

Profile of peginesatide and its potential for the treatment of anemia in adults with chronic kidney disease who are on dialysis

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Abstract: Peginesatide is a synthetic, dimeric peptide that is covalently linked to polyethylene glycol (PEG). The amino acid sequence of peginesatide is unrelated to that of erythropoietin (EPO) and is not immunologically cross-reactive with EPO. Peginesatide binds to and activates the human EPO receptor, stimulating the proliferation and differentiation of human red cell precursors in vitro in a manner similar to other EPO-stimulating agents (ESAs). In Phase II and III studies in dialysis and predialysis patients, peginesatide administered once monthly was as effective as epoetin alfa given thrice weekly (dialysis patients) or darbepoetin given once weekly (nondialysis patients), in correcting anemia of chronic kidney disease as well as maintaining hemoglobin within the desired target range. In the dialysis population, the reported side-effect profile of peginesatide was comparable to that known with other marketed ESAs. In the nondialysis studies, compared with those treated with darbepoetin, patients treated with peginesatide experienced a higher adverse-effect profile. Peginesatide is likely to be licensed for treatment of renal anemia in dialysis patients and not in nondialysis patients. Despite this limitation, peginesatide is likely to prove valuable in treating dialysis patients because of its infrequent mode of administration, thereby allowing for a reduced number of injections, with associated better compliance, reduced cold storage requirement, and improved stock accountability. PEGylated therapeutic proteins can elicit immunological response to the PEG moiety of the therapeutic complex. Only long-term experience and post-marketing surveillance will address whether this immunological response will have any impact on the clinical efficacy or safety of peginesatide in clinical practice.

Keywords: peginesatide, dialysis, chronic kidney disease

Introduction

Prior to the introduction of recombinant human erythropoietin (rhuEPO) in clinical practice, many patients receiving dialysis were severely anemic and needed transfusions to maintain a hemoglobin level greater than 7 g/dL.¹ Consequently, patients suffered many of the consequences of chronic anemia, mainly in terms of volume overload, hyperkalemia, iron overload, blood-borne infections, and allosensitization.²

The introduction of erythropoiesis-stimulating agents (ESAs) has changed the care of patients with kidney disease by increasing hemoglobin levels and thereby avoiding the need for transfusions. The first ESAs to be introduced were short-acting (eg, epoetin alfa and beta) and required administration three times a week. The introduction of darbepoetin, a second-generation ESA and, more recently, Mircera (Hoffmann-La Roche, Basel, Switzerland), a third-generation ESA (EU only), both with extended duration of action, has led to less-frequent dosing with a comparable efficacy.³ All these ESAs

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are derivatives of the parent molecule, rhuEPO. The creation of a drug that is structurally different from rhuEPO, yet capable of stimulating erythropoiesis, could be an interesting therapeutic development. The benefit of such a development could be the elimination of the potential to induce immune response to rhuEPO and therefore compromise its action. In its most severe form, such an immune response could manifest as pure red cell aplasia (PRCA), a severe form of anemia unresponsive to all the currently licensed ESAs, rendering affected patients transfusion-dependent. Such a development could also address other unmet needs in treating anemia in chronic kidney disease (CKD) patients.

Peginesatide, a drug capable of stimulating erythropoiesis, and likely to be licensed for clinical use in the near future, is the first ESA that bears no structural similarity to rhuEPO. This mini review will discuss the data available from Phase II and III clinical trials of peginesatide, focusing on its clinical use and safety profile, and will conclude by discussing its potential role in the field of management of anemia of CKD and possible uncertainties that may be associated with its use in clinical practice.

