36 weeks).Hb response was defined as increase in Hb by ≥1gm/dl above baseline and Hb≥11gm/dl without RBC transfusion in previous 8 weeks [38].

EMERALD 1(n=803) and EMERALD 2 (n=823) studies were also interventional, randomized, parallel group, open label safety/ efficacy studies done in patients with CRF undergoing haemodialysis for 3 months or more and on maintenance therapy with epoetin since 8 weeks or more before randomization. Patients were randomized in two groups (2:1).Group 1 was given peginesatide and group 2 was administered epoetin. Staring dose of peginesatide was adjusted based on epoetin dose during last week of screening before randomization and titrated to achieve target Hb.

Primary outcome measure was mean change in Hb from baseline to 36 weeks. Secondary outcome measures were proportion of patients who received RBC transfusion whose mean Hb level is within the target range of 10.0 - 12.0 g/dl during 8 weeks [39].

In all the four studies, peginesatide met the statistical criterion for non-inferiority for therapeutic efficacy and cardiovascular composite safety endpoint (CSE) [death, stroke, myocardial infarction, congestive heart failure, unstable angina, and arrhythmia] with hazard ratio (HR) 1.06, 90 percent confidence interval (CI) 0.91 – 1.22. Whereas, in EMERALD studies frequency of CSE was similar in both groups (23% versus 24%)[(HR 0.95, 90 percent CI 0.79 - 1.13), In PEARL trials, frequency of CSE was found to be higher (21.6%) in study group as compared to control group (17.1%) [HR 1.34, 90 percent CI 1.03 – 1.73] [40, 41]. These results are not the confirmation for non-inferiority of peginesatide in non-dialysis patients because it is thought that certain imbalances in the baseline characteristics must have influenced the study results. Hence, more exploratory trials in future are needed to confirm the safety of this agent in non-dialysis patients. [42]

CONCLUSION: In conclusion, Peginesatide as once monthly injections is an equally efficacious, safe and non-immunogenic ESA with good haemoglobin stability in anemia associated with CKD patients on dialysis. It will be too early to mark it more superior as compared to epoetin and darbepoetin, but its once monthly convenient dosing certainly makes this novel agent preferable than the existing agents. More exploratory head to head comparative clinical trials are warranted in future to clinically elucidate its efficacy and safety as compared to the existing ESAs.

REFERENCES:

1. Thomas R, Kanso A and Sedar JR: Chronic Kidney Disease and Its Complications. Prim Care 2008; 35:329-44.
2. Hayat A, Heria D and Salifu MO: Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. Patient Preference and Adherence 2008; 2:195-200.
3. Levey AS, Coresh J, Balk E ,Kausz AT, Levin A, Steffes MW, et al: National Kidney Foundation Disease Outcomes Quality Initiative Clinic Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Ann Intern Med 2003; 139:137–47.
4. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 (Suppl. 1):S1–S266.
5. McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang L, et al: The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin 2004; 20:1501–10.
6. National Kidney Foundation: Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults: Am J Kidney Dis 2006; 5 (Suppl. 3):S1–S108.
7. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure: Nephrol Dial Transplant 2004; 19 (Suppl. 2):1–47.
8. Fisher JW: Erythropoietin: physiology and pharmacology update. Exp Biol Med 2003; 228:1–14.
9. Bahal O'Mara N: Anaemia in patients With Chronic Kidney Disease. Diabetes Spectrum 2008; 21:12-9.
10. Schmidt RJ and Dalton CL: Treating anemia of chronic kidney disease in the primary care setting: cardiovascular outcomes and management recommendations. Osteopathic Medicine and Primary Care 2007, 1:1-11.
11. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al : Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006; 355:2085-98.
12. Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al: Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006; 355:2071-84.

