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Perspective

Juggling between the Cost and Value of New Therapies: Does Science Still Serve Patient Needs?

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Abstract: Thalassaemia International Federation (TIF), representing the united voice of people with thalassaemia and their families globally, has been striving for more than three decades to empower research, by academic communities and industry, to focus on developing a safe and effective curative approach for thalassaemia. Such a cure would lead to new lives with equal opportunities and challenges, as for every other person not suffering from a severe chronic disease. A gene therapy product was finally authorised in May 2019 by the European Medicinal Agency, thus marking a milestone in the history of the disease. However, after this conditional authorization, everyone focused on numbers and opted for cost of illness and cost-effectiveness studies, inadmissibly ignoring patients' voices and needs. The product was finally withdrawn from Europe, despite the fact that all implicated stakeholders, including governments, academia and industry always knew that an innovative and complex therapy would be expensive but always supported and fought for its development. In this article, TIF expresses its view on this issue, including some thoughts on how to address the high cost of innovative therapies.

Keywords: thalassaemia; gene therapy

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Decades of hope for a cure vanished into thin air when cost outweighed the value of the first gene therapy for thalassaemia and obliged the manufacturing company to withdraw it from Europe. This may indeed create a precedent for other curative therapies that are currently in the pipeline after many decades of research, raising questions over their future acceptance by those who pay for them, and the fulfilment of their purpose: to cure as many patients as possible.

We, the Thalassaemia International Federation (TIF), representing the united voice of people with thalassaemia and their families globally, have been striving for more than three decades to empower research, by academic communities and industry, to focus on developing a safe and effective curative approach for thalassaemia. When gene therapy marked a historical milestone in the history of the disease [1], we expected a more humane approach by governments, healthcare funders and the industry, and not a series of financial studies that have shattered the dreams of hundreds of thousands of patients globally [2]. If

the developed countries of Europe cannot afford an innovative therapy, what will happen to low- and middle-income countries, where the 80% of the global thalassaemia population lives? More importantly, how can we prevent a detrimental domino effect from ensuing?

In the 1960s and 1970s, physicians started using haematopoietic stem cell transplantation (HSCT) to cure patients with genetic disorders, including thalassaemia. Despite the successful implementation of this approach in both developed and developing countries, and the long and ongoing efforts for further improvements, the limitations for successful outcomes remain the same, i.e., HLA-identical sibling matching and young age [3]. Therefore, the global patient community has been promoting for years the development of another therapeutic approach that could bypass the challenges of HSCT, covering more patients and of a larger age span. Gene-based approaches were those promising to make the dream for a final cure come true. It is very well remembered by all of us involved in the care of this disorder that all reports, conferences and the work of every national patient association in every country across the world and especially of TIF focused on this topic, that reflected one of the most important expectations of patients: better health and quality of life. All patients have been living with this dream and have grown with this hope.

Research on genome-based therapies has been undertaken by many eminent researchers for decades now [4,5]. The journey to find an effective and safe cure was difficult and immensely challenging, with a number of failures on the way, which disheartened and disappointed both patients and scientific communities, until there was finally light at the end of the tunnel a few years ago. This light raised hopes and expectations amongst patients and led TIF to work very committedly with every single scientist, academic, research group and industry expert that focused on such innovative approaches, including the team of the US-based biotech company bluebird bio that undertook the improvement of the vector produced by Leboulch in 1994. Thalassaemia is a debilitating disease with a significant impact on patients' quality of life. Frequent transfusions, chronic pain, inability to concentrate, absence from school and work, discrimination, mental health issues are just a few of the daily challenges of patients. Standard care that includes lifelong regular blood transfusions, iron chelation therapy and multidisciplinary care has achieved an increase in life expectancy [6,7]. But what about those other unmet needs?

With a view to providing patients with accurate and reliable information regarding the safety and effectiveness of this novel therapeutic approach, TIF produced a wealth of educational material on gene therapy and organised a series of events across the world, paving the way for patients to claim their inalienable human rights to life, health, education and work.

The gene therapy product of bluebird bio, called Zynteglo^{TM}, was finally authorised in May 2019 by the European Medicinal Agency. In the minds and souls of the global patient community, after decades of fighting for a curative approach, there has never been any discussion on the cost effectiveness of such approaches versus the standard of care. Their only focus and wish was to reach a day when science could provide a safe cure for their disease and serve its purpose, i.e., to serve human needs. Such a cure would lead to new lives with equal opportunities and challenges, as for every other person not suffering from a severe chronic disease, although a small proportion of the patients, based on TIF's work and gene therapy specific surveys, still express their determination to 'stay on' their standard care as provided in their country. Coming out of their life-long dependency on medications, transfusions and medical treatment has always been and still is however the majority's dream. Certainly, gene therapy comes with some risks that need to be considered, including toxicity of conditioning regimen, failure to reach complete independence from blood transfusion in a minority of cases, durability of the effectiveness of the treatment and need for lifelong specialized medical care. Risks and concerns that were well conveyed to the patients and their families through TIF's specific educational programmes.

Our deep concern is that all stakeholders always knew that an innovative and complex therapy for beta-thalassaemia would be expensive but always supported and fought for its development. Governments and academia provided research grants, the industry invested

in the product's improvement, healthcare professionals and patients monitored the pipeline and hoped for access to Zynteglo^{TM}. When the European Medicines Agency granted Zynteglo^{TM} a conditional market authorisation, everyone focused on numbers and opted for cost of illness and cost-effectiveness studies, inadmissibly ignoring patients' voices and needs. This is because no study and no health economist would ever capture, truly and accurately, the real cost of thalassaemia in terms of pain, uncertainty, fear and quality of life.

