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Peginesatide for the treatment of anemia due to chronic kidney disease – an unfulfilled promise

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Abstract

Introduction—The introduction of recombinant human erythropoietin revolutionized the management of anemia in patients with chronic kidney disease (CKD). In order to circumvent costly recombinant DNA technology, synthetic chemistry techniques were used to manufacture peginesatide, a synthetic peptide that bore no resemblance to previous erythropoiesis-stimulating agents (ESAs), and yet was capable of stimulating erythropoiesis. Compared with other ESAs, peginesatide was deemed to have advantages related to immunogenicity, administration schedule, and cost. Marketing approval was restricted to CKD patients on dialysis because cardiovascular events were more common with peginesatide than with darbepoetin in non-dialysis CKD patients. Unfortunately, unexplained serious adverse drug reactions (sADR) led to quick withdrawal of peginesatide from the market.

Areas covered—This review describes the efficacy and safety of peginesatide in pre-approval clinical trials, sADRs after marketing approval, and lessons learned during its short life-span.

Expert opinion—The case of peginesatide illustrates the difficulties in detecting rare sADRs in trials with limited patient populations and the need for improved pharmacovigilance after marketing approval. However, the need for simpler drug production methods as a result of non-dependence on recombinant DNA techniques and mammalian cell lines remains. Lessons learned during the scientific development of peginesatide can be used in developing other drugs.

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Keywords

Adverse drug reactions; anaphylactic; anemia; chronic kidney disease; erythropoiesis-stimulating agent; epoetin; darbepoetin; hemoglobin; hemodialysis; peginesatide; pharmacovigilance

1. Introduction

CKD patients suffer from renal anemia caused by insufficient production of the endogenously secreted glycoprotein hormone erythropoietin (EPO) in the diseased kidneys. EPO stimulates erythroid progenitor cells in the bone marrow, leading to an increase in red cell production.

Chronic anemia leads to fatigue, reduced physical capacity, impaired cardiac and cognitive function, sleep disorders and an increased requirement for red cell transfusions. The introduction of exogenous replacement of EPO dramatically changed the care of patients with kidney disease by increasing and maintaining hemoglobin levels, and consequently reducing the need for transfusions.

Large-scale production of therapeutic erythropoietin became possible after the advent of recombinant DNA technology. Recombinant human erythropoietin (epoetin) became available in the US in 1989, and in Europe and much of the rest of the world in 1990. The epoetins (alfa and beta) were short-acting, and required administration up to three times a week. A longer-acting epoetin analogue (darbepoetin) was then developed, which could be injected once-weekly or once-every two weeks. (1, 2).

The next development was to pegylate the molecule – attaching a polyethylene glycol moiety to epoetin beta in order to prolong the clearance of the molecule from the circulation. This new molecule was termed methoxypolyethylene glycol-epoetin beta, with an administration schedule of only once a month (3). This ESA received regulatory approval in the European Union (EU), Australia, Canada, Japan, and in the United States (US). Patent litigation prevented this ESA from being launched in the US until 2015, and due to premium pricing, higher costs have limited its use in other countries.

The creation of a drug that is not dependent on recombinant DNA techniques and human EPO, yet capable of stimulating erythropoiesis, was clearly an interesting therapeutic development. The concept of a peptide molecule being able to stimulate erythropoiesis was introduced to the scientific literature in a seminal paper by Wrighton and colleagues in 1996 (4). The initial molecule was called erythropoietin-mimetic peptide 1 (EMP-1), and this agent was able to activate the erythropoietin receptor and stimulate the same intracellular signalling process via the JAK-2 kinase/STAT5 5 pathway. Unfortunately, EMP-1 did not survive as a potential therapeutic agent due to lack of potency.

The concept was, however, developed further by a new pharmaceutical corporation who manufactured a dimeric peptide, linked with a spacer linker to a pegylation chain (as with methoxypolyethylene glycol-epoetin beta) to prolong its circulating half-life *in vivo*. The molecule was initially termed Hematide, and later became known as peginesatide. An

unanticipated benefit of this peptide was that, since it had no structural homology with either native or recombinant erythropoietin, it was able to stimulate erythropoiesis even in the presence of anti-erythropoietin antibodies, thus showing considerable efficacy in patients who were heavily transfusion-dependent as a result of antibody-mediated pure red-cell aplasia (PRCA), a rare syndrome that had been identified among ESA-treated patients primarily with CKD. In a clinical trial, patients with epoetin- or darbepoetin-associated PRCA were treated with peginesatide, and were found to have rapid and long-term resolution of their antibody-mediated anemia, along with a dramatic reduction and subsequent abolition of their transfusion dependence. Similarly, because of its unique amino acid sequence, any antibodies that could be generated against peginesatide would be unlikely to cross-react with erythropoietin, completely avoiding this devastating complication of conventional ESA therapy. (5).