13. Locatelli F, Del Vecchio L and Pozzoni P: Anemia and cardiovascular risk: the lesson of the CREATE trial. J Am Soc Nephrol 2006; 17: S262-S266.
14. Brookhart MA, Schneeweiss S, Avorn J, Bradbury BD, Liu J and Winkelmayer WC: Comparative mortality risk of anemia management practices in incident hemodialysis patients. JAMA 2010; 303:857-64.
15. National kidney foundation: KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis 2007, 50:471-530.
16. Elliott S, Lorenzini T, Asher S, Aoki K, Brankow D, Buck L, et al: Enhancement of therapeutic protein in vivo activities through glycoengineering .Nat Biotechnology 2003;21:414–21.
17. Doss S and Schiller B: Peginesatide: a potential erythropoiesis stimulating agent for the treatment of anemia of chronic renal failure. Nephrol Nurs J 2010; 37:617-26.
18. Maddux FW, Shetty S, del Aguila MA, Nelson MA and Murray BM: Effect of erythropoiesis-stimulating agents on healthcare utilization, costs, and outcomes in chronic kidney disease. Ann Pharmacother 2007; 41:1761-9.
19. Macdougall IC: Hematide, a novel peptide-based erythropoiesis-stimulating agent for the treatment of anemia. Curr Opin Investig Drugs 2008; 9:1034-47.
20. Roger SD: Extended administration of erythropoiesis-stimulating agents for optimising the management of renal anaemia: what is the evidence? Int J Clin Pract 2008; 62:1413-22.
21. Vecchio LD and Locatelli F: New Treatment Approaches in Chronic Kidney Disease-associated Anaemia. European Nephrology 2011; 5:108–11.
22. Moyer MW: New blood-boosting drugs aim to staunch renal anemia .Nat Med 2012; 18:332.
23. Green JM, Leu K, Worth A, Mortensen RB, Martinez DK, Schatz PJ, et al: Peginesatide and erythropoietin stimulate similar erythropoietin receptor–mediated signal transduction and gene induction events .Exp Hematol 2012 Epub ahead of print.
24. Fan Q, Leuther KK, Holmes CP, Fong K, Zhang J, Velkovska S, et al: Preclinical evaluation of Hematide, a novel erythropoiesis stimulating agent, for the treatment of anemia. Exp Hematol 2006; 34:1303-11.
25. Macdougall LC: New Anemia Therapies: Translating Novel Strategies From Bench to Bedside Am J Kidney Dis 2012; 59:444-51.
26. Zakar G: Current issues in erythropoietin therapy of renal anemia. Lege Artis Med 2007; 17:667-73.
27. Woodburn KW, Schatz PJ, Fong KL, Wilson SD, Ferrell T, Spainhour CB ,et al :Preclinical safety and pharmacology of Hematide, a peptidic erythropoiesis stimulating agent (ESA), in rats and monkeys. Drug Chem Toxicol 2008; 31:229–44.
28. Woodburn KW, Wilson SD, Fong KL, Schatz PJ, Spainhour CB and Norton D: Chronic pharmacological and safety evaluation of Hematide, a PEGylated peptidic erythropoiesis-stimulating agent, in rodents. Basic Clin Pharmacol Toxicol 2009; 104:55–63.
29. Woodburn KW, Fan Q, Schatz PJ, Wilson SD, Fong K and Norton D: A subchronic murine intravenous pharmacokinetic and toxicity study of Hematide, a PEGylated peptidic erythropoiesis-stimulating agent. Drug Chem Toxicol 2010; 33:28–37.
30. Woodburn KW, Fan Q, Winslow S, Chen M, Mortensen RB, Casadevall N, *et al*: Hematide is immunologically distinct from erythropoietin and corrects anemia induced by antierythropoietin antibodies in a rat pure red cell aplasia model. Exp Hematol 2007; 35:1201-8.
