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Cost and availability of novel cell and gene therapies

Can we avoid a catastrophic second valley of death?

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During the past years, several advanced gene and cell therapies to target rare genetic diseases have demonstrated long-lasting efficacy: essentially "curing" severe and previously incurable diseases and returning patients to a normal life. These therapies are classified as advanced therapy medicinal products (ATMPs); a few of these have received marketing authorization in Europe and the USA, and more will conceivably follow in the near future (De Luca *et al*, 2019). Their success represents a milestone in medicine that 1 day might be compared with the discovery of antibiotics or the development of vaccines.

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As "advanced" implies, the development of these therapies from the research laboratory to clinical trials is a long and very expensive ordeal. Bringing an ATMP to the market takes years, often decades, and still has a high failure rate (Cossu *et al*, 2018). However, once a therapy is successfully out of this first, biomedical "valley of death" and approved for use, it frequently encounters a second, economic "valley of death" that prevents its use in patients. This problem needs a solution for medical, ethical and economic reasons; readers are also refereed to recent articles dealing with the same problem for haematopoietic diseases (Aiuti *et al*, 2022; Halley *et al*, 2022) or genodermatoses (Palamenghi *et al*, 2022).

The problem

Academies or charities who perform or fund basic and preclinical research generally do neither have the expertise nor the financial resources to conduct clinical trials that are necessary to obtain market authorization for novel drug or therapy. During the past two decades, academic scientists have therefore established collaborations with small or large companies or founded biotechnology start-ups to make the process economically sustainable. Nevertheless, the investments needed to of take an ATMP to marketing authorization are very high, not just due to the costs of running clinical trials but also the manufacturing costs of viral vectors and cellular products and the stringent standards imposed by regulatory agencies to ensure the safety and quality of these products. Moreover, the patient population who would benefit from these therapies is often very small, ranging from several thousand for less rare diseases such as haemophilia, to a few dozen for very rare diseases such as adenosine deaminase (ADA)-SCID immune deficiency or junctional epidermolysis bullosa (JEB).

This dilemma raises two main issues. First, in order to recoup the costs of research and development and production, companies demand a very high price for these therapies, ranging from several hundred thousand to few million euros per patient. This can cause long negotiations with or even rejection by National Health Systems (NHS) unwilling to cover the costs, even for a few patients.

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This led to the withdrawal of two efficacious and approved products—Skysona for adrenoleukodystrophy and Zynteglo for beta-thalassemia—from the European market. Bluebird Bio, the US-based biotech company that developed these products, could not negotiate satisfactory reimbursements for Zynteglo after approval, which meant that they had to negotiate reimbursement costs with each individual European state (https://www.biopharmadive.com/news/bluebird-withdraw-gene-therapy-europe-skysona/608666/). The tragic element is of course the patients who might have been benefitted from these life-saving therapies.

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Second, companies may decide to drop an approved ATMP, even when it is approved and even when a reimbursement policy has been negotiated, just because of insufficient economic return. This is the case particularly for rare diseases, given the very low number of patients. One example is Strimvelis®, a curative treatment for ADA-SCID and the first approved *ex vivo* gene therapy product in Europe (Ferrua & Aiuti, 2017). It was developed through a collaboration between GSK and the San Raffaele Telethon Institute of Gene Therapy in Milan and then transferred to Orchard Therapeutics (OTL; https://www.gsk.com/en-gb/media/press-releases/gsk-signs-strategic-agreement-to-transfer-rare-disease-gene-therapy-portfolio-to-orchard-therapeutics/). After a few patients were successfully treated, OTL recently withdrew the therapy from the market for commercial reasons (https://ir.orchard-tx.com/news-releases/news-release-details/orchard-therapeutics-extends-runway-2024-focusing-hsc-gene/). Glybera withdrew an approved gene therapy product for Type I hyperlipoproteinemia in 2017 after having treated apparently only one patient. On 24 November 2022, Valline Holding Srl decided to withdraw their financial support to Holostem, the company that developed Holoclar®, the first stem cell-based ATMP approved in Europe (Rama *et al*, 2010), and the successful combined cell and gene therapy of JEB (Hirsch *et al*, 2017; Kueckelhaus *et al*, 2021). At the time of writing, Holostem is in liquidation. These are just a few events, but there is a risk that further withdrawals will follow in a market that so far has seen very few AMTPs approved (Fig 1).

