BG Pulse Journal USA
ISSN:1947-2536 http://www.bgpulseusa.com/index.php/bg
BG PULSE JOURNAL

EFFECTIVENESS OF TREATING GENETIC DISEASES BY GENE THERAPY

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Doi: https://doi.org/10.5281/zenodo.22705585

Abstract: This article analyzes the effectiveness of gene therapy in treating genetic diseases, its main molecular mechanisms, and modern technologies. Key therapeutic approaches such as gene addition, gene function restoration, gene expression silencing, and targeted genome editing are covered. The potential of modern gene delivery and gene editing technologies, such as adeno-associated virus (AAV), lentiviral vectors, CRISPR-Cas9, base editing, prime editing, and lipid nanoparticles, is also considered. The results of modern research on the clinical efficacy of gene therapy in spinal muscular atrophy, hemophilia, hereditary retinal diseases, sickle cell disease, and beta-thalassemia are analyzed. Studies show that gene therapy can improve motor function, reduce bleeding, improve vision, reduce vaso-occlusive attacks, and achieve transfusion independence in some monogenic diseases. However, issues such as immunological reactions, off-target effects, vector limitations, long-term safety, high treatment costs, and proper patient selection for therapy were also discussed. In general, gene therapy is a promising treatment method that targets the molecular causes of genetic diseases, and its clinical effectiveness depends on the type of disease, the time of initiation of treatment, the characteristics of the genetic mutation, and the technology used.

Keywords: gene therapy, genetic disorders, gene editing, CRISPR-Cas9, AAV vectors, lentiviral vectors, base editing, prime editing, gene delivery, monogenic disorders, spinal muscular atrophy, hemophilia, beta-thalassemia, sickle cell disease, hereditary retinal disorders.

Genetic diseases are a group of diseases caused by changes in genes, chromosomes, or their function in the human genome, and can manifest clinically in a variety of ways. Monogenic diseases, especially those associated with a single gene mutation, are important targets for genetic therapy. In recent years, the deeper study of the molecular basis of genetic diseases and the development of gene modification technologies have opened up new therapeutic possibilities in the treatment of these diseases.

Current treatments for many genetic diseases are primarily aimed at controlling the symptoms of the disease or temporarily compensating for the missing biological function. While such approaches may improve the patient's clinical condition, they do not directly address the underlying genetic cause of the disease. Therefore, the development of treatment strategies aimed at the molecular cause of the disease has become one of the important areas of modern medicine and molecular biology.

Gene therapy is an innovative therapeutic approach aimed at solving this problem, the main goal of which is to modify the genetic material in a cell for therapeutic purposes or to restore its function. Gene therapy uses strategies such as delivering a healthy gene copy to a cell, restoring the function of a missing gene, suppressing pathological gene expression, or targeting a specific part of the genome for editing. In modern gene therapy, viral vectors such as adeno-associated virus (AAV) and lentivirus, as well as gene editing technologies based on CRISPR-Cas systems, are being extensively studied. The clinical importance of gene therapy has been increasing in recent years. Clinical studies in various genetic disorders have shown the therapeutic efficacy of this approach. For example, gene-based treatment in spinal muscular atrophy has been found to have positive effects on motor functions and survival rates. A systematic review and meta-analysis published in 2024 reported higher survival rates and reduced need for mechanical ventilation in patients treated with onasemnogene abeparvovec.There are also important results on the effectiveness of gene therapy in hemophilia. AAV-based gene therapy has been shown to increase the expression of clotting factors VIII or IX in clinical trials, reducing the number of bleeds and the need for prophylactic treatment. However, adverse effects such as post-treatment immune reactions and elevated liver enzymes indicate the need for long-term monitoring of the safety of this method.

Hereditary retinal diseases are also an important area of clinical application of gene therapy. Voretigene neparvovec (Luxturna) has shown the potential to improve vision function as a gene therapy for hereditary retinal diseases associated with biallelic mutations in the RPE65 gene. Subsequent real-world clinical data also suggest that there may be clinically significant improvements in some visual function measures after this treatment.Another important area of gene therapy is the use of gene addition and CRISPR-Cas9-based gene editing technologies to treat sickle cell disease and beta-thalassemia. The goal of therapy in these diseases is to improve the clinical course of the disease by restoring hemoglobin production or reducing its pathological formation. Recent clinical advances have shown the potential of gene editing technologies to become a practical therapeutic tool in inherited blood diseases.