Peginesatide: structure and preclinical data

Peginesatide is a synthetic, dimeric peptide that is covalently linked to polyethylene glycol (PEG). Its molecular weight ranges between 45.0 to 50.5 kDa.⁴ The amino acid sequence of peginesatide is unrelated to that of rhuEPO and is not immunologically cross-reactive with rhuEPO.⁴ This characteristic potentially reduces the risk of PRCA, and theoretically may provide a rescue treatment for patients affected by such condition. Peginesatide binds to and activates the human EPO receptor, stimulating the proliferation and differentiation of human red cell precursors *in vitro* in a manner similar to ESAs.⁵ A predictable, dose-related effect on reticulocyte and hemoglobin levels has been observed in rats and monkeys.^{6,7}

Clinical efficacy

In a Phase I study to evaluate the safety and pharmacodynamic effects of single, intravenous doses (0.025, 0.05, and 0.1 mg/kg) of peginesatide in 28 healthy male volunteers, all doses were well tolerated, with safety profiles comparable to that of placebo. Peginesatide showed a dose-dependent increase in reticulocytes. The 0.1 mg/kg dose was associated with a statistically significant increase in hemoglobin from baseline compared with the placebo group. That effect was sustained for more than 1 month.⁴

Peginesatide: experience in correcting anemia in CKD patients not on dialysis

The efficacy of peginesatide in correcting anemia in CKD patients was demonstrated in a Phase II trial. Patients who were not on dialysis, and not receiving treatment with ESAs in the 12 weeks before study drug administration, were sequentially assigned to 1 of 10 cohorts that differed in starting peginesatide dose (different body weight-based or absolute doses), route of administration (intravenous or subcutaneous), and frequency of administration (every 4 or 2 weeks). Across all cohorts, 96% of patients achieved a hemoglobin response. A dose-response relationship was evident for hemoglobin increase. Comparable subcutaneous and intravenous peginesatide doses produced similar hemoglobin responses. Rapid rates of hemoglobin rise and hemoglobin excursions > 1 g/dL tended to occur more frequently with once-fortnightly dosing than with once-monthly dosing. This study provided the first proof that peginesatide administered every 4 weeks can increase and maintain hemoglobin level in nondialysis CKD patients.⁸

Phase III studies have demonstrated that dialysis patients maintained on epoetin alfa can be switched successfully to once-monthly peginesatide (unpublished data).

In CKD patients not on dialysis, although once-monthly peginesatide was noninferior to darbepoetin alfa in both correction of anemia and maintenance of hemoglobin within target range, higher proportions of adverse events and serious adverse events were observed in the peginesatide treatment group compared with the darbepoetin treatment group (unpublished data). The cause of such increased incidence in the peginesatide group compared with the darbepoetin group is unclear. But based on these results, peginesatide is likely to receive licensing approval only for the treatment of anemia in dialysis patients and not for CKD patients not on dialysis.

Correction of anemia in patients with pure red cell aplasia

Because anti-EPO antibodies have not been observed to cross-react with peginesatide,^{9,10} peginesatide was studied as a potential treatment in CKD patients with anti-EPO antibody-mediated PRCA.

In a Phase II, open-label, multiple-dose study to evaluate the ability of peginesatide administered monthly to increase and maintain hemoglobin levels in these transfusion-dependent patients, 14 patients were treated with peginesatide for a median of 28 months. The median hemoglobin concentration increased from 9.0 g/dL

(with transfusion support in 12 out of 14 patients) before treatment, to 11.4 g/dL at the time of the last administration of peginesatide; transfusion requirements diminished within 12 weeks after the first dose, after which 13 of the 14 patients no longer required regular transfusions.¹¹

The level of anti-EPO antibodies declined over the course of the study and became undetectable in six patients. One patient who initially responded to treatment had a diminished hematologic response a few months later despite increased doses of peginesatide and required transfusions again; this patient was found to have antibodies against peginesatide.¹¹

Antibody responses and clinical effects in clinical studies

Peginesatide differs from ESAs derived from human EPO in that it is a synthetic, dimeric peptide that does not share structural homology with human EPO. Among 139 patients enrolled in a Phase II study, two patients (1.4%) had detectable levels of peginesatide-specific neutralizing antibodies. Those two patients showed no evidence of de novo anti-EPO antibodies, and no new cases of PRCA were reported in any patient receiving peginesatide.⁸

Peginesatide: a role in the management of anemia in dialysis patients?

