WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Advances in Gene Therapy for the Treatment for Genetic Diseases

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ABSTRACT:

Gene therapy shows promise as a treatment approach that seeks to fix or substitute genes with healthy Ones to prevent and manage genetic disorders. It explores a range of methods, for gene delivery including vectors, Physical and chemical approaches, and cutting-edge technologies like artificial chromosomes. Tools such as CRISPR Cas9 have made genetic modifications more precise and efficient. Approved gene therapies for conditions like Leukaemia, inherited diseases, and spinal muscular atrophy highlight the progress in this field. Despite its benefits, gene Therapy faces challenges related to costs, regulatory hurdles, ethical considerations, and ensuring long-term safety and Efficacy. Notable treatments like Kymriah, Luxturna, Upstaza, Skysona, Viltolarsen, Zolgensma, and many more Demonstrate how gene therapy can enhance outcomes. The field is rapidly evolving with research focusing on improving Techniques, broadening applications, and increasing accessibility of these groundbreaking treatments. Collaboration Among researchers, healthcare professionals, government bodies, and private sector entities is essential for realizing the Impact of gene therapy, on healthcare.

Keywords: gene therapy products, hereditary disorder, drugs, management, mechanism of action.

1. Introduction

Gene therapy is a promising treatment strategy that aims to repair or replace defective genes with healthy genes to Prevent and treat genetic diseases. There are over, 7000 genetic diseases affecting more than 350 million children Globally, while treatment is available only for 5% of these diseases. [1]. Breakthrough events in this field are marked by the first successful clinical trial in the 1990s and the approval of Glybera in 2012 [2]. Gene therapy shows promise in treating a diverse array of diseases, from muscular dystrophies and neurological Disorders to blood conditions and rare genetic disorders. By delivering functional copies of faulty genes, this approach Has the potential to treat previously uncurable conditions [3]. In recent years, gene therapy has gained rapid progress through successful clinical trials, refined vector technologies and other sophisticated delivery systems. This shows gene therapy can revolutionize medicine. However, gene therapy still faces challenges such as high cost, regulatory hurdles, ethical issues, long term efficacy and safety [4]. This review provides a comprehensive overview of recent advances in gene therapy, focusing on approved drugs and their clinical applications. The review covers the range of approved gene therapies across various medical fields, including rare genetic disorders, oncology, and inherited diseases. By examining these approved therapies, we aim to highlight the tangible progress in translating gene therapy research into clinical practice.

2. Methods of gene delivery

Viral Vectors

All gene therapy needs an efficient and safe delivery agent to transfer healthy genes into the host cells. Viruses modified to lose their pathogenesis are the most commonly used agents.

1. **Adenoviruses**: These are one of the viral vector platforms used in gene therapy. They are commonly based on human adenoviruses that are commonly known to cause upper respiratory infection. They are modified to lose their ability to replicate, pathogenesis while carrying the gene of interest. But a challenge with adenovirus is that the immune system can recognize and attack them, reducing its effectiveness.
2. **Adeno-Associated Viruses (AAVs):** These are viruses that do not cause disease and are considered safer for use in gene therapy. They also elicit a milder immune response compared to other viral vectors, making them popular choices for gene therapy applications. However, they have low packing capacity [5].
3. **Lentiviruses (Retroviruses):** Lentiviral vectors are based on retroviruses, such as HIV. They can carry a larger genetic load and are efficient at integrating genetic material into the host cell's genome, providing the potential for long-term gene expression. However, one significant

concern with lentiviral vectors is the risk of insertional mutagenesis, where the integration of the vector into the host genome could potentially disrupt normal gene function or lead to oncogenesis [6].

4. **Herpes viruses**: These viruses can be engineered to target neurologic diseases. They are useful in oncolytic therapies and vaccine to large fragments of gene [7].

Components of Viral Vectors: Each viral vector consists of key components including the protein capsid/envelope for encapsulating genetic material, the transgene of interest for conferring a desired effect, and the regulatory cassette controlling gene expression. Design aspects and considerations for these components vary among different viral vector platforms. Adenoviruses, Adeno-Associated Viruses, and Lentiviruses have been at the forefront of preclinical and clinical successes in gene therapy. Researchers and clinicians have been exploring these platforms extensively due to their potential in treating various genetic diseases and cancers [6].

Gene therapy can be delivered using: ex vivo and in vivo procedures. Each has unique characteristics and applications:

a) In vivo gene therapy: Genetic material is injected straight into the patient's body using this method. Usually, the therapeutic genes are introduced into non-viral or viral vectors and delivered to target particular organs or cells in the body.

b) Ex vivo gene therapy: This method involves altering cells outside the body (ex vivo) before reintroducing them to the patient. The patient has taken their cells out, genetically altered in laboratory settings, and then given back to the patient [8].