2. Pharmacology

Like EMP-1, peginesatide binds to and activates the human erythropoietin receptor and stimulates erythropoiesis in human red cell precursors in vitro. It causes activation of the JAK 2/STAT 5 pathway, and results in an increase in erythroid progenitor cells, notably CFU-E and BFU-E, in both erythroleukemic and primary bone marrow culture (6).

Pharmacokinetic data suggest that the maximal plasma concentration and area under the plasma concentration versus time curve (AUC) increase with peginesatide dose. Following subcutaneous (SC) administration, the maximum concentrations of peginesatide are reached in approximately 48 hours. The bioavailability of peginesatide following SC administration is approximately 46%. Peginesatide is not metabolized and urinary excretion is the predominant route of elimination. The mean half-life of peginesatide in dialysis patients is 47.9 ± 16.5 hours following IV administration. The pharmacokinetics of peginesatide in patients with CKD on dialysis are not altered by age, gender or race based on population pharmacokinetic analyses. The potential for a drug-drug interaction between peginesatide and drugs metabolised by CYP isozymes or drug transporters is negligible. (7).

Peginesatide increases the reticulocyte count, followed by increases in hemoglobin. The rate of hemoglobin increase varies among patients and depends upon the drug dose. (8).

3. Efficacy

The efficacy and safety of peginesatide as compared with other ESAs have been demonstrated in four large phase 3 randomized, active-controlled, open-label, multicenter studies. The primary efficacy endpoint for each study was the change in hemoglobin for 52 weeks or more.

The studies in CKD patients on dialysis demonstrated maintenance of hemoglobin in patients who were being treated with epoetin at the time of study entry EMERALD 1 and 2 studies (9). The studies in non-dialysis patients with CKD compared peginesatide with darbepoetin, in order to achieve and maintain target hemoglobin levels PEARL 1 and 2 studies (10).

In the EMERALD studies, CKD patients undergoing hemodialysis were administered peginesatide IV or SC once every 4 weeks (n= 1066), or continued to receive epoetin one to three times per week (n=542). Peginesatide was non-inferior to epoetin in maintaining target hemoglobin levels of 10 to 12 g/dl. Rates of confirmed hemoglobin excursions and transfusions were similar in the two groups (9).

In the PEARL studies, ESA-naïve patients with CKD not undergoing dialysis received either peginesatide (n=656) or darbepoetin (n=327) SC. Peginesatide (administered monthly) was non-inferior to darbepoetin (administered every 2 weeks) in increasing and maintaining hemoglobin levels between 11.0 and 12.0 g/dl (10).

4. Safety

Phase 3 studies evaluated the cardiovascular safety of peginesatide by using an adjudicated composite safety endpoint (9, 10). This endpoint included stroke, myocardial infarction, congestive heart failure, unstable angina, arrhythmia, and death from any cause.

Among dialysis patients, the rates of cardiovascular safety events were similar in patients treated with peginesatide and epoetin. The combined safety endpoint occurrence was similar in the two groups; the point estimate was approximately 1 and it was consistent across patient subgroups.

However, the rates of cardiovascular events and mortality were statistically and clinically greater among ESA-naïve CKD patients not undergoing dialysis who were treated with peginesatide versus darbepoetin. The composite safety endpoint developed in 22% of peginesatide- versus 17% of darbepoetin-treated patients ($p<0.05$). Because of this toxicity result, the manufacturer did not request peginesatide approval to treat anemia among CKD patients not on dialysis.