It is now over 20 years since rhuEPO was first used to treat anemic CKD patients. During this period, the market was dominated with recombinant human EPO or its derivatives. The imminent introduction of peginesatide to the anemia market provides an exciting opportunity to physicians and clinical researchers alike to use a drug that is structurally unrelated to EPO, yet capable of producing its desired therapeutic effects. There are several potential advantages to using an EPO mimetic agent to treat anemic CKD patients.

Peginesatide: a PEGylated EPO mimetic dipeptide

The conjugation of small proteins with PEG, or PEGylation, has become an increasingly common method of improving the half-life of biological products, mainly through reducing the urinary excretion of the molecule¹² but also by reducing the enzymic degradation due to the increased steric bulk.¹ In addition, PEGylated biological products often exhibit a reduced affinity for the target receptor compared with the native precursor. This reduced affinity can lead to a lower

elimination by target-mediated clearance mechanisms, and prolonged half-life of the PEGylated product. Finally, the addition of the PEG moiety can have beneficial effects on the immunological profile of a molecule by reducing the ability of the compound to raise antibodies in humans.¹³ All these characteristics make the development of peginesatide an attractive therapeutic alternative to other ESAs in the treatment of anemia in patients with CKD.

A novel peptide

Being structurally different from other licensed ESAs, peginesatide may be ideally used whenever other ESAs cannot be used (eg, intolerance to therapeutic proteins, non-neutralizing anti-EPO antibodies). Although not within its current license application, its use as a rescue therapy in patients with EPO-induced red cell aplasia may provide a marketing leverage over other available ESAs.

A long-acting preparation

The use of a long-acting ESA in treating anemia in dialysis patients provides a unique opportunity to create maximum value for patients and healthcare providers alike by reducing waste through improved quality, efficiency, and safety. A long-acting ESA may have the following potentials:

- It may offer more flexibility in ESA dosing and administration compared with the existing shorter-acting preparations.
- It may release more time for health workers to treat more patients and attend to more complicated cases.
- Monthly administration would allow hospital pharmacies to request the drug when needed, with little need for storage.
- The reduced number of injections (from 100–150 injections per patient year to 12 injections per patient year) may translate into a reduced need for cold storage capacity, reduced risk and asset-value loss in the case of cold storage interruption, reduced wastage, and reduced number of missed doses.
- Once-monthly dosing may help address clinical governance issues by facilitating accurate stock, prescription, and administration reconciliation.

The use of peginesatide may provide the opportunity to reduce overall patient exposure to ESA

Preliminary post hoc analysis of Phase III studies of peginesatide in dialysis patients suggests that for patients receiving high epoetin doses at baseline (ie, prior to switch to

peginesatide), the relative dose of peginesatide is significantly lower than that for those receiving low epoetin doses at baseline (unpublished data). This suggests that, for patients requiring a high maintenance dose of epoetin, switching to peginesatide may provide the opportunity to reduce overall drug exposure without compromising therapeutic efficacy. Whether this may translate into a better outcome for patients may need further long-term trials to determine.

Peginesatide: residual uncertainties

Before peginesatide establishes itself as a therapeutic alternative to other licensed ESAs, it has to overcome a few challenges.

The position of ESA therapy in the current anemia market

The results of two large multicenter studies have suggested a possible association between high hemoglobin level and increased cardiovascular events in patients with CKD.^{14,15} In addition, post hoc analyses of these studies suggests a direct association between ESA dose and survival in CKD patients.^{16,17} Becoming increasingly aware of these data, clinicians are actively trying to minimize ESA utilization, and to rely alternatively on parenteral iron therapy. This is compounded by the fact that national and international guidelines on anemia management have brought therapeutic target hemoglobin in ESA-treated patients to a lower level in response to the results of these multicenter studies.^{18,19}

Price

As more ESAs are introduced into the ever-expanding anemia market, the marketing price of ESA products is being reduced by the pharmaceutical industry to maintain their position in the anemia market. This is particularly relevant in Europe, where several biosimilars have been in the market for over 4 years now. This is also important given the current financial climate where healthcare providers are continually exploring new avenues to make health service delivery more affordable and cost-effective. Peginesatide has to be marketed at a price that allows it to compete with other well-established ESAs.

