PERSPECTIVE


UHDB TRUST

Patisiran's path to approval

Carlos Heras-Palou explains his part in making patisiran the first RNA-interference therapeutic available to people with rare diseases.

In 2004, after a few months of experiencing increasing pain in my hands and feet, I was diagnosed with hereditary transthyretin (hATTR) amyloidosis, a progressive degenerative disease. Following diagnosis, most people have a life expectancy of 3 to 15 years.

This rare condition, which affects about 10,000 people worldwide, is caused by the misfolding of a protein called transthyretin (TTR) that is produced in the liver and which normally carries both the thyroid hormone thyroxine and vitamin A in the blood.

At the time, I was 39, married with two children aged 1 and 2, and had my dream job working as a surgeon. After my diagnosis, I could not see how we would manage as a family if I had to stop working because the disease was affecting my hands. I was worried about telling my brother and sister, and the impact of the news on them and their families. The prognosis was very bad, but after a short period of despair, I felt I had to put up a fight even if I could see no chance of winning it.

I went to see Philip Hawkins, who was then clinical director at the National Amyloidosis Centre in London. At the time of my diagnosis, two treatment strategies seemed logical. The first was to find a molecule to stabilize TTR, prevent misfolding and stop abnormal proteins from forming. The second was to silence the gene that encodes TTR, to block production and halt the progression of the disease.

A liver transplant was one option to slow disease progression, because a transplanted organ doesn't produce the abnormal protein. Blocking production of TTR in the liver could deliver similar results. At the time, regulating or editing a gene was nowhere near possible. I didn't think anyone would invest a fortune to treat such a rare disease.

Researchers at Alnylam, a drug company in Cambridge, Massachusetts, founded in 2002 to develop RNA interference (RNAi) therapeutics, had mastered the technique of producing snippets of double-stranded RNA known as small interfering RNA (siRNA). They began to look for a disease model to test their laboratory discovery, ideally one with an unmet need, caused by a known protein, with a known, validated gene target, made in an organ to which a drug could be delivered, and for which gene-silencing would result in the reduction of a measurable biomarker. After discussion between the Alnylam research team and Hawkins, hATTR amyloidosis was chosen.

Within a year, the company was reliably manufacturing siRNAs. But these early molecules were plagued by a surplus of negative charges, making them prone to degradation. A delivery system had to be designed and tested — a task that proved more difficult than initially expected, taking 10 years in total. In a clinical trial, ALN-TTR01 was tested on a group of 32 people, but the drug lowered the level of TTR in the blood in only one person. Then a second carrier for siRNA was tried and seemed to work well — *in vitro* in a transgenic mouse model and in a phase I human study.

In 2013, my younger sister was also diagnosed with hATTR amyloidosis. She was offered a liver transplant or the option to enrol in the phase II trial of Alnylam's new drug: ALN-TTR02, also known as patisiran.

She was one of 29 people who received different doses of the drug. The results seemed spectacularly good for patients on the higher doses.

In the subsequent phase III trial, two-thirds of participants received patisiran and one-third received a placebo. I was one of the 225 people enrolled in that study, which ran from November 2013 until August 2017. The results were published in July 2018 (D. Adams *et al. N. Engl. J. Med.* **379**, 11–21; 2018) and found that the drug reduced TTR production by about 81%. The following month, patisiran was approved by both the US Food and Drug Administration and the European Medicines Agency (EMA). I was the patient representative at the EMA's meeting in London. It felt like a historic occasion. After 16 years of work and an investment of about US$3.5 billion by Alnylam into RNAi therapeutics, this was the start of a new era for people with hATTR. I was also a patient representative on the UK National Institute for Health and Care Excellence committee that decided in August to recommend that patisiran be used to treat damage to peripheral nerves due to hATTR amyloidosis.

Knowing that a drug exists that can stop the progression of a disease yet is not available to patients is extremely frustrating. Watching people get worse and die while a drug goes through the regulatory process is heartbreaking. But from a scientific point of view, it has been only 20 years since a new biological observation resulted in a drug being made widely available to patients. Twenty years is short from a scientific-development point of view. For a patient, it feels like a lifetime.

KNOWING THAT A DRUG EXISTS THAT CAN STOP THE PROGRESSION OF A DISEASE YET IS NOT AVAILABLE TO PATIENTS IS FRUSTRATING.

Hereditary ATTR amyloidosis is an autosomal dominant condition, which means there is a 50% chance of each of my children having the gene for the disease. The proportion of people who carry the mutation and show symptoms is variable for unknown reasons. In Sweden, for example, it is around 20%, and in Portugal around 80%.

But from my perspective, the future looks bright for people with hATTR amyloidosis and their families. We now know that there is an effective treatment and that our children will not have to go through the pain and anxiety of this devastating disease.

A new form of the drug under development can be injected subcutaneously once every three months, instead of the current intravenous infusion every three weeks. This is thanks to advances in the chemistry of stabilizing the RNA. In the future, many diseases currently without treatment will be easily managed by a yearly injection of a specific siRNA.

Fifteen years after my initial diagnosis I remain reasonably well, with a good quality of life. I continue to work as a hand and wrist surgeon and thoroughly enjoy my job, carrying out operations and teaching the next generation of hand surgeons. I feel fortunate to be one of the first people to benefit from this new class of drug.

There are 7,000 recognized rare diseases, and hundreds of them should be treatable with RNAi therapeutics. Everything is out there to be done, and everything seems possible. ■

Carlos Heras-Palou *is a hand and wrist surgeon at University Hospitals of Derby and Burton NHS Foundation Trust.*
e-mail: carlos.heraspalou2@gmail.com