However, despite the high potential efficacy of gene therapy, this method has a number of limitations. These include the effective delivery of the therapeutic gene to the desired cells and tissues, the immune system's response to viral vectors, off-target changes during gene editing, the long-term maintenance of treatment efficacy, and the high cost of therapy. In addition, the blood-brain barrier and the unique biological properties of neurons pose additional challenges when delivering genes to certain organs, particularly the central nervous system.Therefore, the true clinical efficacy of gene therapy should be assessed not only by the positive results after treatment, but also by its safety, long-term effects, patient quality of life, and adverse effects. Although modern clinical studies show that gene therapy can achieve significant therapeutic results in some genetic diseases, additional studies are needed to determine the long-term effectiveness and safety of this approach.

Basic Mechanisms of Gene Therapy

Gene therapy is a modern treatment strategy that aims to target the molecular causes of genetic diseases. Its main essence is to correct the disease mechanism by modifying the genetic material in the cell, restoring the function of a missing gene, or reducing the effect of a pathological gene. Modern gene therapy uses several molecular approaches, including gene addition, gene replacement, gene silencing, and targeted genome editing.

1. Gene addition and gene function restoration

One of the most basic mechanisms of gene therapy is to deliver a healthy copy of a gene that is missing or non-functional due to disease to a cell. In this case, a therapeutic gene is introduced into target cells using a special vector, which ensures the production of the desired protein in the cell. This approach is particularly important in monogenic diseases, where a deficiency of a specific protein occurs as a result of a single gene mutation.

Both viral and non-viral vectors can be used to deliver therapeutic genes to cells. Among viral vectors, adeno-associated virus (AAV) and lentiviruses are platforms that are widely used in clinical trials. AAV vectors have gained importance in in vivo gene therapy due to their relatively high transduction efficiency, tissue tropism, and relatively low immunogenicity.

For example, in some hereditary diseases, the production of a missing protein is restored by delivering a functional gene copy to the patient's cells. This approach may not completely reverse the genetic cause of the disease, but it can help reduce clinical symptoms by compensating for the functional product of the defective gene.

2. Gene replacement

In gene replacement therapy, a functional copy of the gene that causes the disease is used for therapeutic purposes. This approach can be used in diseases caused by a lack of an essential protein due to a mutated form of the gene.

A significant advantage of gene replacement or delivery of a functional gene copy is that it is not necessary to correct each mutation in the existing genome individually to achieve a therapeutic effect. However, the effectiveness of this method depends on the delivery of the therapeutic gene to the desired cells, its sufficient expression, and the resulting protein being biologically active.

Additionally, the limited genetic payload capacity of AAV vectors can pose a problem when delivering certain large genes. As a result, there has been a great deal of recent attention paid to the development of smaller gene editing tools and next-generation vectors.

3. Gene expression suppression

In some genetic diseases, the problem is not a lack of a particular protein, but rather the over- or harmful activation of a pathological gene. In such cases, gene therapy may be focused on reducing the expression of the disease-causing gene.

RNA interference, antisense oligonucleotides, and modern gene editing or epigenetic control technologies can be used to silence gene expression. These strategies serve to control the molecular mechanism of the disease by reducing the transcription of the pathological gene or the production of its product.

4. Genome-targeted editing

One of the fastest-growing areas of gene therapy is targeted genome editing. In this method, a specific part of the genetic material is identified and modified using special molecular tools. One of the most studied technologies is the CRISPR-Cas system.

In the CRISPR-Cas9 system, guide RNA directs the Cas9 enzyme to a specific DNA sequence in the genome. Cas9 cuts the DNA at this site, triggering the cell's natural DNA repair mechanisms. As a result, the target gene activity can be altered or editing aimed at correcting a particular mutation can be carried out .Later generations of CRISPR technology — base editing and prime editing — are making it possible to make more precise genetic changes without cutting the two

strands of DNA in a classical way. Base editors allow for the replacement of certain nucleotides with other nucleotides, while prime editors allow for more complex genetic changes. These technologies are considered promising avenues for increasing the precision and safety of gene therapy.