The exact mechanism of the increased cardiovascular risk observed in the ESA-naive non-dialysis patients is unclear, but it appears different from that of aggravated pharmacodynamics resulting in high hemoglobin levels. The appraisal review of peginesatide by consultants to the European Medicines Agency included a comment that a poor initial hematopoetic response to ESA treatment in subjects not previously receiving ESAs may be associated with an increased cardiovascular risk (11,12). However, this insight is controversial and not universally accepted. Dialysis patients in the phase 3 study had previously received ESAs but non-dialysis patients had not. The increased cardiovascular risks of peginesatide were highest in ESA-naïve non-dialysis patients who showed a poor hemoglobin response upon initiation of study treatment. It is not possible to rule out that this increased risk could also emerge in the ESA-naïve dialysis population since it will also include patients with a poor response when treatment is started. (11). The phase 3 studies identified that 1.2% and 0.9% of peginesatide-treated patients developed peginesatide-specific binding and neutralizing antibodies, but clinical immunogenicity did not develop. (9,10) The finding that antibodies to peginesatide did not neutralize erythropoietin activity while antibodies to ESAs did is important. Among dialysis patients, peginesatide-specific

neutralizing antibodies developed in eight patients; nobody developed anti-erythropoietin antibodies, and no PRCA cases were reported.

The safety of peginesatide among CKD dialysis patients was subsequently addressed in one post-approval epidemiologic study. The relative risks of early mortality and morbidity in peginesatide-treated dialysis CKD patients were compared with matched epoetin alfa-treated patients (13). Relative to administration of epoetin alfa, first administration of peginesatide was acutely associated with higher risk of death or hospitalization as a result of cardiovascular morbidity or symptoms. Although this was not a randomized controlled trial, the results of this epidemiologic study were nevertheless of some concern.

Peginesatide received marketing approval in March 2012. Soon thereafter, the FDA started receiving reports of severe anaphylaxis. The FDA had required a phase 4 study that aimed at evaluating efficacy, safety, and logistics. Altogether 28 anaphylactic reactions were reported from this post-approval study containing about 20 000 patients (14). They all occurred within 30 minutes of peginesatide administration, and all were associated with first dose IV administration of peginesatide from multi-dose vials with preservatives. Due to these sADRs, the manufacturer voluntarily withdrew peginesatide from the market in February 2013. The rate of sADRs was high, and the fatal anaphylaxis rate was 1 per 2,500 peginesatide-treated patients.

Of major concern is whether these sADRs can be adequately managed. Patients received peginesatide within a well-controlled clinical environment, where adequate treatment was available and presumably given in a timely fashion, but this did not prevent the life-threatening or fatal outcomes.

Peginesatide was launched only in the US. The Japanese manufacturer did not apply for approval in Japan as no clinical trials had been conducted there. An application for a marketing approval was under review in the EU at the time of withdrawal from the US market. Soon after, the manufacturer withdrew the application after the EU regulatory authorities had evaluated the dossier and given a provisional opinion that the drug would not be approved due to safety concerns (11).

5. Expert Opinion

5.1. Peginesatide and lessons on pharmacovigilance

The case of peginesatide has widespread implications, particularly with respect to the safety of medicines in general and biologicals in particular.

The drug development process must provide information for informed decisions about potential risks and benefits. Drugs with a negative risk-benefit ratio are removed from the market, or possibly their use is limited for specific indications or populations most likely to benefit from them.

Pre-approval studies of most drugs include about 500 to 3000 participants for relatively short durations. These studies are designed to be large enough for demonstrating efficacy and

detecting common side-effects. However, rare sADRs are often observed only after the drug is administered to larger and more diverse patient groups.(15)

Regulators constantly monitor sADRs post-approval and report them to safety agencies in an effort to identify toxicities. Some countries have established separate safety registries for biologicals, others rely more on post-approval pharmacovigilance initiatives. These initiatives contain spontaneous reports, computerized claims or medical record databases, and formal post-approval studies. The purpose is to detect problems early so that cases such as the Eprex-induced antibody-mediated PRCA outbreak could be prevented (16). Root cause analysis of PRCA cases indicated that a post-approval formulation change led to an immunologic toxicity (neutralizing antibody formation) when the drug was administered SC. After changing the administration route from SC to IV, the rate of Eprex-induced antibody-mediated PRCA was reduced more than 95 %. Cold chain breaches have also been suggested as a cofactor in causing this toxicity (17).

During clinical studies conducted prior to FDA approval, six peginesatide-treated patients experienced a mild allergic reaction following the first drug dose but no severe anaphylaxis occurred. Post-approval sADRs differed from the study cases profoundly both in severity and in nature. The pre-approval cases were mild and mainly resolved in the dialysis unit. The post-approval cases included serious reactions requiring hospitalization, and led to life-threatening or fatal outcomes. Pre-approval safety problems of peginesatide concentrated on cardiovascular toxicity, and hypersensitivity was not considered to be of major concern by study investigators, the manufacturer, or the FDA. Only in retrospect it may be argued whether these mild reactions should have been seen as a safety signal. It is unclear whether no severe hypersensitivity reactions were seen in the pre-approval studies because of statistical reasons or because of other factors.