3. Types of gene therapy

Gene therapy consists of somatic and germline gene therapy. Somatic gene therapy involves introducing the therapeutic gene into somatic cells, such as muscle, skin, or blood cells, that are not involved in reproduction without altering the patient's germ line, thus avoiding the risk of passing the changes on to future generations, making it currently more efficient in research due to fewer ethical concerns. On the other hand, germline gene therapy targets egg or sperm cells, potentially impacting future offspring through many generations [2],[9].

Physical and Chemical Methods

Other methods of delivery without using viral vectors include the use of physical force to insert therapeutic genes into cells. These include electroporation, magnetopration, sonoporation, optoporation. Each of these methods provides unique opportunities for gene delivery in different contexts. The choice of method depends on the specific application, desired precision, and scale of the gene delivery required. For instance, optoporation has been used in neuroscientific research to deliver genes to specific neurons, enabling the study of neural circuits and brain function. Chemical methods, such as lipid nanoparticles and polymer-based carriers, carry DNA or RNA into cells. These non- methods are safer with a reduced risk of immune reactions and insertional mutagenesis, but are less efficient when compared to viral vectors [10].

Other methods

Human artificial chromosomes are advanced genetic vectors capable of carrying larger gene constructs or gene clusters compared to viral vectors. They are similar to natural chromosomes, but are smaller and simpler in structure [11]. Recent advancements are focused on improving their transfer into various cell types. Additionally, innovative approach such as using larger DNA constructs and epigenetic seeding have significant implication in their development enabling more precise and efficient construction of these artificial chromosomes [12]. Neo-organ implants are a cutting-edge approach that integrates tissue engineering with gene technologies to treat genetic disease. In gene therapy, they are being explored across different organ systems. For example, neo-organs can produce and release insulin in response to glucose levels, thereby regulating blood sugar levels naturally. This approach bypasses the need for external insulin administration for diabetics.[13]Researchers have successfully implanted engineered organs into rodents, but translating this progress to humans is challenging.

4. Gene editing tools

Engineered nucleases such as zinc finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN), mega nucleases (MegNs), and clustered regularly interspaced short palindromic repeats (CRISPR) nucleases are crucial gene therapy tools. These nucleases target and slice the DNA at a specific location for precise gene manipulation. Among these, CRISPR-Cas9 presents advantages over the other tools in terms of simplicity, versatility and, efficiency [5],[14]. In the CRISPR-Cas9 method, a guide RNA directs the Cas9 enzyme to the target DNA site. After biding with the target DNA, Cas9 enzyme breaks the double stranded DNA. The precision and programmability of Cas9 makes it a powerful tool to edit genes across various organisms [14].

5. History of gene therapy

In 1962, Professor William Szybalski discovered gene therapy could correct mutations by adding DNA into cells. After three decades of research, the first successful clinical trial for gene therapy was conducted on a 4-year-old girl with adenosine deaminase deficiency. Over the years, many successful clinical trials have been undertaken, along with setbacks. However, researchers have learned from these experiences and developed safer drugs. The first human gene therapy to receive market approval was Glybera® in 2012, marking a culmination in the field of gene therapy [2]. The breakthrough in

CRISPR-Cas9 has opened new possibilities for treating genetic disorders, leading to the award of the Nobel Prize in Chemistry to Doudna and Charpentier in 2020. The CRISPR-Cas9 system is a genome-editing tool that uses a guide RNA to direct the Cas9 enzyme to recognize and cleave specific DNA sequences, allowing for precise editing and modification of genes.[5] In 2019, it was first used to treat Victoria Gray while she had sickle cell disease [15]. Most recently, in December 2023, the FDA approved Casgevy, the first CRISPR-Cas9-based therapy for sickle cell disease, marking a significant milestone in the clinical application of this technology [5].

6. Gene Therapy Products

Gene therapy has emerged as successful treatment option for various genic disorders. Over the years, this filed has witnessed significant advancements leading to approval of several drugs. In this section, and in Table 1 , we will discuss the gene therapy approved to treat genetic diseases along with their mechanism of action, dose and adverse drug reactions.

Zolgensma

Zolgensma (onasemnogene abeparvovec; Novartis gene therapies) is FDA-approved to treat spinal muscular atrophy (SMA) in children under two years old. SMA, a genetic disease, causes voluntary muscle wasting due to the absence of the survival motor neuron 1 (SMN1) gene, leading to infant death [16].

It delivers a functional copy of the SMN1 gene via the adeno-associated virus 9 vector (AAV9). Zolgensma is effective in pediatric patients with SMA type 1, but its long-term effects are unknown. The approved dose is 1.1 × 10 14 vector genomes per kilogram (vg/kg) of body weight, administered as a single intravenous infusion over 60 minutes [16]. Commonly observed side effects in clinical studies were liver injury, increased levels of amino transferases, changes in platelets and troponin I levels, vomiting and hypersensitivity reactions.

Before administration, liver function, platelet counts, and troponin-I levels should be monitored. No dosage adjustments are needed for renal or hepatic insufficiency. Before therapy initiation, prednisolone 1 mg/kg is recommended, started one day before the infusion, and continued for at least 30 days to reduce liver injury [17]. Zolgensma is an effective treatment option, even though it is expensive compared to alternative options such as Spinraza and Evrysdi [16].

