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ANAEMIA

The safety and efficacy of peginesatide in patients with CKD

Kai-Uwe Eckardt

Recently published data from four phase 3 safety and efficacy trials show that the synthetic peptide-based, erythropoietin mimetic, peginesatide, is noninferior to conventional erythropoiesis-stimulating agents in increasing haemoglobin levels in patients with chronic kidney disease (CKD). However, peginesatide therapy increased the risk of a combined cardiovascular end point in patients with CKD not on dialysis.

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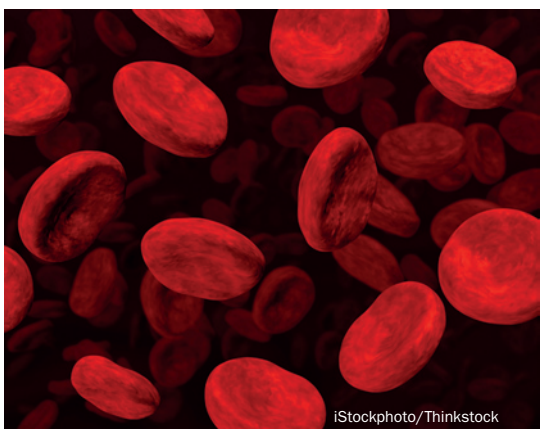
Erythropoietin serves as the main regulator of erythropoiesis through its interaction with erythropoietin receptors on erythroid progenitor cells; however, the functional relevance of erythropoietin receptors outside the bone marrow remains controversial. When recombinant human erythropoietin was developed for the treatment of renal anaemia, the structure of the endogenous molecule was mimicked as closely as possible to maximize the efficacy and specificity, and minimize the antigenicity of the agent. The subsequently developed erythropoietin derivatives, darbepoetin α and methoxy polyethylene glycol-epoetin β, have structural modifications that increase their duration of action (enabling longer dosing intervals) despite reduced receptor affinity. In 1996, investigators first reported that systematically derived small peptides that are structurally unrelated to erythropoietin can substitute for the complex glycoprotein and activate the erythropoietin receptor.[1] In March 2012, the synthetic, peptide-based, pegylated erythropoietin mimetic, peginesatide, was approved by the FDA for the treatment of anaemia in adult patients with chronic kidney disease (CKD) on haemodialysis. Findings from the phase 3 trial program that laid the basis for this approval were recently reported in *The New England Journal of Medicine*.[2,3] These data also explain why the current license is limited to patients with CKD on dialysis.

The trial programme consisted of four event-driven, randomized, controlled open-label trials that were designed to compare the safety and efficacy of peginesatide with that of conventional erythropoietin-stimulating agents (ESAs) in patients with CKD.[2,3] Two pairs of similarly designed studies were conducted in patients on haemodialysis (EMERALD 1 and 2; $n = 1{,}626$)[2] and in patients not on dialysis (PEARL 1 and 2; $n = 983$).[3] Patients on haemodialysis were switched from epoetin α or epoetin β to peginesatide once monthly or maintained on epoetin 1–3-times weekly, whereas those not on dialysis were treated *de novo* with either peginesatide once monthly or darbepoetin once every 2 weeks. In each trial, patients were randomized 2:1 to receive peginesatide; thus, approximately 1,700 patients were exposed to the new drug.

The studies showed that the efficacy of dose-adjusted peginesatide to increase and/or maintain haemoglobin levels in a target range of 110–120 g/l (PEARL 1 and 2) or 100–120 g/l (EMERALD 1 and 2) was noninferior to that of conventional ESAs; the curves of mean haemoglobin levels during 100 weeks post-randomization were virtually overlapping in all four studies.[2,3] Given the mode of action of peginesatide and the results of previous phase 1 and phase 2 dose-finding studies,[4,5] these data are reassuring but not surprising. Unexpectedly, however, in patients not on dialysis the incidence of the cardiovascular composite safety end point (comprising death from any cause, stroke, myocardial infarction or a serious adverse event of congestive heart failure, unstable angina or arrhythmia) was greater in those who received peginesatide than in those who received darbepoetin (21.5% versus 17.1%, HR 1.32, 95% CI 0.97–1.81).[3] The incidence rates of sudden death, unstable angina, arrhythmia and acute renal failure were also numerically higher with peginesatide than with darbepoetin in patients not on dialysis.[3] No such differences in the rates of safety end points were seen in patients on haemodialysis or in the combined safety analysis of all four trials.[2]