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If these problems cannot be solved, we have to face three dreadful consequences: patients who may have been saved from fatal diseases will die; companies may become discouraged from investing further work and money in Europe; and the whole field of ATMPs may collapse due to stagnation.

Other factors

There are a few additional issues aside from the commercial viability of ATMPs for rare diseases that need to be considered. First, whichever solution is proposed in the EU or the USA should be adopted internationally once differences in regulation and reimbursement procedures are settled, though these may take several years at best. Unfortunately, developing countries may remain excluded from accessing these therapies, unless patients travel to specialized centres in Europe or the USA to receive the therapy. This is a problem to be addressed once the initial issues are solved.

Second, when deciding on reimbursement, NHS should balance the cost of therapy against the cost of palliative, often expensive treatments over a long time. This can take from a few years in case of early fatal diseases, such as early-onset neurodegenerative diseases and some forms of epidermolysis bullosa (EB), up to decades for diseases such as haemophilia, muscular dystrophies or several genodermatoses. Moreover, NHS should consider the economic value of returning a patient and her/his family/caregivers to a normal, productive life. Finally, and most crucially, the mission of NHS is to provide to all citizens the best treatment available, not the cheapest. The burden on the general health budget would be necessarily negligible for very rare diseases and still tolerable for less rare diseases. Once (and if) these therapies became available for treating common

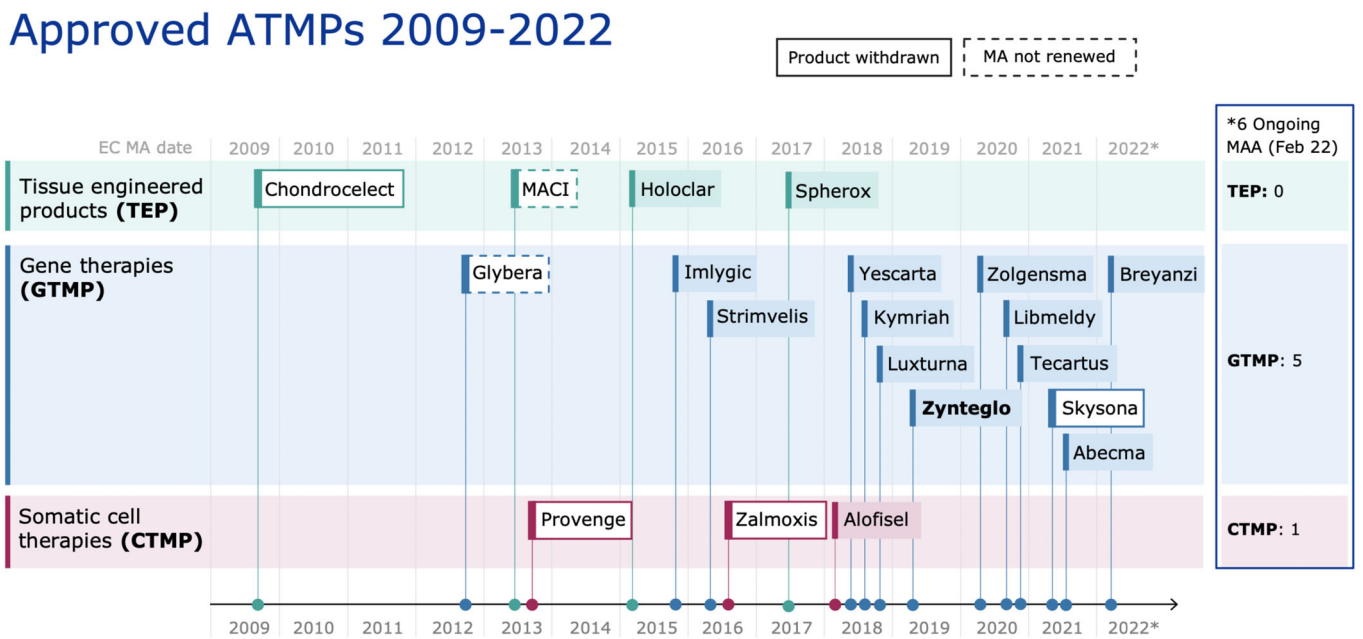

Figure 1. Overview of approved ATMPs from 2009 to 2022, including those that have been withdrawn or not renewed.
Source: https://www.ema.europa.eu/en/documents/presentation/presentation-awareness-raising-development-evaluation-atmps-pcelis-ahidalgo-simon-ema_en.pdf

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conditions, such as diabetes or cardiovascular diseases, economies of scale would enable companies to make a profit even with substantially reduced prices.