Luxturna

Luxturna (voretigene neparvovec; Spark therapeutics) is the first gene therapy approved to treat genetic diseases. It is used to treat inherited retinal disorders caused by mutations in the human retinal pigment epithelial 65 kDa protein (RPE65) gene.

Luxturna delivers the therapeutic RPE65 gene to retinal cells. The dose of Luxturna is 1.5 × 10 11 vector genomes (vg) per eye in a total volume of 0.3 mL administered no fewer than 6 days apart. It is administered as a single dose to the retinal pigment epithelium via transretinal injection into the subretinal space by pars plana vitrectomy. Luxturna is a safe drug with transient, non-serious reactions that resolve on their own. However, retinal detachment occurred in one patient during clinical trials. Administration of a systemic oral corticosteroid is recommended for days, starting 3 days before administration of Luxturna into the first eye. The corticosteroid dose should be tapered During the next 10 days. Luxturna is not recommended for patients under 12 months of age in the USA [18].

Strimvelis

Strimvelis (GSK2696273;GlaxoSmithKline) is the first ex vivo stem cell gene therapy approved in May 2016 for patients With adenosine deaminase severe combined immunodeficiency (ADA-SCID) with no suitable stem cell donor. It is a rare Inherited disorder that leads to accumulation of purine metabolites due to adenosine deaminase deficiency. Patients Lack both humoral and cellular immunity, and without treatment, they are likely to die within 2 years [19].

Strimvelis transduces autologous CD34+ cells to express the ADA gene, providing a one-time treatment option for ADA- SCID. Strimvelis is currently only available at the Hospital San Rafaele Telethon Institute for Gene Therapy in Milan, Italy. Treatment is only possible if patient's can donate around 4 million purified CD34+ cells/kg for its manufacture. Patients are maintained on intravenous immunoglobulin (IVIG) during treatment with Strimvelis or HSCT, and Eventually discontinue IVIG if treatment is successful.

Regarding the safety of Strimvelis, leukemia-like lymphoproliferative disorders have been identified in patients with other forms of SCID after gene therapy, but none with ADA-SCID. Since only some patients have been tested out, still more studies are needed to confirm its safety. However, Strimvelis is safer than HSCT because it's autologous, eliminating GvHD risk from allogenic transplants, and is cost- effective when a suitable HLA-matched related donor isn't available [20].

Skysona

Skysona (Elivaldogene autotemcel; Bluebird bio) is a lentiviral vector-based gene therapy that is FDA - approved for asymptomatic or mildly affected boys aged 4 to 17 with early cerebral adrenoleukodystrophy (CALD). It is an X-linked disorder characterized by rapidly progressive and irreversible neurocognitive degeneration, often resulting in early death. Mutation in the ABCD1 gene leads to the accumulation of long-chain fatty acids in the body in the nervous system. Male children are at higher risk of developing CALD [21].

Skysona transfers the functional ABCD1 gene into patient's hematopoietic stem cells (HSC) through transduction of autologous CD34 cells with lenti-D lenti viral vector. After infusion, the transduced CD34+ HSC engraft in bone marrow and differentiate. The minimum recommended dose is 5.0x10 6 CD34+ cells per kg of body-weight. Adverse effects Include hematological malignancies (with some patients), mucositis, nausea, vomiting, diarrhea, decreased appetite, febrile neutropenia, alopecia, and seizures. Laboratory abnormalities include leukopenia, lymphopenia, neutropenia, anemia and hypokalemia are also identified [21].

Eteplirsen

Eteplirsen (Exondys 51; Sarepta Therapeutics) is a gene therapy used to treat Duchenne muscular dystrophy (DMD). It is a fatal neuromuscular disorder affecting around 1 in 3,500–5,000 male births that is characterized by progressive muscular deterioration [22]. It is an inherited X-linked recessive fashion and is caused by loss-of-function mutations in the DMD gene coding for dystrophin, a cytoskeletal protein that stabilizes the plasma membrane of muscle fibers. Eteplirsen was approved by the US FDA in September 2016, making it the first and currently only FDA-approved drug for DMD [23]. Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) drug that causes exon 51 skipping of the DMD gene, which restores the reading frame of DMD, allowing successful translation to functional dystrophin protein. Other PMOs approved by the FDA: are Golodirsen, Viltolarsen, and Casimersen; So far, 30% of patients with DMD can be theoretically treated with the PMO drugs approved by the FDA [24]. These are discussed in the further sections.