31. Woodburn KW, Schatz P, Wilson S, Fong K, Wagner VO, Gudi R, *et al*: Genotoxic assessment and toxicity evaluation of peginesatide in CByB6F1 hybrid mice .Drug Chem Toxicol 2011;34:240–9.
32. Lewis EM, Hoberman AM, Fong KL, Schatz PJ, Wilson SD and Woodburn KW: Peri- and Postnatal Rodent Development of Hematide, an Erythropoiesis-Stimulating Agent. Birth Defects Research 2010; 89:155–63.
33. Stead RB, Lambert J, Wessels D, Iwashita JS, Leuther KK, Woodburn KW, *et al*: Evaluation of the safety and pharmacodynamics of Hematide, a novel erythropoietic agent, in a phase 1, double-blind placebo-controlled, dose-escalation study in healthy volunteers. Blood 2006; 108:1830–4.
34. Macdougall IC, Wiecek A, Tucker B, Yaqoob M, Mikhail A, Nowicki M, *et al*: Dose-finding study of peginesatide for anemia correction in chronic kidney disease patients. Clin J Am Soc Nephrol 2011; 6:2579-86.
35. Macdougall IC, Rossert J, Casadevall N, Stead RB, Duliege AM, Froissart M, et al: A peptide based erythropoietin-receptor agonist for pure red-cell aplasia. N Engl J Med 2009; 361:1848-55.
36. Besarab A ,Locatelli F, Covic A, Edouard M, Bernardo M, Macdougall L, et al: "Safety and Efficacy of Peginesatide for Treatment of Anemia in Hemodialysis Patients Previously on Epoetin Alfa or Beta." National Kidney Foundation Spring Clinical Meetings (NKF), Las Vegas. April 2011. Abstract 33.
37. Schiller B, Zeig SC, Hura C, Levin N, Kaplan M, Tang H, *et al*: Safety and efficacy of peginesatide for treatment of anemia in hemodialysis patients previously on epoetin alfa. National Kidney Foundation Spring Clinical Meetings (NKF), Las Vegas. April 2011. Abstract 274.
38. Macdougall JC, Provenzano R, Pergola PE, Zabaneh R, Sharma A, Spinowitz BS, *et al*: Primary Results from Two Phase 3 Randomized, Active-Controlled, Open-Label Studies (PEARL 1 and PEARL 2) of the Safety and Efficacy of Hematide™/Peginesatide for the Correction of Anemia in Patients with Chronic Renal Failure Not on Dialysis and Not Receiving Treatment with Erythropoiesis-Stimulating Agents. Late-breaking clinical trials. J Am Soc Nephrol 2010; 21:2B.
39. Schiller B, Locatelli F, Covic AC, Martin ER, Clark RV, Zeig S, et al: Primary Results from Two Phase 3 Randomized, Active-Controlled, Open-Label Studies (EMERALD 1 and EMERALD 2) of the Safety and Efficacy of Hematide™/Peginesatide for the Maintenance Treatment of Anemia in Patients with Chronic Renal Failure Who Were Receiving Hemodialysis and Were Previously Treated with Epoetin Alfa or Epoetin Beta. Late-breaking clinical trials. J Am Soc Nephrol 2010; 21:2B.
40. Affymax. Affymax and Takeda Announce Phase 3 Trials Meet Primary Endpoints for Investigational Drug, Hematide (TM) /peginesatide, to Treat Anemia in Chronic Renal Failure with Some Differences Noted in Secondary Analyses. Business Wire. 2010 Jun 21. http://www.investors.affymax.com/releasedetail.cfm? Release ID=481068.
41. Fishbane S, Besarab A, Schiller B, Provenzano R, Covic AC, Macdougall IC, et al: Results from a Composite Safety Endpoint Used to evaluate the Cardiovascular Safety of Hematide™/Peginesatide in Patients with Anemia Due to Chronic Renal Failure. Late-breaking clinical trials. J Am Soc Nephrol 2010; 21:1B.
42. Hogan M: Peginesatide as Safe and Efficacious as Epoetin in Trials of Dialysis Patients. Nephrology times 2010; 3:8-10.

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