The reason for this safety signal and why it was observed only in patients not on dialysis remains unclear. Baseline differences between the group of PEARL participants who received peginesatide and those who received darbepoetin (including slightly older age and higher rates of diabetes and cardiovascular disease in the former group), might have conferred a higher cardiovascular risk to those on peginesatide.[3] However, adjustment for these imbalances could not fully account for the observed harmful effects of peginesatide. There was no evidence of a difference in blood pressure between patients treated with peginesatide and those treated with darbepoetin, nor was there evidence that haemoglobin excursions above the target range caused composite safety end-point events. As the study was open label, some of the combined end-point components could have been subject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to reporting bias, potentially resulting in a higher reporting rate in association with the novel drug. However, the end points were carefully adjudicated by an end-point committee who were blinded to drug exposure to minimize investigator bias.

> “...further clinical studies are needed to assess the long-term risks of peginesatide therapy...”

The fact that no increased cardiovascular risk associated with peginesatide therapy was observed in patients on haemodialysis although they received 2.5–3.0-fold higher doses of peginesatide than the smaller group of patients not on dialysis, could argue against persistent and relevant adverse effects associated with this new drug. However, it is well established that pharmacological doses of ESAs can be harmful and their risk–benefit relationships—particularly in patients not requiring dialysis—are far from unequivocal.[6] Increased risks of adverse events have been identified in patients with CKD targeted with conventional ESAs to haemoglobin levels at or above 130 g/l, but no association has been demonstrated with achieved haemoglobin levels.[7–9] This finding suggests that high ESA doses *per se* may contribute to adverse effects, presumably through their effects on extra-erythropoietic receptors. An important, albeit difficult question to answer is whether the interaction of peginesatide with extra-erythropoietic erythropoietin receptors differs from that of conventional ESAs. Investigation of downstream signalling from the various receptors is required to understand potential differences in mechanisms of action. In addition, further clinical studies are needed to assess the long-term risks of peginesatide therapy, particularly in patients with CKD not requiring dialysis. A limitation of the current, otherwise elegant study programme is that the drug was compared only to darbepoetin in patients not on dialysis, whereas only a comparison with placebo would enable the risk–benefit relationship of the agent to be established directly. The time for a placebo-controlled anaemia trial in patients with CKD not on dialysis might not have been ripe when the peginesatide phase 3 program was designed but the situation has since changed, particularly following the publication of data from TREAT,[9] and the unexpected safety findings of the current studies underscore the necessity for such an approach.

On the basis of the current data, peginesatide was approved in the USA for correction of anaemia in adult patients on haemodialysis but not for patients with CKD not on dialysis. Unfortunately, the advantage of less-frequent dosing with monthly injections would be more relevant in the latter patient group, as would the increased stability and reduced storage requirements of the erythropoietin-mimetic. Thus, as cost constraints increase, price might become the most important determinant of peginesatide use in patients on dialysis. In addition to the large group of patients on dialysis for whom peginesatide is an alternative treatment option, a very small group of patients exists for whom the novel approach of peptide-based stimulation of the erythropoietin receptor represents a true breakthrough. As the structures of erythropoietin-mimetic peptides are unrelated to that of erythropoietin, anti-erythropoietin antibodies do not cross-react with peginesatide. The agent thus provides an ideal rescue therapy for patients with anti-erythropoietin antibodies who suffer from pure red cell aplasia or less-severe forms of antibody-induced erythropoietin resistance.[6,10]

Note added in proof

On 23 February 2013, Omontys® (peginesatide) was recalled in the USA as a result of postmarketing reports of serious hypersensitivity reactions—including fatal reactions in approximately 0.02% of patients—that occurred within 30 min after the first dose of intravenous administration (http://www.fda.gov/Safety/Recalls/ucm340893.htm). Such reactions were not observed in the clinical trial programme.[2,3]

Competing interests
The author declares associations with the following companies: Affymax, Amgen, Bayer, GlaxoSmithKline, Johnson & Johnson and Roche. See the article online for full details of the relationships.

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ACUTE KIDNEY INJURY

Creatinine and AKI—through a glass, darkly

John R. Prowle

Pickering *et al.* report that unchanging plasma creatinine levels after resuscitated cardiac arrest can indicate substantial acute kidney injury (AKI) as confirmed by increased levels of AKI biomarkers and increased mortality. This finding illustrates the limitations of plasma-creatinine-based diagnosis of AKI in early critical illness.

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Important new data from Pickering and colleagues illustrate the limitations of plasma creatinine concentrations for the diagnosis of acute kidney injury (AKI) in the setting of critical illness.[1] To examine the effect of acute severe illness on plasma creatinine concentrations, the researchers applied a 2-compartment, variable