In a clinical trial, Eteplirsen was well tolerated and showed no side effects at the maximal dose of 20 mg/kg/week given as an IV infusion for 12 weeks. One patient experienced a documented case of significant myocardial fractional shortening; however, this was linked to a DMD-related issue rather than a medication-related side effect. Safety concerns about lung, kidney, liver, or bone marrow function that went beyond the typical DMD phenotype were not discovered. In a clinical investigation, Eteplirsen at a dose of 30 mg/kg/week or 50 mg/kg/week showed a similar safety profile 48 weeks after treatment. As of this point in the course of treatment, the medication was well tolerated, neither renal nor hepatic function was impaired, serum chemistry and characteristics seemed normal considering the severity of DMD, and no T-cell-based immune response was developed [23].

Viltolarsen

Viltolarsen (Viltepso; NS pharma, Inc.) like other PMO works by binding to exon 53 of the DMD gene, causing this exon to be skipped during the processing of the mature mRNA. This exon skipping restores the reading frame of the DMD gene, allowing for the production of a functional dystrophin protein [25].

Viltolarsen is recommended to be administered intravenously at a dose of 80 mg/kg of body weight weekly. In clinical trials, mild treatment-associated adverse drug reactions of Viltolarsen included proteinuria, eczema, high diastolic pressure, and low ejection fraction. Adverse effects like proteinuria were initially observed but later eliminated as a side effect, with no participants quitting the study due to adverse events. Common adverse events observed in participants receiving Viltolarsen included nasopharyngitis and upper respiratory tract infection, with most adverse events being mild and resolved without changing the dose or withdrawal from the study [26].

A one-year supply of Viltolarsen for a child weighing 25 kilograms is expected to be $587,000, which further makes accessibility difficult for patients who make an average income. This cost is further expected to increase in the future when the child grows up, due to increased body weight. For decades, it has been difficult to design therapies that cater to all patients with DMD due to the variability in mutations among them [24].

Golodirsen

Golodirsen (Vyondys 53; Sarepta Therapeutics) is a PMO that specifically targets exon 53 of dystrophin pre-mRNA, resulting in its exclusion from the final mRNA product and leads to the production of a partially internally deleted dystrophin protein with intact C and N-terminal regions. Roughly 7.7% of DMD patients have mutations that can have their reading frame restored by skipping of exon 53 [27].

In a phase ½ clinical trials, 25 children with DMD amenable received 30 mg/kg Golodirsen, which showed a significant increase in exon 53 skipping was associated with dystrophin protein expression at week 48. Although no severe adverse effect has been observed in the clinical development program, monitoring of renal function is prudent, given the findings of nephrotoxicity with other PMO [28].

Casimersen

Casimersen (Amondys 45; Sarepta therapeutics) is an antisense oligonucleotide therapy developed by Sarepta therapeutics in 2022 to treat DMD in patients with a mutation of the DMD gene that is amenable to exon 45 skipping. The recommended dose of Casimersen is 30 mg/kg/week, administered intravenously over approximately 30 minutes to an hour [29]. Casimersen is an antisense PMO drug designed to target genetic mutations that are amenable to exon 45 skipping in patients with DMD. It binds to the DMD pre-

mRNA 3′ splice site, blocks the splicing signal near exon 45, causing the spliceosome to skip it. By

excluding exon 45 during mRNA processing and restoring the frame, a dystrophin isoform protein is produced [30].

In clinical trials, adverse events that occurred more frequently in patients who received Casimersen versus placebo included upper respiratory tract infections, cough, pyrexia, headache, arthralgia, and oropharyngeal pain. Less common adverse drug reactions were nausea, ear pain and/or infection, dizziness, light-headedness, and post-traumatic pain [31]. Casimersen has no contraindications; however, patients with decreased kidney function should be monitored closely [29].

Kymriah

Kymriah (tisagenlecleucel; Novartis Gene therapies) is used to treat patients up to 25 years old with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL). The patient's T cells are genetically modified to express a chimeric antigen receptor (CAR) that targets the CD19 protein on the malignant B cells. These modified T cells are then infused back into the patient to identify and destroy the CD19- expressing cancerous B cells. It is approved by the FDA in 2017 [32].

The dose is calculated based on body weight. In a clinical trial, patients received a single infusion of Kymriah at 0.2- 5.0×10 6 CAR+ viable T cells/kg body weight for patients ≤50 kg and 0.1-2.5×10 8 CAR+ viable T cells for patients >50 kg [33]. Studies show Kymriah is safety and effective, with complete responses and sustained remissions in pediatric Patients. This has increased the survival rate from less than 10% in the 1960s to greater than 90% today. In the latest Follow-up analysis of the ELIANA trial, it was reported that 49% of patients who achieved complete remission after Treatment remained free from relapse after 5 years. This outcome is significant given the aggressive nature of relapsed or refractory ALL, highlighting the long-lasting benefits of CAR-T cell therapy [32]. Adverse effect noted in trials include high fever, hypotension, hypoxia, encephalopathy, confusion, aphasia, delirium, seizures and multi-organ failure. Cytokine release syndrome is the most common toxicity of CAR-T cell therapy which is primarily managed with IL-6 receptor antagonist such as tocilizumab corticosteroids and other supportive care [32].