Peginesatide-associated anaphylaxis was detected only post-approval but these events were reported to the FDA quickly. The onset was sudden, facilitating clinical concerns that peginesatide was the likely causal agent. In addition, the phase 4 safety study required by the FDA sped up their detection. Prospective monitoring systems conducted in the context of pilot introductions of newly approved drugs may be a good method for identifying unexpected sADRs.

To date, the phase 4 peginesatide safety study is among the few such examples of successful early detection of sADRs. The strengths of this study included 1) prospective assessments conducted by manufacturer-employed nursing personnel, 2) extensive pre-study training, 3) weekly logistics meetings conducted amongst personnel at the limited number of sites participating in the initial phase of the study, 4) planned interim analyses conducted in order to identify efficacy, safety, or logistics concerns, and 5) an unplanned interim analysis conducted seeking to amplify a safety signal immediately after the initial severe hypersensitivity events were reported.

5.2. Peginesatide-associated anaphylaxis: possible causes

The causes of peginesatide sADRs are still under investigation. It is unclear whether this safety issue is related to the active drug itself, to the final product or batch, to a population at

increased risk, or a combination of these factors. Peginesatide sADRs have not been traced back to particular batches or breaches of cold chain storage protocols during shipping of peginesatide. Prior exposure to ESAs, demographic characteristics, and coexisting device or drug sensitivities have not been associated with the mechanisms of toxicity. However, CKD patients on dialysis are vulnerable with multiple cardiovascular co-morbidities, and this increases the risk of poor outcomes if such events occur.

Pegylation is one of the sADR causal factors that has been considered. A large clinical trial was recently terminated early due to anaphylaxis following IV administration of REG1, a novel anticoagulation system containing a synthetic pegylated anticoagulant (18). The authors acknowledged that allergic responses to polyethylene glycol moieties, such as that attached to pegnivacogin in the REG1 system, have been reported, although they seem to be rare.

Other possible causes for peginasatide anaphylaxis such as complement-mediated disease have also been proposed, although no published studies support these hypotheses. An interesting observation is that severe anaphylaxis has been associated with intravenous administration of peginesatide, iron, and REG1 (18, 19), while antibody-mediated pure red cell aplasia is exclusively associated with subcutaneous instead of intravenous administration of ESAs.(18, 20, 21).

Of note is that the drug formulation used almost exclusively in the peginesatide pre-approval clinical studies differed from the formulation which was administered in the post-approval setting. Efficacy and safety were tested in approximately 2300 patients prior to FDA approval using preservative-free single-dose vials, while only 40 patients received peginesatide from multi-dose vials with preservatives in a pharmacokinetic study. However, this study supported FDA approval of multi-dose vials with preservatives, and all post-approval use was with this drug formulation.

Some studies suggest that a drug interaction with phenols, one of the preservatives in the multi-dose vials, could be causally linked to the sADRs seen with peginesatide. Studies have reported significant release of histamine and the potential for mast cell activation (22), subvisible particles in the multi-dose vial formulation, and/or the potential for excessively rapid infusion of peginesatide to induce anaphylaxis (23). These insights provide support for a theory that the formulated vehicle, instead of the purified drug substance produced an anaphylactoid reaction due to direct activation of mast cells. Preapproval mild reactions were associated with preservative-free single vials, and instead, post-approval serious reactions occurred with peginesatide administered from multi-dose vials with preservatives. Could the change in formulation from a single-dose vial to a multi-dose vial with preservatives be the “straw that broke the camel's back?”

A slight formulation change without change in indications, duration of use, or route of administration rarely leads to new toxicities. However, altering the formulation of a drug may possibly lead to serious consequences. The cause of Eprex-associated PRCA was traced back to a changed drug formulation. The case of peginesatide also demonstrates how dangerous it may be to re-formulate a therapeutic agent (as a drug with preservatives in a

multi-dose vial) and then release it after FDA approval for general use based on safety findings from a very small pre-approval pharmacokinetic study.