5. Delivery of genetic material to target cells

The effectiveness of gene therapy depends not only on the therapeutic gene or gene editing tool itself, but also on how effectively it is delivered to the desired cells. Therefore, the delivery system, which is the system that delivers the genetic material to the cell, is an important component of gene therapy.

Delivery systems are divided into two main groups: viral and non-viral vectors. Viral vectors include AAV, lentivirus, and adenoviruses. Non-viral systems include lipid nanoparticles and other synthetic carrier platforms.

AAV vectors are particularly widely used in in vivo gene therapy. One of their important features is the ability to deliver genes to specific tissues using different serotypes. However, the limited payload capacity of AAV, pre-existing immune responses, and adverse immunological reactions associated with high doses remain significant challenges in clinical use.

Lentiviral vectors, on the other hand, are particularly important in ex vivo gene therapy. In this, cells are taken from the patient, in laboratory conditions, therapeutic gene or gene editing components are introduced into them, and modified cells are sent back to the patient. Lentiviral gene addition and CRISPR-based gene editing strategies have been actively studied clinically in hemoglobinopathies, including beta-thalassemia and sickle cell disease .

6. Ex vivo and in vivo gene therapy

Gene therapy can be divided into ex vivo and in vivo approaches depending on the method of administration.

In ex vivo therapy, a patient's cells are removed from the body, genetically modified in the laboratory, and then returned to the patient. This method allows for the testing of genetic changes before the cells are administered to the patient. Some gene therapies based on hematopoietic stem cells use this strategy.

In vivo therapy, on the other hand, involves directly delivering a therapeutic gene or gene editing tool to a patient's body. In this case, the vector must reach the desired tissue or cells and exert a therapeutic effect. The main advantage of this approach is the absence of the need for pre-isolation of cells, but the delivery of genetic material to the target tissue and the control of immunological risks can be complex.In general, the mechanism of gene therapy is selected based on the molecular cause of the disease. If the disease is caused by a deficiency of a functional gene product, gene addition or restoration of gene function may be appropriate. If the activity of a pathological gene causes the disease, gene expression silencing or genome editing strategies are used. Therefore, the clinical effectiveness of gene therapy directly depends on the genetic characteristics of the disease, the selected technology, the type of vector, and the efficiency of delivery of the therapeutic gene to the target cells.

Modern technologies in gene therapy

The development of gene therapy is closely related to the creation of new technologies that allow for the effective delivery of therapeutic genes to cells and precise genome editing. Currently,

adeno-associated virus (AAV) and lentiviral vectors are used as important gene delivery platforms. Meanwhile, genome editing technologies such as CRISPR-Cas9, base editing, and prime editing are expanding the ability to directly modify genetic mutations.

1. Adeno-associated virus (AAV) vectors

AAV is one of the most studied viral vectors in gene therapy. It has relatively low pathogenicity and allows the delivery of genetic material to various tissues. For this reason, AAV-based approaches are being extensively studied, particularly in gene therapies targeting the eye, liver, muscle, and central nervous system.

An important advantage of AAV technology is the ability to selectively deliver genes to specific cells and tissues using different serotypes and capsid variants. AAV-based gene therapy has gained particular clinical importance in ophthalmology. For example, the use of voretigene neparvovec in the treatment of hereditary retinal diseases associated with mutations in the RPE65 gene is one of the successful examples of the AAV platform in clinical practice.

However, AAV vectors have some limitations. Their genetic payload capacity is relatively small, making it difficult to deliver large therapeutic genes. Additionally, the patient may have a pre-existing immune response to AAV or immune reactions may occur after treatment. Therefore, research is ongoing to improve AAV capsids, create new serotypes, and reduce the immunogenicity of the vector. PPubMed

2. Lentiviral vectors

Lentiviral vectors are another important platform used to deliver genetic material to cells. Their main feature is their ability to integrate genetic material into the cell genome. Therefore, they are important, especially in ex vivo gene therapies, where long-term gene expression is required.

In the ex vivo approach, specific cells, such as hematopoietic stem cells, are obtained from the patient. These cells are genetically modified in the laboratory using a lentiviral vector and then returned to the patient. This approach is being used in gene therapies for the treatment of inherited blood disorders, including beta-thalassemia and sickle cell disease.