Restricted license

The drug is likely to be licensed for the treatment of renal anemia in chronic dialysis patients only. Based on the available safety data, Affymax (Palo Alto, CA) is not seeking marketing authorization for the treatment of renal anemia in patients not on dialysis. Given the fact that the majority of

dialysis patients start ESA therapy before they start dialysis, patients may need to switch to peginesatide as they commence renal replacement therapy. A peginesatide marketing campaign may need to establish a strong reason to convince stakeholders of the benefits of switching patients as they commence renal replacement therapy.

Peginesatide: just another ESA?

Although structurally different from rhuEPO, peginesatide acts in a mechanism similar to other ESAs available for clinical use (ie, via stimulation of EPO receptors), has to be administered parenterally, and possibly shares the same safety profile as other ESAs. Clinicians will ask for a convincing case to switch patients from existing ESAs that have been in clinical practice for over a decade, with well over one million patient/year exposure and a well-documented safety profile,²⁰ to the newly introduced peginesatide, with comparatively limited safety data and relatively limited information on clinical experience.

Compliance

With the use of long-acting ESA in treating chronic dialysis patients, there is a need to ensure a maximum compliance with ESA administration. In a cross-sectional study on UK dialysis patients, concordance (defined as receiving $\geq 90\%$ of the prescribed dose) ranged from 24% to 33%.²¹ While missing a single injection of a short-acting ESA preparation may result in a transient reduction of the overall area under the curve of ESA blood level, missing a whole monthly ESA injection may translate into a more significant and protracted drop in the area under the curve, with possible consequences on hemoglobin levels. Therefore, for units contemplating the use of monthly ESA preparation for their dialysis preparation, a robust drug accountability/risk-management plan should be established to minimize the risk of missed dose, or of over- or underdosing. Nevertheless, it is also important here to note that the above study found that reduced frequency of administration was associated with fewer missed doses.

Metabolic fate of PEGylated ESA in CKD patients

The clearance via metabolism of the PEGs that are typically used to alter the pharmacokinetics of biological products (molecular weight of 5000 or greater)^{22,23} is likely to be insignificant. This is because the metabolism of PEG is molecular weight-dependent, with high-molecular-weight PEGs (>4000) showing less metabolism.²⁴ The major route of elimination of PEG occurs through passive glomerular

filtration and is dependent on molecular weight.²⁴ Human excretion balance studies have shown that 86% and 96% of PEG 1000 and 6000 were excreted in the urine 12 hours after intravenous administration.^{25,26} These data raise questions about the metabolic fate of peginesatide as well as other PEGylated ESAs in patients with CKD, particularly in dialysis patients, many of whom have a markedly diminished or even zero glomerular filtration rate. In these patients, PEG is likely to accumulate in tissues in patients who receive long-term treatment with the drug. In fact, there are no systematic long-term studies that show: (1) whether PEG is excreted completely or partly remains in the body, (2) where it is accumulated, and (3) its effects at the sites of accumulation.²⁷ Ideally, the fate of any pharmaceutical product should be addressed via relevant pharmacokinetic studies, but this is impossible to achieve with PEGylated proteins in clinical practice. This is due to several reasons; first, identifying metabolites of PEG will be difficult because the PEGs used always have polydispersed molecular weight.²² Second, subtle changes in mass due to metabolism will be undetectable by mass spectrometry because of the range of molecular weights present in the PEG. Also, it has been shown that PEG can suppress ionization in a mass spectrometer.²⁸ In addition, humans and animals are commonly exposed to PEG via a variety of environmental sources, which means that it is likely that human plasma, urine, and other body fluids contain a range of PEGs and PEG metabolites. When the trace doses of most PEGylated biological products are combined with the ubiquitous “contamination” likely to be seen in animals and humans, it is unlikely that the approach to metabolite identification would be successful.²⁷ Therefore, only post-marketing long-term surveillance will be able to address the long-term effects of the use of PEGylated ESAs in patients with CKD.

