Pulling the plug on the first gene therapy drug

May 2 2017, by Ricki Lewis, Phd

Glybera was the first gene therapy approved in the western world. It treats lipoprotein lipase deficiency.

2017 is supposed to be the year that FDA finally approves a gene therapy. But last week, the company behind the first approved gene therapy in Europe, uniQure.com, announced that it won't "pursue the renewal of marketing authorization" that expires October 25.

What happened? Is the move a setback for gene therapies in the pipeline? I don't think so.

Headlines echoed the news release from the Netherlands-based company:

- Biotech Firm Pulls Pioneering Gene Therapy Due to No Demand
- First Gene Therapy Ever Approved Calling it Quits
- The World's Most Expensive Medicine is Being Pulled from the Market

A $1.4 million drug doesn't seem to make sense, but I don't think seeking an immediate fortune was ever the intention for Glybera, used to treat an enzyme deficiency. DNA Science covered much of the story in New Miracle Drugs: What Would You Pay?

My book about gene therapy was published in 2012, the year that the European Medicines Agency (EMA) approved Glybera. I was certain that the first approvals in the US would come within, at most, three years. The book focused on what is now called RPE-mediated inherited retinal disease, but back in 2012 was Leber congenital amaurosis type 2. That trial has had spectacular results; phase 3 results haven't been published yet. Other candidates include two forms of severe combined immune deficiency (SCID-ADA and SCID-X1), two leukodystrophies (ALD and MLD), and perhaps forms of Batten Disease, Sanfilippo syndrome, or hemophilia.

The first clinical trial for gene therapy in the US began in 1990.

Glybera's roots reach back to a few years before that, to the laboratory of Michael Hayden at the University of British Columbia.

A rocky regulatory road

I'd heard presentations from UniQure scientists at meetings, and chatted with some of them when I had a table to sell my books at the Phacilitate Cell and Gene Therapy meeting in Washington, DC, in late January 2013. Because of the book, the editors of that month's print Scientific American, "The Future of Science" issue, had asked me to contribute a one-page piece on gene therapy.

At that meeting, UniQure's chief business officer, Hans Preusting, discussed Glybera's development. He and others readily acknowledged the high price, but stressed that the treatment could establish a vector gene-delivery system that would work, like a cassette player, for other indications. I envisioned a future facility into which different loaded gene therapy vectors could simply plug in, like those places where you get different flavors of frozen yogurt oozing from separate spigots.

Costs would eventually come down. Remember when hand-held calculators were stand-alone devices selling for $100?

Glybera treats what was then called lipoprotein lipase deficiency but is now also called familial chylomicronemia syndrome (what is it with changing disease names???). It causes extremely high blood triglyceride levels and, in some patients, recurrent excruciating abdominal pain. Rash and enlarged liver and spleen are also part of the picture. Some of the worst cases are in children and teens.

Existing triglyceride-lowering drugs are ineffective because the cause differs. So the only approach, nearly impossible to do, is to eat as little fat as possible. The gene therapy is delivered in 42 injections into leg

muscles, once, with a viral (AAV1) vector. The disease affects one in a million people.

The regulatory road, said Preusting, was "rocky. "We started the submission dossier at the end of 2009 and it was validated by EMA in January 2011." Milestone assessments brought hundreds of questions. "EMA and the Committee for Advanced Therapies (CAT) said the data were not convincing enough, due to the small dataset, to say there's a clinical benefit from Glybera. But it wasn't a unanimous decision, so they encouraged us," he said.

The company, then known as Amsterdam Molecular Therapeutics (AMT), went back to work and then refiled Glybera as an ultra orphan drug regulated for "exceptional circumstances" – the sickest patients. This time CAT approved it but the Commission for Medicinal products (CHMP) in humans still said no.

The number is much higher now of people with sight restored thanks to gene therapy. Credit: Foundation Fighting Blindness

Preusting provided the business view. "We were publicly traded in Amsterdam. The stock decreased by 50% after the first non-approval, and again after the second. In that moment in time we were a penny

stock. How do you finance a company with hardly any value? Fortunately we had very loyal investors. We took AMT off the stock market and founded a new company, private, UniQure."

Then, surprisingly, the EMA asked the CHMT to look at the data again – and when they did they saw clinical benefit for the 14 sickest patients out of an original 27, assessed by lowered frequency of pancreatitis attacks. Their lipid levels fell and they could eat foods they couldn't tolerate before. One patient even had a baby.

By July 2012, both CAT and CHMP were on board. "This was a major major event in the space of gene therapy, for the whole field," said Dr. Preusting.

By October, Glybera received final approval under exceptional circumstances with a five-year marketing authorization. Patients began treatment in 2014.

Since then, whether or not to test a gene therapy on the sickest patients has evolved to depend on the nature of a disease. For Glybera doing so led to approval, but in one publicized case in the U.S., two young daughters of well-connected Hollywood parents received gene therapy for a form of Batten disease when the younger child had not yet shown symptoms. For some gene therapy trials older children are too sick to meaningfully respond and yield useful information. Hannah Sames, whom I've written about many times, was just weeks from being too sick to have her gene therapy for giant axonal neuropathy last July.

Out of my element

Oddly, the folks at UniQure had read my one-pager in Scientific American, but had no idea I'd written a book about gene therapy. Based on that, they asked me to participate in Investor Day in midtown

Manhattan a year after I'd heard Dr. Preusting at the gene therapy conference, January 2014. I was to give a short, introductory overview of the "space," a term I usually associate with the final frontier.

I'm used to speaking at biology conferences, where the dress code is, er, casual. But a Wall Street crowd? I sent snaps of myself in business suits from the dressing room of Talbot's to the nice PR people for UniQure, and the powers-that-be shaped my presentation to cover the diseases in their pipeline. (Disclosure: I was paid.)

After the talks came the panel discussion, livestreamed. I was placed front and center, being the only XX, and was mortified when I wasn't asked a single question. But I was encouraged that many in the audience of investors were female scientists.

The conference focused more on the pipeline, such as hemophilia B and Huntington disease, than Glybera. But honestly I don't remember much about Investor Day, not because it was more business than science, but because when I was headed back upstate on Amtrak, my daughter called to tell me that just after I'd left, Bruce Springsteen and Bono had given an unannounced, free concert 2 blocks from the meeting!!! She had waited until my train was north of Poughkeepsie because she knew I'd leap from it.

The decision not to renew Glybera's marketing authorization is based on numbers, not safety or efficacy. It works, for the right patients. But costs for long-term surveillance and continuing clinical study proved prohibitive.

"Glybera's usage has been extremely limited and we do not envision patient demand increasing materially in the years ahead," the news release quoted uniQure CEO Matthew Kapusta.

According to Rare Disease Report, only one patient actually paid the $1.4 million for Glybera. About 500 people in Europe have the disease and 323 in the US.

My brief foray into the business side of gene therapy reaffirms that I prefer to view gene therapy's success through the lens of the kids I've reported on: Corey, the star of my book, who would be blind without gene therapy; Eliza, who is becoming more verbal since her procedure; and Hannah, who can sit unaided and pick up small bits of food. From gains like eyesight, to the ability to sing a nursery rhyme, gene therapy is on its way – despite the economic stumbles.

Gene therapy's time will come, and I hope it is soon.

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