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Third, ATMPs require rigorous and independent controls regarding safety and efficacy as a requisite for marketing approval. In 2014, the EMA approved conditionally—that is, requiring additional confirmatory data postapproval—Ataluren, a small molecule causing the skipping of premature termination codons in Duchenne Muscular Dystrophy (https://www.ema.europa.eu/en/medicines/human/EPAR/translarna). Two years later, NICE recommended the reimbursement of Ataluren at an estimated cost of 314,300 GBP per patient per year (https://www.fdanews.com/articles/176326-nice-recommends-reimbursement-for-ptc-therapeutics-translarna) even if evidence of efficacy was scarce, the approval was controversial and followed by inconclusive results in a phase III trial (McDonald *et al*, 2017).

Finally, profit is the reason d'être for companies and it would be disingenuous to expect them to prioritize patients over profit as this would risk economic unsustainability. This holds true for both smaller biotech firms and large pharmaceutical companies with a broad range of products. However, large pharma could more easily shoulder a lower price tag for an ATMP or use the fact that it provides an effective cure for an incurable disease when negotiating the price structure of a broad portfolio of drugs with regulatory authorities. By contrast, the portfolio of small companies may be limited to treatments for a few rare diseases, and their financial sustainability depends entirely on securing a substantial profit from its sales. A high price tag would reward innovation and promote the development of new treatments for orphan diseases. Nonetheless, and given their strict dependence on the success of only one or few products, authorities should carefully scrutinize their clinical development plans and lobbying strategies. For instance, although patients' associations should be involved in making decisions about new therapies, patients and their parents are also at risk of manipulation. Indeed, FDA investigations have revealed irregularities and misconduct in several clinical trials (Dal-Ré *et al*, 2020), which blurred the boundaries between genuine drug companies and unethical private stem cell clinics (Cossu *et al*, 2020). Generally, regulation and oversight should prevent the approval of unproven and uncontrolled therapies (Sipp *et al*, 2017) or fraud such as the Stamina case (Abbot, 2013).

Possible solutions

There is no magic bullet that could solve this problem, but there are possible measures that governments, NHS, academics, regulators, patient associations and companies could agree on.

First, the development of a new ATMP is usually supported by public funding, whether from governments or charities, for preclinical development and sometimes even early-phase clinical trials. It is usually at this stage where companies step in, and it is here that the trials sponsor begins to communicate and negotiate with regulatory authorities the level of safety, efficacy and quality, and costs. More transparent planning, a clear roadmap agreed upon by all parties and starting the negotiations for the price at an early stage should result in a reimbursement plan that would stand a higher chance to be accepted by various NHS once the therapy has been approved.

Second, if, for commercial reasons, no company takes up the clinical development or if a licensor company decides to halt the development of a clinically safe and efficacious product for which there is no alternative satisfactory treatment, then supranational entities or national governments could step in and support academia or charities to ensure further clinical development, register and patient access. We were therefore pleased to learn that a recent initiative, AGORA, intends to increase access to life-saving gene therapies (https://www.gosh.nhs.uk/news/euro-group-to-boost-access-to-life-saving-gene-therapies/). Nonetheless, a lot of work remains to be done. To circumvent the bottleneck of GMP production, government-sponsored or academic GMP-grade facilities are needed. Some of these could eventually be qualified to produce and administer cell or gene products on a regular basis upon approval, with regulatory authorities involved to minimize costs and to ensure safety. Yet, there are two problems with this solution: implementing such a strategy will take many years even under the best scenario while children remain without a life-saving therapy since tomorrow; and such schemes and facilities will have to rigorously select only efficacious and promising therapies to prevent anyone from "jumping on the bandwagon," claiming efficacy for their product.

"To circumvent the bottleneck of GMP production, government-sponsored or academic GMP-grade facilities are needed."

We present here just a possible solution to prevent the second valley of death for advanced and life-saving therapies. Of course, it will require more discussions and in-depth evaluation by experts from across sectors to modify and implement such a scheme—or even replace it by a more efficient alternative. It is, nonetheless, a much-needed starting point for discussing and eventually addressing the problem that thousands of patients cannot be cured for merely commercial reasons.

Disclosure and competing interests statement

MDL is a cofounder and member of the Board of Directors of Holostem Terapie Avanzate, Srl, Modena, Italy, and a consultant for J-TEC, Japan Tissue Engineering, Ltd.

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