PEGylated ESA: a possible immune reaction?

It has been shown that PEG, which is not supposed to show any opsonization, can in fact induce specific as well as nonspecific recognition by the immune system, thereby leading to a response of the body to intravenously administered PEG formulations.

Anti-PEG antibodies

Animal studies have clearly shown that some PEGylated proteins can elicit antibody formation against PEG.^{29–31} This anti-PEG response can accelerate the clearance of PEGylated proteins.^{32–34} In humans, PEG antibodies can be produced and may limit therapeutic efficacy, and may even

reduce tolerance of PEG–asparaginase in patients with acute lymphoblastic leukemia,³⁵ and of pegloticase in patients with chronic gout.^{36,37} Of major importance is the recent finding of a 22% to 25% occurrence of PEG antibodies in 350 healthy blood donors.^{35,38} It has been suggested that this increase is most likely due to greater exposure to PEG and PEG-containing compounds in cosmetics, pharmaceuticals, and processed food products.³⁵ These authors recommend that patients should be screened for pre-existing anti-PEG and monitored for the development of anti-PEG throughout the course of treatment with any PEG containing agent.³⁵ It is not clear whether this immunological response to PEG may have contributed to the unfavorable hematological response observed among nondialysis CKD patients treated with peginesatide compared with those treated with darbepoetin in Phase III studies. In addition, the available clinical data on peginesatide did not evaluate the prevalence of anti-PEG antibody response among patients treated with peginesatide. It is hoped that this aspect will be addressed in the upcoming publication of the results of Phase III clinical trials of peginesatide in patients with CKD.

PEG-induced complement activation

It has been shown that PEG, administered at doses equivalent to those used to bind therapeutic proteins, can generate complement activation products in human serum on a time scale of minutes via activation of the alternative complement pathway. PEG-induced complement activation has been reported to cause anaphylaxis.^{39,40} An immediate hypersensitivity reaction (HSR) in 5% to 10% of treated patients was shown for different PEG-containing liposomal carriers.²⁷ Complement activation with subsequent HSR was demonstrated with 99mTc-labeled 2 kDa methoxy-PEG-liposomes for the treatment of Crohn's disease.⁴¹ The PEGylated liposome formulation of doxorubicin used in anticancer therapy also caused HSR in up to 25% of patients, despite pretreatment with corticosteroids and antihistamines, and without prior sensitization.³⁹ This PEG-induced effect may be of particular relevance among some groups of CKD patients who are known to have impaired alternative complement activation as a possible mechanism of initiation and progression of their kidney disease, such as patients with mesangiocapillary glomerulonephritis/dense deposit disease or certain forms of hemolytic uremic syndrome.

Conclusion

Peginesatide is a novel peptide with no structural similarity to rhuEPO, yet capable of stimulating erythropoiesis in patients

with anemia of CKD. It is likely to gain a license for treating anemia in CKD patients who are on dialysis. Peginesatide may also be used as a rescue therapy in patients who develop EPO-induced PRCA. Once licensed, long-term clinical experience may provide insights on its potential as an ESA-minimizing agent in patients requiring large maintenance ESA doses. Peginesatide will probably have the same hematological safety profile as other available ESAs. PEG present in the therapeutic PEGylated proteins may contribute to the adverse-event profile, probably through activation of anti-PEG antibodies and complement consumption via the alternative pathway. Only long-term clinical experience/pharmacovigilance data will determine the exact place of peginesatide in the field of anemia management in patients with CKD.

Disclosure

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