New blood-boosting drugs aim to staunch renal anemia

For the nearly 90% of individuals with severe chronic kidney disease who suffer from anemia, the standard of care can be burdensome. Two or three times a week, these individuals must visit dialysis clinics to receive injections of epoetin, a recombinant version of the erythropoietin hormone that stimulates red blood cells to form. Although longer-lasting protein analogs of erythropoietin are available, the only one approved in the US—Amgen's Aranesp (darbepoetin)—still requires biweekly injections for individuals on dialysis.

Longer-acting agents for dialysis patients could be on the way, though. In December, a US Food and Drug Administration advisory committee voted overwhelmingly to approve peginesatide, the first once-monthly anemia drug for individuals on dialysis. The treatment requires fewer injections and also boasts a unique structure that helps it circumvent a rare yet serious complication of epoetin drugs. The regulatory agency expects to make a final decision before the end of March.

Although the $3 billion US renal anemia market has long been dominated by Thousand Oaks, California–based Amgen, which also makes the epoetin drugs Epogen and Procrit, the newer agent, peginesatide, was developed by the Palo Alto, California–based firm Affymax. Last year, two phase 3 clinical trials in the US and Europe showed that peginesatide is as effective as epoetin at maintaining target hemoglobin levels in patients on dialysis. The researchers excluded individuals not on dialysis from the trials because earlier data suggested that the drug increases their risk of death and heart disease for as yet unknown reasons.

Peginesatide, which Affymax is co-developing with Japan's Takeda, works much like epoetin in that it binds the erythropoietin receptor on red blood cell precursors in bone marrow to activate red blood cell production. But because the molecule contains a stabilizing polyethylene glycol chain, it is shielded from degrading enzymes and has a longer half-life, which means less frequent injections. Plus, peginesatide is a small peptide with a different structure than the native protein, which means it avoids a rare complication associated with epoetin: a small percentage of people who receive the medication develop antibodies against it that neutralize both the drug and the body's endogenous erythropoietin, effectively halting blood cell production and making their anemia worse. That peginesatide avoids this cross-reactivity provides "a huge advantage," says Michael Choi, clinical director of nephrology at the Johns Hopkins School of Medicine in Baltimore.

If also cleared by the European Medicines Agency, peginesatide will be the second once-monthly renal anemia drug available in Europe, joining Mircera, a continuous erythropoietin receptor activator developed by Switzerland's Roche. Mircera won European and US approval in 2007 but was subsequently pulled from the US market because it infringed on an Amgen patent.

A square peginesatide

Peginesatide, if approved, would be available only to patients on dialysis, who comprise 380,000 of the 26 million people in the US with chronic kidney disease. So, companies are working towards developing broader-reaching anemia therapies, too.

One such strategy involves gene therapy. For example, the US-Israeli biopharmaceutical company Medgenics is advancing a cell–based erythropoietin gene therapy, called Epodure, for predialysis patients. The treatment involves harvesting a sliver of tissue from beneath a person's skin, transducing it with an adenovirus engineered to express the gene encoding erythropoietin and then implanting the altered tissue back into participants several weeks later. In early clinical data presented in November at the American Society of Nephrology's Kidney Week meeting in Philadelphia, the company reported that treatment with Epodure provided more than six months of elevated hemoglobin levels in around half of the trial participants, with the longest effect maintained 30 months out from treatment.

By far the least intrusive therapy would be a pill to treat renal anemia, and San Francisco–based FibroGen is working toward that goal. The company has developed an oral drug that ramps up production of endogenous erythropoietin by stabilizing hypoxia-inducible factor 1α (HIF1α), a protein required for its expression. Although the company abandoned its first HIF1α stabilizer in 2007 after a study participant died of liver failure, preliminary results from an ongoing phase 2 trial look promising. In data announced at last year's Kidney Week meeting, the company's second-generation molecule, FG-4592, proved more effective and safer than the original.

Affymax

A vial disease: Peginesatide helps tackle anemia.

One lingering concern with FibroGen's approach is that HIF1α affects a number of biological pathways, not just the production of red blood cells. So, researchers are still waiting on longer-term data to gauge whether the molecule causes any "unintended or undesirable consequences beyond stimulating erythropoiesis," notes Jeffrey Berns, a nephrologist at the University of Pennsylvania Perelman School of Medicine in Philadelphia.

Still, the idea that individuals with anemia could one day replace injections with a pill is exciting, Choi says. "We're going to be waiting with bated breath."

Melinda Wenner Moyer

India opens malaria vaccine center

PUNE, INDIA — The news last year that the world's leading experimental malaria vaccine, known as RTS,S, was showing early promise in large-scale phase 3 testing reinvigorated the scientific community in its quest to control the devastating disease, which kills more than 1.2 million people globally each year according to the latest estimates (*Lancet*, **379**, 413–431, 2012). But, in addition to developing products such as RTS,S that protect against the clinical manifestations of malaria, researchers also hope to create vaccines that disrupt the parasite's life cycle. To that end, two Seattle-based nonprofits have partnered with India's Gennova Biopharmaceuticals to help make such a transmission-blocking vaccine a reality.

At a ribbon-cutting ceremony here at the Pune International Biotech Park on 30 January, officials from PATH's Malaria Vaccine Initiative (MVI), the Infectious Disease Research Institute (IDRI) and Gennova gathered to inaugurate a $7.9 million facility dedicated to manufacturing vaccines. PATH put up $3.5 million for the newly launched