Superdrugs & Supertherapies: High prices to pay for miracles…

Editorial Article

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Today, in Istanbul and other parts of our country, at bus stops, metro stations and on various street corners, we can hear the heartbreaking cries of parents of children with SMA (Spinal Muscular Atrophy) Type-1 seeking financial resources for exorbitantly priced treatment. In fact, this is a gene-based life-saving treatment that is effective in pediatric patients under two years of age with just one dose. This miraculous treatment costs patients approximately $2.1 million. This miraculous treatment costs patients around $2.1 million. But that is not all, and it is not the most expensive either, there are others worth mentioning.

After a rocky start, gene therapy is on fire and drawing intense interest from the biopharmaceutical industry—and it's still evolving and improving. In fact, the journey of fundamental developments in gene therapy begins with the discovery of the DNA structure by Watson and Crick in the year of 1953. The concept of gene therapies first emerged in the 1960s, when the feasibility of adding new genetic functions to mammalian cells began to be studied. Several methods for this purpose were tested, including injecting genes directly into a living mammalian cell via a micropipette and exposing the cells to a DNA precipitate containing the desired genes. Later, scientists developed theories that viruses could also be used as a vehicle or vector to deliver new genes to cells. Among the avenues of biomedical sciences, humanity's fast lane, but hard journey to gene therapies began in the 1990s. There are various versions of gene therapies forming different highways to arrive final destination of therapy. But unfortunately, some of these highways of gene therapies have turned into dead-end streets:

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- Gene therapy ver. 1.0 - First introduction of corrected genes
- Gene therapy ver. 2.0 - Improved viral vectors
- Gene therapy ver. 3.0 - Gene editing and base editing
- Miscellaneous genetic therapies

Gene therapy ver. 1.0 - First introduction of corrected genes: Seemingly, the first successful example of gene therapy was obtained with a 4-year-old girl in 1989. The girl, Ashanthi de Silva, who was the hero of the first successful gene therapy was born with severe combined immunodeficiency (SCID), a disease caused by a deficiency of the enzyme adenosine deaminase (ADA). Without ADA, T cells were dying and not be able to fight invading infections. Injections of a synthetic ADA enzyme were being helpful only temporarily. This application, which seemed like a success at first glance, encouraged scientists on the subject and they applied gene treatments for various genetic diseases. After a few years of gene therapies using this methodology have been reported to cause very severe side effects, including leukemia, fatal immune responses, which were mainly due to activation of some oncogenes by viral vector used. Gene therapies which use this technique have been stopped.

Gene therapy ver. 2.0 - Improved viral vectors: In the early 2010s, gene therapy was in a renaissance age. Scientists discovered improved viral vectors to deliver genetic therapies. They also added some regulatory elements called promoters and enhancers to direct the activity of genes. These elements were defining where, when, and at what level the genes should be turned on. Popular viruses for gene therapy include adenoviruses, adeno-associated virus, and lentiviruses. Agustín, born in 2010, had suffered from X chromosome-linked severe combined immunodeficiency syndrome (SCID-X1) and had spent the first few months of his life in isolation. He became the first patient to receive gene therapy with improved viral vector at Boston Children's and today is an active fifth-grade soccer and tennis player.

Gene therapy ver. 3.0 - Gene editing and base editing: While traditional gene therapy uses viruses to transfer healthy genes into cells, compensating for a faulty or missing gene, this newer generation of gene therapy employs various fine-tune molecular tools and divided into two methodologies: a) Gene editing b) Base editing. Gene editing precisely target troublesome genes and create a cut or break in their DNA. It can knock out a defective gene, place a new DNA sequence, or both in a "cut and paste" operation. The common gene editing systems of today are CRISPR/Cas 9, zinc-finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs). Base editing is even more

fine-tuned, specifically replacing DNA bases found in defective genes. It takes advantage of CRISPR's targeting capabilities but relies on specific enzymes to chemically alter a gene's code one by one—changing a C to a T or an A to a G, for example. In contrast to gene editing, base editing has not yet been tested in clinical trials, but it offers the promise of more precision, efficiency, and safety.