Lumasiran

Lumasiran (Oxluma; Alnylam Pharmaceutical), a novel drug has shown promising results in reducing urinary oxalate levels marking a significant advancement in the management of Primary Hyperoxaluria-1 (PH1). [34] PH is a rare genetic disease characterized by excessive production and excretion of oxalate leading to kidney failure. PH has different types, with PH1 being the most common and severe form, caused by a genetic defect in the AGXT gene that encodes for a liver-specific peroxisomal enzyme called alanine-glyoxylate aminotransferase that is involves in amino acid metabolism and prevention oxalate accumulation [35].

Lumasiran is a synthetic small interfering RNA that inhibits enzyme glycolate oxidase, leading to decreased oxalate levels in the body. The drug is administered subcutaneously. Lumasiran's pharmacokinetics show rapid absorption, primarily liver distribution, short plasma half-life, and non- CYP450-dependent metabolism [34]. The dose is based on the body weight of the patient. For example, Patients weighing 10 kg receive 6 mg/kg once a month for three months, followed by 3 mg/kg monthly. Patients weighing 10-20 kg receive 6 mg/kg once a month for the first three months, then 6 mg/kg every 3 months. Adverse effects of Lumasiran were reported in clinical trials, such as abdominal pain, headache, rhinitis, nephrolithiasis, cough and injection site reactions. Serious adverse events were rare, with only a few patients experiencing them during the trials. Importantly, most adverse events were not considered to be directly related to the drug, indicating a favorable safety profile of Lumasiran [34].

Zynteglo

Zynteglo (betibeglogene autotemcel; Bluebird bio) is the first cell-based gene therapy used for adults and children with beta thalassemia requiring regular blood transfusion. It is a hereditary blood disorder effecting approximately 4.4 of every 10,000 live births. Zynteglo has shown promising results, with the majority of patients who required at least eight transfusions annually before treatment remaining transfusion independent for over 12 months post-administration [36].

The dose of Zynteglo is determined according to the body weight of an individual and the administration is Predominantly by intravenous injection. Preparatory clinical studies demonstrated that the modified β- globin was produced at significant levels to maintain the normal level of adult hemoglobin in the patients,

possibly eliminating the need for red cell transfusions [37]. It is administered as single treatment that introduces healthy and functional copies of β-globin genes (βA-T87Q) through transduction of autologous hematopoietic stem cells with a lentiviral vector [38]. Headache, hemophagocytic

lymphohistiocytosis, acute respiratory distress syndrome, and idiopathic pneumonia syndrome are among the adverse effects that have been documented in patients taking the product [39].

Vyjuvek

Vyjuvek (Beremagene geperpavec; Krystal bioteck) is the first topical gene therapy approved by the FDA on May 19, 2023 to treat dystrophic epidermolysis bullosa (DEB).[40] DEB is a rare inherited skin disorder that leads to weak skin that easily blisters and tears from minor friction and trauma. Vyjuvek shows its action by delivering COL7A1 gene to restore type VII collagen (C7) protein of the affected skin cells to improve skin integrity and strength [41].

This therapy has shown promising results in clinical trials, with a phase 3 study demonstrating that Vyjuvek led to significantly higher rates of complete wound healing at 3 and 6 months compared to a placebo, indicating its efficacy in treating this rare genetic skin disease. Dose ranged from 4×108 to 1.2×109 plaque-forming units depending on the baseline wound size and remained fixed thereafter for the remainder of the trial [40].

Common adverse effects associated with the treatment include pruritus and mild systemic side effects like chills. Further research is needed to explore the long-term effects and side effects of Vyjuvek to establish its durability and safety profile for broader clinical use. However, Vyjuvek offers hope for individuals with DEB, potentially providing relief from blistering, promoting wound healing, and reducing long-term complications of the disease [41].

Libmeldy

Libmeldy(Atidarsagene autotemcel; Orchard therapeutics) is a cell-based gene therapy medicinal product intended for the treatment of metachromatic leukodystrophy (MLD). MLD is a rare genetic disorder that causes progressive damage to the white matter of the CNS and peripheral nerves due to the accumulation of fatty substances. It is characterized by deficient activity of lysosomal enzyme arylysulfatase A, most commonly due to arylysulfatse A (ARSA gene) [42].

Libmeldy gene therapy involves collecting a patient's stem cells, modifying them to express the ARSA gene using a lentiviral vector, and reinfusing them to restore ARSA enzyme production in the brain and nervous system, thus preventing harmful sulfatide build-up and treating Metachromatic Leukodystrophy.

The recommended dosage for Libmeldy is a minimum of 3 × 10 6 CD34+ cells/kg of body weight. In clinical studies, doses up to 30 × 10 6 CD34+ cells/kg have been administered. All patients (100%) experienced at least one grade 3 or higher adverse events. The most frequently reported grade 3 events were febrile neutropenia (79%), gait disturbance (52%), and stomatitis (41%). Four patients (14%) experienced grade 4 events, including dysphagia in two patients, metabolic acidosis in one patient, and veno-occlusive disease and atypical hemolytic uremic syndrome in one patient [43].