The main advantage of lentiviral vectors is their ability to carry a relatively large genetic load and provide long-term expression. However, the ability to integrate into the genome can pose risks associated with the placement of genetic material in different parts of the cell's genome. Therefore, modern lentiviral vectors are being developed with special designs to increase safety.

3. CRISPR-Cas9 technology

CRISPR-Cas9 is one of the most important modern technologies for targeted genome editing. In this system, guide RNA (gRNA) directs the Cas9 nuclease to a predetermined DNA sequence in the genome. Cas9 creates a double-stranded break in the target DNA region. The genetic sequence is then modified using the cell's natural DNA repair mechanisms .

A significant advantage of CRISPR-Cas9 is its relatively high targeting specificity and ability to perform a variety of genetic modifications. Strategies are being developed to use technology to stop the activity of a pathological gene, correct certain mutations, or restore the desired genetic function.

The clinical significance of CRISPR technologies has been particularly evident in hereditary blood diseases. In sickle cell disease, strategies have been developed to genetically modify the

patient's hematopoietic stem cells ex vivo to increase the production of fetal hemoglobin. This is one of the key milestones in the transition of CRISPR-based therapies from laboratory technology to clinical treatment.

However, there is a possibility that CRISPR-Cas9 technology will also cause changes in unintended regions of the DNA. Such off-target changes are an important issue in terms of the safety of the therapy and require the evaluation of the accuracy of genetic editing before clinical use.

4. Base editing

Base editing is an improved form of CRISPR technology that allows for the direct replacement of certain nucleotides with other nucleotides. Unlike the classic CRISPR-Cas9, some variants of base editing perform targeted nucleotide changes without creating a complete double-strand break in both strands of DNA.

For example, modern base editors allow for the modification of the genetic code by converting cytosine to thymine or adenine to guanine under certain conditions. This feature holds great promise for treating genetic diseases associated with certain point mutations.

The main advantage of Base editing is the possibility of relatively accurate correction of certain mutations and a reduction in the need for double-stranded DNA breaks typical of classical CRISPR-Cas9. However, technology cannot correct all types of mutations. In addition, off-target base changes and editing efficiency are still important areas of research.

5. Prime editing

Prime editing is one of the more flexible genome editing technologies. This system uses a combination of Cas9 nickase and reverse transcriptase enzymes, as well as a custom prime editing guide RNA (pegRNA). Prime editing allows for the introduction of point mutations, small insertions, and deletions in DNA.

A key aspect of prime editing is that it does not require the complete double-stranded DNA break that classic CRISPR-Cas9 does. This theoretically allows for more precise implementation of certain genetic changes. Studies have shown the therapeutic potential of prime editing in correcting mutations associated with genetic diseases .

However, prime editing is still in the early stages of development in many areas, and further research is needed to determine its efficacy, delivery to the desired cells, and long-term safety. Efficient delivery of large prime editing components to cells is one of the main challenges in the clinical application of the technology.

6. Lipid nanoparticles

In addition to viral vectors, non-viral systems are also being developed to deliver genetic material. One of their important representatives is lipid nanoparticles. Lipid nanoparticles can be used to deliver RNA or other nucleic acids to cells.

Advantages of this technology include biological adaptability, manufacturing capabilities, and the absence of certain limitations inherent in viral vectors. However, issues such as selective delivery to the desired tissue, stability in the body, and the rate of uptake by cells are still being improved.

The effectiveness of gene therapy in treating genetic diseases

In assessing the effectiveness of gene therapy, in addition to laboratory indicators, important criteria are the patient's clinical condition, reduction of disease-specific symptoms, improvement in functional capacity, reduction in the need for blood transfusions or continuous medications, and changes in quality of life. Current clinical trials show that gene therapy can achieve a single or long-term therapeutic effect in some monogenic diseases. However, the effectiveness depends on the type of disease, the patient's age, the stage of the disease, the genetic mutation, and the chosen therapy technology.

