How erythropoietin transformed the lives of kidney disease patients

In The Journal’s latest article on landmark drugs, Jenny Bryan takes a look at erythropoietin alfa, which allowed people with advanced kidney failure to look healthy, go to work and exercise again.

In the early years of biotechnology, when there was more spin than substance to the claims of the fledgling industry, enthusiasts could point to just three marketed products from the massive investment. One of them was recombinant erythropoietin epoetin alfa (Epogen), marketed by Amgen — one of the few successful early biotech companies.

Epogen and subsequent erythropoiesis-stimulating agents (ESAs), as they are now commonly called, have transformed the lives of thousands of people with chronic kidney disease (CKD) by treating their anaemia. “Before erythropoietin, you always knew people had kidney failure when you saw them in the street. They were very pale, they had no energy and they couldn’t walk very far. Now, with their haemoglobin levels nearer normal, they can look healthy, go to work, and take exercise even when they have advanced disease and are waiting for a transplant,” explains Ashraf Mākhal, consultant nephrologist, Morriston Hospital, Swansea.

A century of discovery

In 1906, French researchers proposed that a humoral factor, which they called hemopoietine, was responsible for controlling red blood cell production.1 By transfusing a rabbit with plasma from one that had been bled, they triggered rapid production of immature red blood cells (RBCs) in the healthy animal. Other groups repeated and expanded on the research over the next 40 years, each time with similar effects and, in 1957, it was suggested that the kidney was important for controlling RBC production.2 However, it took another 20 years to confirm that the RBC-boosting substance, by now called erythropoietin (EPO), is produced primarily in the peritubular interstitial cells of the kidney and, to a lesser extent, in the liver.3 Purification of human EPO followed and, when the EPO gene was cloned,4 sufficient quantities of the substance could be produced for clinical studies in end stage renal disease.5,6

In one of the first studies in 10 patients with end-stage renal failure and anaemia, mean haemoglobin (Hb) rose from 6.1g/dl to 10.3g/dl following intravenous recombinant human EPO after each dialysis over a 12-week period.5 In another study of 25 anaemic patients with end-stage renal disease undergoing dialysis, dose-dependent increases in erythropoiesis were seen following recombinant EPO treatment, with 12 out of 18 patients who had required transfusions no longer needing them.6

Dr Mākhal explains that, before EPO, the treatment of anaemia in renal patients was a grey area and patients had Hb levels as low as 4.5g/dl, well below the normal 13–15g/dl. “We only treated patients if they had symptoms, such as chest pain or shortness of breath. If they had no energy, we gave them a blood transfusion, although that increased their risk of hepatitis infection and exposed them to antigens which reduced their chances of finding a suitable donor for transplant,” he says.

Expanding uses

First licensed in 1989, epoetin alfa was not an instant hit. With little experience of products produced from bacteria, physicians were concerned about safety.

But, as the number of patients treated worldwide increased, further types of recombinant EPO were introduced and prices began to fall, it became standard practice to treat renal patients’ anaemia more aggressively, and Hb levels were pushed closer and closer towards normal.
where some authorities have recommended avoiding EPO altogether and treating anaemia with intravenous iron instead,” says Dr Mikhail.

NIce guidance and the recently updated UK Renal Association guidelines recommend that ESAs should be offered to patients with CKD and anaemia, who are likely to benefit in terms of quality of life or physical function.10,11 The Renal Association also advises that ESAs should be used to avoid transfusion in patients considered suitable for transplantation.12 Both guidelines recommend maintaining Hb levels between 10.5 and 12.5g/dl.

Dr Mikhail explains that anaemia treatment should be carefully tailored to each renal patient, balancing the need for both ESA and IV iron treatment. He adds that, although there is no evidence that renal patients whose haemoglobin is naturally high have a raised mortality, problems seem to arise when large amounts of ESAs are needed to push up the Hb. Optimising the iron dose can help reduce the need for ESAs. “In the UK, we take an individualised approach. It would be fine to get the haemoglobin as high as 12g/dl if we are only using a small amount of EPO. But we’d be much more worried about someone who demonstrated resistance to EPO and required a lot of drug to get their haemoglobin even up to 10g/dl,” he says.

Biosimilars raise new questions

The arrival of biosimilar brands of recombinant EPO raised concerns about the effects of treating patients with products which, owing to the nature of biologically produced compounds, are similar but not identical to the original brand.12 The European Medicines Agency has published guidance on the testing of biosimilars, including recombinant EPOs,12 and the Medicines and Healthcare products Regulatory Authority has advised that prescriptions for all biological products should be written by brand name, so that automatic substitution of biosimilars does not occur when the medicine is dispensed.

“Biosimilar brands of EPOs are being used in a few renal units in England, but not yet in Wales, and everyone is being cautious about them until they are more widely used. The extra competition in the market should help to bring down prices, but the main concern is that, if you switch brands of EPO, you may get fluctuations in haemoglobin, and you could end up wasting money trying to sort things out. When we have more data in a few years’ time, we’ll have a better idea of where the biosimilars fit in,” says Dr Mikhail.

Other advances in EPO technology have included longer-acting versions that need to be injected less often and, most recently, the development of a synthetic peptide-based ESA called peginesatide, which is immunologically distinct from EPO. Dr Mikhail predicts that the product, which recently completed phase III trials, could be particularly useful for patients who have developed antibodies to conventional EPO brands. “In the short term, I can’t see any real move away from EPO, and it’s undoubtedly revolutionised the way we manage our renal failure patients,” says Dr Mikhail.

“By treating their anaemia effectively without transfusions, EPO has greatly increased the number of people with renal failure who are suitable for transplants. Without EPO, far more people would have to remain on dialysis, which is worse for them and much more expensive for the NHS,” he said.

References