Miscellaneous genetic therapies: Some other new techniques are blurring the line between gene therapy and conventional drug treatment. For instance, antisense oligonucleotides (ASOs) are new type of drugs consist of short, synthetic pieces of DNA or RNA that aim at the messenger RNA made by the defective gene. As another approach, RNA interference, uses small RNAs for silencing a targeted gene by neutralizing the gene's mRNA. The messenger RNAs (mRNA) and the microRNA (miRNA) used for some COVID-19 vaccines are regarded as a form of gene therapy too. This RNAs introduce genetic code that cells then use to make the coronavirus spike protein, stimulating people to produce antibodies to the virus.

Today, there are approximately 400 gene therapy studies worldwide on ClinicalTrials.gov and more than a dozen approved gene therapy drugs on the market. It is only a matter of time before newer ones enter the pharmaceutical market. These products related to this issue, which will shape the future of pharmacy and medicine, are called "super drugs". These drugs, which are the products of advanced biotechnology, have been developed for the treatment of diseases that are currently fatal, and some of them offer a definitive solution to diseases with a single dose of miraculous treatments. However, these are not only miraculous ones but also the most expensive therapies known in medical/pharmaceutical market. Here is a summarized list of most expensive drugs in US, and most probably in the world:

1. Lenmeldy®: Cost: $4.25 million per one-time treatment, Use: Metachromatic leukodystrophy (MLD), FDA Approval Date: March 18, 2024 (Gene editing therapy)

2. Hemgenix®: Cost: $3.5 million per one-time dose, Use: Hemophilia B, FDA Approval Date: November 22, 2022 (Improved virus vector-based gene therapy)

3. Elevidys®: Cost: $3.2 million per one-time dose, Use: Duchenne Muscular Dystrophy (DMD), FDA Approval Date: June 22, 2023 (Gene editing therapy)

4. Skysona®: Cost: $3 million per one-time dose, Use: Cerebral Adrenoleukodystrophy (CALD), FDA Approval Date: September 16, 2022 (Improved virus vector-based gene therapy)

5. Zynteglo®: Cost: $2.8 million per one-time dose, Use: Beta-thalassemia, FDA Approval Date: September 16, 2022 (Improved virus vector-based gene therapy)

6. Zolgensma®: Cost: $2.1 million per one-time dose, Use: Spinal Muscular Atrophy (SMA) Type 1, FDA Approval Date: May 24, 2019 (Improved virus vector-based gene therapy)

7. Myalept®: Cost: $1.3 million annually, Use: Lipodystrophy / Leptin deficiency, FDA Approval Date: February 24, 2014 (Leptin replacement therapy)

8. Danyelza®: Cost: $1.2 million annually, Use: Neuroblastoma, FDA Approval Date: November 25, 2020 (Monoclonal antibody therapy)

9. Zokinvy®: Cost: $1.2 million annually, Use: Progeria and Progeroid Laminopathies, FDA Approval Date: November 20, 2020 (Enzyme inhibitor)

10. Kimmtrak®: Cost: $ 1.1 million annually, Use: Uveal Melanoma, FDA Approval Date: January 25, 2022 (Immunotherapy).

The first six drugs on the list of the most expensive drugs are gene-based therapies. Another feature of some of these therapies is that they are specifically designed for each individual. This situation also causes the prices of some gene-based treatments to become uncertain. Whatever it is, these drugs are game changer in their characters and promise better management of certain fatal diseases. That is not all, there are also engineered cell therapies approved for certain indications, mainly CAR-T cells.

It is anticipated that gene and cell-based treatments will diversify and increase in the future, and even cloned organs will be used for treatment purposes. It is said that these future drugs and treatments could extend human lifespan to 150 years. However, it is also obvious that these will create very important socio-economic and scientific problems. First, how will access be made to medicines that are economically difficult to access even today? Experts on the subject suggest that prices may fall over time as technology becomes more widespread and advanced. However, there is no glimmer of hope in this regard yet. What if more advanced treatments emerge that cost more than what we have today? Moreover, it is known that many countries in the world have reduced or even eliminated drug/treatment reimbursements in order to reduce healthcare expenses. Fearing that in the future, the world will be one where only the rich can live longer and more quality lives. Second, this situation will also lead to striking demographic changes in the world population. How will these demographic changes in the world population affect today's environmental and

climate problems? Third, what will happen with these treatments in terms of side effects and unexpected effects in the longer term? Finally, it is obvious that developments in this field will cause radical scientific changes in the fields of pharmacy and medicine.