5.3. Peginesatide and the future of ESAs

The development of peginesatide represents a triumph for translational science. The concept of a peptide mimicking a large protein many times its size, with no structural homology between the peptide and the protein, is truly remarkable, generated by the availability of candidate peptide libraries. There have, however, been massive hurdles for this novel peptidic ESA. Firstly, the original molecule (EMP-1) was not potent enough to continue development as a therapeutic agent. This hurdle was overcome by dimerizing a similar peptide, and attaching it to a pegylation chain via a space linker to create peginesatide. Phase 1 and 2 clinical trials of this molecule were successful, and a small trial in antibody-mediated PRCA induced by other ESAs showed remarkable efficacy. Unfortunately, phase 3 trials with the non-dialysis CKD population (PEARL) suggested possible cardiovascular harm in this patient population. Thus, the FDA accepted the more reassuring data from the EMERALD clinical trials and approved the drug only for use in hemodialysis patients.

The drug finally entered the market, only to be withdrawn less than a year later due to the discovery of unexpected sADRs. Clearly, the FDA had no choice but to endorse this decision. The hypothesis remains that if the drug was administered from single-dose vials without preservatives it could be an acceptably safe product. It is not known if the route of administration is also important. Testing this hypothesis would undoubtedly be high risk, although there is a real need for a new ESA that is safe and effective when administered to CKD patients who do not respond to high doses of the originator products.

Despite negative overall risk-benefit, peginesatide holds some important improvements over other ESAs, and because of them, it had hopes of being popular among physicians, patients and payers alike. First, as noted in pre-approval clinical trials, peginesatide use was not associated with any instances of antibody-mediated pure red cell aplasia (a distinction versus other ESAs). (5, 9-10, 24). A second potential benefit is the administration of peginesatide on a monthly schedule, facilitating high compliance compared with epoetin and darbepoetin. The cost is a third potential benefit, since the manufacture of this synthetic peptide by chemical techniques is considerably cheaper than the use of recombinant DNA technology. Mean cost savings have been estimated at 20% to 30% for peginesatide versus other ESAs. Peginesatide is no longer on the market, but the need for a long-acting synthetic ESA with less immunogenicity remains.

During its one year on the market, the uptake of peginesatide in the US dialysis setting occurred in a step-wise fashion with increasing numbers of dialysis centers converting to peginesatide from other ESAs. Altogether, about 25 000 patients used the drug (11).

The scenario of ESAs is becoming more and more complex. For example, the introduction of biosimilar ESAs presents new therapeutic options - but they may also bring new safety concerns about whether they will cause an increase in antibody-mediated PRCA.

What is the future of peginesatide? In the opinion of the authors, there is little doubt that the risk-benefit profile is favorable for patients with antibody-mediated PRCA, particularly if the drug is administered subcutaneously from a single-dose vial. Antibody-mediated PRCA carries a considerable burden of co-morbidity, as well as a dependence on regular blood transfusions with concomitant iron overload, and early mortality. In our opinion, the benefits of peginesatide in this setting definitely outweigh the risks.

It is uncertain whether peginesatide could be reincarnated under this guise, given all the regulatory and economic hurdles in developing a product for an extremely rare indication. If safety hurdles can be overcome, we believe that peginesatide would be warmly welcomed back into the therapeutic arena as the only credible option for antibody-mediated PRCA. However, it is important to continue investigation into the causes of peginesatide-associated anaphylaxis. Understanding the pathophysiology is essential as the findings have important implications for anticipating anaphylaxis that might occur with other pharmaceuticals.

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Drug summary box

Drug name (generic)	Peginesatide
Phase (for indication under discussion)	Voluntary withdrawal by the manufacturer from the United States market in 2013
Indication	Anemia treatment among adult CKD patients receiving hemodialysis
Pharmacology description/ mechanism of action	Peginesatide mimics the structure of erythropoietin and stimulates erythropoiesis in red blood cell precursors in a manner similar to recombinant ESAs
Chemical structure	Peginesatide is a synthetic dimeric peptide, attached to polyethylene glycol (“ pegylated”) by a unique space linker and composed of two 21 amino acid chains. The peptide structure shares no homology with first and second generation ESAs, erythropoietin and darbepoetin.
Pivotal trials	*A phase 2 study investigating whether peginesatide can stimulate erythropoiesis in CKD patients with PRCA due to antierythropoietin antibodies (5) *EMERALD 1 and 2 phase 3 studies evaluated the efficacy and safety of peginesatide in previously ESA-treated patients with anemia due to CKD on dialysis (9) *PEARL 1 and 2 phase 3 studies evaluated the efficacy and safety of peginesatide in patients with anemia due to CKD and not on dialysis or ESAs (10)