Casgevy

Casgevy (Exagamglogene autotemcel; Vertex Pharmaceuticals) is a gene-editing therapy used to treat blood disorders known as beta thalassemia and sickle cell disease in patients 12 years and older. It is a one-time infusion of genetically modified stem cells that can produce functional hemoglobin, reducing the need for frequent blood transfusions and alleviating symptoms of these conditions [44]. The recommended dosage for Casgevy is a single infusion of genetically modified stem cells, which is tailored to each patient based on their body weight. The exact dosage is not specified in the available information, but it is mentioned that the dose depends on the patient's body weight [45].

It is approved in the US and Europe to treat thalassemia major and severe sickle cell disease. It is available through prescription only and must be administered in an approved center by a trained doctor. Casgevy uses the CRISPR Cas9 enzyme to repair the gene sequence to produce healthy hemoglobin and improve the health of the red blood cells. This can save beta thalassemia patients from needing frequent blood transfusions and can also prevent vaso- occlusive crises in sickle cell disease patients. Casgevy is associated with some side effects, including low levels of platelets and white blood cells during the engraftment period. Patients may also experience side effects related to other medicines administered as part of the treatment regimen. It is important for patients to discuss these risks with their healthcare provider and follow their instructions carefully [46].

Lyfgenia

Lyfgenia (lovotibeglogene autotemcel; Bluebird Bio) is a one-time gene therapy approved by the FDA for the treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events. It is manufactured by bluebird bio Inc. and uses a lentiviral vector for genetic modification [47].

When a patient has Lyfgenia, their blood stem cells are genetically altered to create HbAT87Q, a haemoglobin derived by gene therapy that works similarly to adult normal haemoglobin A produced in people without sickle cell disease. HbAT87Q red blood cells are less likely to sickle and obstruct blood flow. The patient is subsequently given these altered stem cells. Created from the patient's own modified blood stem cells, it is administered as a single-use, one-dose infusion as a component of a hematopoietic stem cell transplant. Stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anaemia, and leukopenia are typical adverse effects. A black box warning for hematologic malignancy is also present. Patients who use this medicine should have ongoing cancer screenings for the rest of their lives [48].

Upstaza

Upstaza (eladocagene exuparvovec; PTC Therapeutica, Inc.) is a one-time gene therapy used to correct the underlying genetic deficiency of aromatic L-amino acid decarboxylase (AADC) for patients 18 months and older in age. AADC deficiency is a rare disease with inborn error of neurotransmitter biosynthesis characterized by movement disorders, developmental delays, and autonomic symptoms from birth. The DDC gene encodes the AADC enzyme, which converts L-3,4- dihydroxyphenylalanine (L-DOPA) to dopamine. Mutation in the DDC gene results in reduction or absence of AADC enzyme activity, causing a reduction in the levels of dopamine and the failure of most patients with AADC deficiency to achieve developmental milestones [49]. Individuals suffer from frequent vomiting, behavioural issues, trouble sleeping, and upsetting seizure-like oculogyric crises that cause the eyes to roll up in the skull [50].

Upstaza is a recombinant adeno-associated virus serotype 2 (AAV2)-based gene therapy containing the human DDC gene. It delivers the healthy DDC gene directly into the putamen of the brain to increase the AADC enzyme and restore dopamine production. Upstaza is given at a dose of 1.8 × 10 11 Vg delivered as four 0.08-mL (0.45 × 1011 vg) infusions. Patients should be closely watched for risks associated with general anesthesia during the peri-operative period, procedure-related problems, and complications related to their underlying condition. Patients may experience exacerbation of symptoms of their underlying AADC deficiency as a result of surgery and anesthesia. Prevalent adverse effects noted include fever for 3– 4 weeks after the operation and dyskinesia [51].

Upstaza requires highly skilled professional and sophisticated centers for its administration, and more information about its safety And efficacy is yet to be discovered.

Rexin-G

Rexin-G (Mx-dnG1; Epeius Biotechnology) is a retroviral vector that contains a cytocidal cyclin G1 gene mutation [52]. Rexin-G was approved in the Philippines in 2010 to treat solid tumours [53].

The Rexin-G is based on the expression of cyclin G1 in tumor cells that arrests the cell cycle in G1 phase and thus triggers cell death and apoptosis. In a phase I/II clinical trial for gemcitabine-resistant pancreatic cancer, the patients received escalating doses of Rexin-G intravenously from 1 × 10 11 colony-forming units (cfu) 2–3× a week (dose 0–1) to 2 × 10 11 Cfu 3× a week (dose 2) for 4 weeks. The data showed that Rexin-G is safe and well tolerated and prolongs survival of patients [54]. Following its approval in the Philippines, it was tested in a phase I/II study to treat various cancers including pancreatic cancer, sarcoma, breast cancer, and osteosarcoma. US FDA granted Rexin-G orphan drug designation for osteosarcoma and soft tissue , sarcoma in 2008 and fast-track designation for pancreatic cancer in 2009, and it is still being tested in trials [55].

