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Will the floodgates open for gene therapy?

In a matter of days, a momentous event will occur: a gene therapy will, for the first time anywhere in the Western hemisphere, be available commercially with full marketing approval.

Towards the end of July, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the approval in the European Union of a treatment called Glybera (alipogene tiparvovec) from a small Dutch company, uniQure biopharma. Unless matters get untypically administratively complicated, it should be only a matter of days before the European Commission endorses this recommendation, making the approval official.

Admittedly, the event will probably not compare in terms of impact on the public's imagination with the first manned moon landing, the first test tube baby or even the sequencing of the human genome. But within its own limited firmament, the first gene therapy to be sold legally in Europe will be an affair of some significance.

Gene therapy enthusiasts are comparing Glybera's imminent approval to the US approval in 1986 of Orthoclone OKT3, the first monoclonal antibody (mAb) approved for use in humans. Back in those simpler times, enthusiasts then thought OKT3 would open the floodgates for a plethora of therapeutic antibodies.

And in a way, it did. But first there was only a trickle. The flood came much later. In that sense, the comparison between Glybera and OKT3 may well be appropriate. OKT3 was very much a prototypic antibody therapeutic. It was the first clinical product of the unpatented Köhler and Milstein technology that had been described some 11 years earlier. Researchers had developed mAbs against a vast range of targets and had already shown, preclinically at least, the exquisite specificity of many of them. Boosters of the technology fondly, and correctly, imagined a procession of mAbs for all sorts of conditions marching upon a market desperate for drugs targeting highly defined molecular markers. In the end, it did happen…only the timing was a bit wrong. The problem was, OKT3 sidestepped one fundamental deficiency of 1986 murine antibody drugs.

OKT3 was approved in an era when clinicians had not defined the limitations that the human-anti-mouse-antibody (HAMA) effect would impose on the use of mouse-derived antibodies. The basic problem seems obvious now: in response to mouse antigens, humans mount an immune reaction that tends, at the least, to severely limit repeated dosing of the same (or other) mouse antibodies. Not only that, but the immune response itself can be dangerous.

OKT3 conveniently circumvented this drawback because its target was CD3 on T cells, the binding of which leads to apoptosis. As a treatment for the suppression of organ transplant rejection, the murine mAb not only was used in patients who already were immunosuppressed but also was given as an acute treatment for the first 7 days after transplantation. Thus, neutralizing antibodies were not a problem. HAMA? SchmAMA! OKT3 was OK.

Glybera may be OK, too. It is a gene therapy for lipoprotein lipase (LPL) deficiency, an ultra-rare inherited disorder that affects no more than two people per million in the general population. Affected people can't break down fat and try to manage their disease by strictly limiting fat in their diet. That is difficult, leading to life-threatening pancreatitis in a high proportion of patients. Glybera addresses the underlying LPL deficiency through multiple intramuscular injections of an adeno-associated virus vector that delivers functional LPL genes to muscle cells.

Getting Glybera to market has been a struggle. The company that had started its development—a now-defunct Dutch startup called Amsterdam Molecular Therapeutics (AMT)—submitted its approval file in December 2009. The gene therapy protocol, which includes repeated administration of the functional gene and immunosuppression to prevent 'rejection' of the treatment didn't go down well with regulators.

After nearly two years of head scratching, see-sawing and scientific bureaucracy, the CHMP declared the treatment "non-approvable" in October 2011, causing AMT to halve its workforce to sit out the process. In February, as AMT was irreversibly bound for liquidation, Dutch investor Forbion put forward €6 ($7.5) million to found uniQure biopharma as a vehicle to acquire AMT's assets, including Glybera.

It subsequently became clear that there was some wiggle room that would allow Glybera onto the market. The CHMP recommended marketing authorization only under "exceptional circumstances," under which uniQure will have to monitor patient outcomes and feed the information straight to the European Medicines Agency.

Jörn Aldag, the CEO of uniQure (and before that the CEO of AMT), maintains that the approval of Glybera puts gene therapy "where [mAbs] were in the late 1990s, when they were just visible, but tiny." He predicts a "steep growth curve" (p. 807).

He may well be right. The relatively rich pipeline of gene therapy candidates already in human trials suggests there may be a surge in the number of gene therapies approved over the next few years.

What is less certain, however, is whether there will be a noticeable flood of patients treated. Many of the gene therapies in clinical development are treatments for very rare, single-gene deficiencies: Leber's congenital amaurosis, severe combined immunodeficiency, Wiskott-Aldrich syndrome and the like. Among these Mendelian disorders, the hemophilias—themselves hardly common conditions—represent a pinnacle of frequency. Even for these kinds of conditions, there may be HAMA moments in the future—potential immune attenuation of efficacy, safety issues related to constructs or vectors, not to mention competition from existing enzyme replacement therapies that have been available for many years. For more complex illnesses—and gene therapy is being explored for heart disease and cancer, too—it remains far from clear that the technical challenges will be quickly overcome.

So Glybera's approval is unlikely to augur a flood of gene therapy drugs for blockbuster markets that transform the drug business in the manner of mAbs. But even if gene therapies turn out to be nichebusters rather than blockbusters, their successful commercialization is a remarkable achievement nonetheless.