As patients, we strongly condemn this shift of focus that does not reflect decades of discussions and efforts and our willingness and struggle to have the choice of access to any treatment that would improve our quality of life and needless to underscore the need for whom, consequent to various medical challenges, this treatment may constitute their only solution for survival. We condemn this discriminatory behaviour against us, given that patients in other disease areas already receive experimental therapies bearing a hefty price tag. The withdrawal of an authorised gene therapy from Europe will most probably slow down or even halt the access of people with thalassaemia to curative approaches, rendering the future of thalassaemia treatment gloomy at the very least. Depriving patients of a chance to be cured is, at minimum, unethical.

Moreover, if governments want novel therapies to remain on the shelf, why invest in them? Why encourage researchers to focus on their discovery and improvement? We are fully aware of the fact that countries do not have unlimited funds and financial resources. That is why a number of countries, in the European Union for example, opted for joint procurements in the context of regional alliances, such as the Valletta Declaration or the BeneluxA initiative. Such alliances would increase their negotiating powers for the purchase of expensive medicines and therapies, making them available to every patient in need.

Therefore, what is of utmost importance is for all interested stakeholders, and especially the industry and the academic teams engaged in the development of medicines, to seek and be engaged in early and transparent dialogue, from early drug discovery to preclinical studies, clinical development, regulatory review and finally post-market monitoring, with the aim to identify safety and cost hurdles early on and render costly therapies affordable and accessible to funders and patients, respectively.

Moreover, the developers of medicines, after having invested considerable amounts of money in developing and commercialising a product that addressed a rather rare disorder in the EU, should not be left exposed to failure but be given the necessary space, time and adequate motivation to mitigate problems, whether regulatory or with regard to market access, and eventually make their product available to as many patients as possible.

The process that sets the price for an advanced medicinal product such as Zynteglo should ideally be transparent and involve all implicated stakeholders, including patients. In this context, a centralized European mechanism would strengthen patient positions and perhaps the revision of the pharmaceutical strategy and not only, in the EU, along with multiple other initiatives from relevant bodies will contribute significantly to the investigation and identification of other ways to strengthen and safeguard access to such innovative and, by definition, costly treatments, including new pricing methods and evaluation of the real cost. Additionally, a central, special fund on innovative therapies should be created and managed by the European Commission. Such a fund could be a viable solution, or part of a solution to support and compliment national funds and allow Member States to provide their patients with novel therapies. Setting criteria on which innovative therapies should be covered by a central fund and on how such a fund will be funded is a crucial but very complex discussion that obviously falls outside the scope of this article.

Governments need to act more proactively, develop synergies and discuss pricing early on, taking into account the lessons of the past and the challenges to come. Attending physicians, along with patients, should become actively and meaningfully involved in the development process from the very early stages in order to be proactive and ready to

provide concrete information to their competent national authorities including the potential number of patients that could benefit from the different authorised innovative therapies as well as the short-, medium- and long-term plans for the access of eligible patients to such therapies, thus facilitating the national efforts of decision makers acknowledging the concerns and obligations of Governments to safeguard the sustainability and resilience of the health care systems and the fair distribution of funds across diseases.

Given the fact that Zynteglo requires a sophisticated infrastructure that apparently restricts its use to few specialized centres, European and national regulations regarding the eligibility of centres add a further level of complexity. Thus, simplifying such bureaucratic procedures could potentially lower costs and hurdles for the adoption of this and other similar therapies.

Besides patients and patient organizations, all implicated stakeholders, including physicians, researchers, healthcare authorities, funders and pharmaceutical companies, should be involved in the discussion on how to provide access to novel costly therapies. In this context, TIF often organizes workshops engaging all implicated stakeholders in discussing different topics concerning the optimal care of patients with thalassaemia and other haemoglobinopathies.

Health policy makers, health insurance authorities and healthcare funders certainly need to consider the competing needs for access to expensive therapies by different patient groups and prioritize resource allocation accordingly. Finding a compromise among patient needs, public interest and pharmaceutical industry interest is a challenging equation to solve. The issue is further complicated by the fact that the cost of similar or comparable therapies may be quite diverse among different indications or diseases or even different countries. The model of "payment for outcome" endorsed for other similar treatments such as chimeric antigen receptor (CAR)-T cell therapy for malignancies, according to which if a treatment fails, the pharmaceutical company does not receive the full sum but only a portion, could be a fair way of lowering the cost of innovative therapies and help convince healthcare funders to endorse these therapies. Although such a paying model proposed by the Zynteglo producing company to the EU countries was not well received.

We should bear in mind that everyone has a role to play and that we all share the same responsibility for the sad decision of bluebird bio to withdraw its services (even temporarily) from Europe. No government, industry or academic/regulatory body has the right to deprive patients of their choice or even more importantly their need to have access to an innovative curative therapy. This is a huge and unacceptable violation of human and patients' rights endorsed for decades now by relevant EU and international bodies.

Life cannot be measured using mathematical models. We thus strongly believe that science needs to be available, accessible and most importantly, at the service of patient needs.

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