Zalmoxis

Zalmoxis (Nalotimagene carmaleucel; MolMed), is an adjuvant drug for patients with severe blood malignancies having partially matched stem cell donors. Zalmoxis helps the patient's immune system to recover and reduce risk of graft-versus-host disease.

Zalmoxis consist of donor-derived T-cells, when infused into the patient, they restore the patient's immune function and can also attack any remaining cancer cells, providing an anti-tumour effect. These cells are genetically engineered to express a suicide gene known as Herpes Simplex Virus Thymidine Kinase (HSK- TK) that can be triggered by administering ganciclovir in case of any graft versus host disease. This can selectively eliminate modified T cells, preventing from causing further self-harm. The European Medicines Agency (EMA) granted Zalmoxis conditional marketing authorization in 2016, emphasizing its potential benefits despite the incomplete data. An interim analysis of a Phase III trial revealed that Zalmoxis did not significantly extend the period patients remained disease-free compared to standard treatments, leading to the suspension of the trial. This development puts the conditional approval of Zalmoxis at risk, pending further regulatory review and analysis [56].

Yescarta

In 2017, FDA authorised Yescarta (Axicabtagene Ciloleucel; Kite Pharma), an anti-cancer gene therapy, making it the first CAR-T cell therapy [57].

Patient's own T cells are genetically modified to use them as a gamma-retroviral vector. This vector expresses a chimeric antigen receptor (CAR) targeting CD19, consisting of a murine anti-CD19 single- chain variable fragment linked to CD28 and CD3-zeta co- stimulatory domains. After a brief manufacturing process that takes about 10 days, these CAR-T cells are infused back into the patient, where they target and destroy CD19-positive cancer cells, offering a tailored immunotherapy for certain lymphomas [58].

Yescarta costs around $373,000 per dose. Initially approved for large B cell lymphoma, it's now being tested for melanoma and pancreatic cancer, potentially broadening its use [59].

Imlygic

Imlygic (Talimogenel aherparepvec) is used for melanoma and pancreatic cancer. It contains a genetically modified HSV-1 oncolytic virus vector that has Granulocyte macrophage colony stimulating factor (GM- CSF) gene at the y34.5 loci. This enables the virus to replicate in cancer cells, causing anti-tumor activity [60]. The cost of Imlygic is USD 65,000 per treatment, Imlygic was approved by the USA FDA in 2015 for use in patients.[59] The recommended starting dose of T-VEC is 10 6 (1 million) PFU Per mL, up to a maximum of 4 mL. Subsequent doses are 10 8 (100 million) PFU per mL, up to a maximum of 4 mL. Most of the adverse reactions reported were mild or moderate in severity, such as fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. The most serious adverse reaction reported was cellulitis [61].

Hemgenix

Hemgenix reduces abnormal bleeding in people with hemophilia B by enabling the body to continuously produce factor IX, the deficient protein in hemophilia B, a rare and life-altering condition. People with hemophilia B are highly susceptible to bleeding episodes in joints, muscles, and internal organs, resulting in pain, swelling, and potential damage [62,63].

It uses a non-infectious viral vector called adeno-associated virus 5(AAV5) that carries the more potent version of Factor IX gene (padua variant) to the target cells in the liver, to produce factor IX proteins which are comparatively more active. The recommended dose of Hemgenix is 2 × 10 13 genome copies (gc) per kilogram of body weight, administered via a single intravenous infusion. Regulatory approval processes have validated Hemgenix's efficacy and safety in managing hemophilia B. The most common adverse effects associated with Hemgenix are Dizziness, facial swelling, fever or chills, headache, nausea or vomiting, skin rash, trouble breathing, weakness [64].

Tecartus

Tecartus (Brexucabtagene autoleucel) is approved for the management of Acute lymphoblastic leukemia (ALL). Acute lymphoblastic leukemia (ALL) is a type of cancer affecting the blood and bone marrow, particularly challenging for adults [59]. Tecartus is a CD19-directed, genetically modified autologous T-cell immunotherapy that targets CD19-expressing cancer cells and normal B cells. This therapy modifies T cell called CAR T cell, it is designed to identify and attach to the CD19 protein on cancer cells [65].

Tecartus is provided as a patient-specific cell suspension in a single infusion bag. It is administered intravenously at a target dose of 2 × 10^6 CAR T cells per kilogram of the patient's body weight. Tecartus has been approved for use by health authorities in both the USA and Europe, highlighting its

recognized efficacy and safety in the treatment of ALL. The Most common adverse effect was pyrexia, cytokine release syndrome , low blood pressure, brain-related issues, fatigue, rapid heartbeat, infections, chills, and low oxygen levels [59,66].

Breyanzi

Breyanzi (lisocabtagene maraleucel) is a chimeric antigen receptor T-cell therapy(CAR-T cell) for treating relapsed or refractory large B-cell lymphoma (LBCL) in adults who have undergone at least two prior lines of systemic therapy. This includes other various subtypes of LBCL [67]. LBCL is a type of blood cancer that affects B lymphocytes. B cell lymphomas are the most common type of non-Hodgkin's lymphoma (NHL) and can be aggressive or indolent [59]. Breyanzi was approved by the US FDA in 2022.

Breyanzi uses a lentiviral vector to genetically modify the patient's T cells to express a chimeric antigen receptor (CAR) that targets CD19, a protein found on the surface of B cells. The CAR is made up of CD8+ and CD4+ cell components, which work together to recognize and attack the cancer cells. The modified T cells are then infused back into the patient, where they multiply and attack the cancer cells. The therapy is administered at a strength of 1.1–70 × 10 ^6 CAR+ viable T cells/mL for each component [68].

Carvykti

Carvykti (ciltacabtagene autoleucel) is a gene therapy approved for treatment after almost three years of multiple regulatory events following its Investigational New Drug Application submission to the FDA in 2018. The product uses a lentiviral vector (LVV) to introduce an anti-B cell maturation antigen (BCMA) chimeric antigen receptor (CAR) into the patient's own T cells. These genetically modified T cells are designed to target and destroy cancer cells expressing BCMA, specifically in multiple myeloma (cancer of the plasma cells) [69].

The recommended dose of Carvykti is 0.5-1.0 × 10^6 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1 × 10^8 CAR-positive viable T cells per single infusion.[70] Most of the side effects were non-serious—anemia, thrombocytopenia, neutropenia and cytokine release syndrome. These events were managed and resolved within a median of four days. As of date on phase 1b/2 trial has been done and more data on long term safety and efficacy of Carykti has to be obtained [69].

7. Challenges

Gene therapy clinical trials worldwide have steadily increased over the years, with the USA leading globally. With the increasing success and investment in gene therapy, it is time to pay attention to factors related to the manufacture and commercialization of products to ensure they are available to the masses [71]. Also, gene therapy can serve as a single treatment resulting in a lifelong cure, so it remains a question how companies can recover the huge investments they have committed [72]. Currently, CAR T cells are manufactured through ex vivo modification of T cells obtained from individual patients, which requires specialized teams and facilities. To address this challenge, efforts are being made in cryopreservation and transport of gene-modified cells, which will allow modification at a central location and make gene therapy more accessible to patients globally [71].

Gene therapy product development in India is under constant evolution. Currently, there are no committed centers for gene therapy large scale manufacture. Many Hospitals and organizations have taken initiated to bring gene therapy research in India, such as Indian Association for the Cultivation of Science (IACS), Kolkata, has developed an indigenous ASO production method to treat DMD. This product has known for its low cost and is approved for clinical trial in pediatrics in India [73]. The Indian Council of Medical Research (ICMR) is responsible for developing gene therapy and conducting clinical trials in India. 'National Guidelines for Gene Therapy Product Development and Clinical Trials' was launched in 2019 which aimed to bring gene delivery-mediated options for patients suffering from genetic diseases in India [74]. The Indian Council of Medical Research (ICMR) and other organizations are pivotal in regulating and promoting clinical trials targeting various disorders, including cancer, retinal diseases, and neurodegenerative conditions. Collaborative efforts, both globally and locally, will bolster India's position in the global gene therapy landscape, ultimately providing life-changing treatments to patients nationwide. Financial support and stability from the government, along with streamlined regulatory processes, are crucial for sustaining growth in gene therapy research in India. Awareness of current developments can bridge the information gap between stakeholders, ushering in revolutionary therapy for genetic disorder patients [75].

8. Conclusions

Gene therapy has revolutionized medicine by offering treatments for previously incurable genetic diseases. Through numerous successful clinical trials, advancements in vector technologies, and innovative delivery systems, the field has expanded rapidly. Methods such as human artificial chromosomes and neo-organ implants are pushing boundaries with precise interventions, while gene editing tools like CRISPR-Cas9 have brought unprecedented precision and efficiency to gene modification. However, challenges such as high costs, regulatory hurdles, ethical considerations, and ensuring long-term efficacy and safety persist. Addressing these issues is crucial for advancing gene therapy and broadening its applications. Despite these challenges, pioneering therapies like Zolgensma for spinal muscular atrophy, Luxturna for inherited retinal disorders, and Kymriah for leukaemia exemplify the transformative potential of gene therapy. These successes underscore the promise of improving patient outcomes and making gene therapy more accessible globally as research continues to refine techniques and expand applications. Collaboration among global and local stakeholders, supported by government backing, and streamlined regulations, is essential. By fostering such collaboration, we can ensure that transformative treatments reach patients nationwide, further cementing its role in the global gene therapy landscape.

Acknowledgment

We would like to thank Srinivas Institute of Medical Sciences & Research Centre and Srinivas college of pharmacy for their support throughout the work.

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