1. Effectiveness of gene therapy in spinal muscular atrophy

Spinal muscular atrophy (SMA) is a severe hereditary neuromuscular disease caused by pathogenic changes in two alleles of the SMN1 gene. In the disease, the lack of SMN protein leads to the degeneration of motor neurons, resulting in muscle weakness and impaired motor function. Therefore, SMA has become one of the most important clinical applications of gene therapy.

SMA is based on the delivery of a functional SMN1 gene to cells via the AAV9 vector onasemnogene abeparvovec. The goal of therapy is to restore SMN protein production and maintain motor neuron function.

In a phase III clinical trial called STR1VE, 22 infants with symptomatic SMA type 1 received a single infusion of onasemnogene abeparvovec. At 18 months of follow-up, 59% of patients achieved the ability to sit independently for at least 30 seconds, compared to 0% in the untreated natural history group. In addition, 91% of patients survived to 14 months without death or permanent ventilation, compared to 26% in the natural history group used as a control.

Starting treatment as early as possible in SMA can have a significant impact on effectiveness. This is also demonstrated by the SPR1NT study, which was conducted in presymptomatic patients. All babies with two copies of the SMN2 gene and a high risk of developing type 1 SMA achieved the ability to sit independently for at least 30 seconds by 18 months of age. All of them survived without permanent ventilation by 14 months of age.

The results were even better in presymptomatic children with three copies of the SMN2 gene and a high risk of developing type 2 SMA: all 15 children were able to stand independently by 24 months, and 14 were able to walk independently.

These results suggest that the effectiveness of gene therapy in SMA may be higher when used before or at a very early stage of clinical disease progression. Therefore, newborn screening and early detection of the disease are important factors in improving the clinical efficacy of gene therapy.

2. Effectiveness of gene therapy in hemophilia

Hemophilia is a hereditary disorder of the blood clotting system, with hemophilia A primarily involving a deficiency of clotting factor VIII, and hemophilia B involving a deficiency of factor IX. In conventional treatment, the missing clotting factor is administered regularly. The goal of gene therapy is to ensure long-term production of the desired clotting factor in the patient's own cells.

Hemophilia BDA AAV5-based etranacogene dezaparvovec therapy has shown significant clinical results. In a Phase III HOPE-b study, 54 patients had decreased annual bleeding after treatment. The annual bleeding rate was 4.19 in the pre-treatment period, which decreased to 1.51 in the 7–18 months after therapy. Factor IX activity was also increased and the need for routine factor IX prophylaxis in patients was dramatically reduced.

Long-term retention of these results has also been observed. In the 5-year follow-up results published in 2025, patients receiving etranacogene dezaparvovec had an average annual bleeding rate of 0.14 for all hemorrhages, and all participants stopped factor IX prophylaxis. No serious safety issues were reported during the study.

Hemophilia A has also shown clinically meaningful results in the phase III GENEr8-1 study with valoctocogene roxaparvovec. In a three-year follow-up, the annual rate of bleeding requiring treatment decreased from an initial 4.8 to 0.8 in the post-treatment period. The use of factor VIII, on the other hand, was down by about 96.8 percent from the baseline. PPubMed

Thus, the main clinical advantage of gene therapy in hemophilia is to ensure the production of clotting factor in the body itself and reduce the need for regular factor prophylaxis. However, long-term follow-up is needed to assess the long-term efficacy and immunological safety of therapy.

3. Efficacy of gene therapy in hereditary retinal diseases

Inherited retinal diseases are considered one of the most promising targets for gene therapy because the eye is anatomically relatively isolated, allowing for the direct delivery of the therapeutic gene to the desired tissue.

Voretigene neparvovec is a gene therapy developed for hereditary retinal dystrophy associated with biallelic RPE65 mutations. A phase III randomized trial included 31 patients. Over a one-year follow-up, the mean improvement in the Multiple Light Level Mobility Test (MLMT) score was 1.8 light levels in the treated group, compared to 0.2 light levels in the control group. 65% of treated patients successfully passed the test even at the lowest test light level, while no such result was observed in the control group.

Follow-up studies have shown that these functional improvements can be maintained for several years. A study evaluating 3–4-year outcomes observed that functional vision improvements following voretigene neparvovec were maintained over the long term.

These results demonstrate that gene therapy can improve functional vision in some inherited eye diseases where effective treatment options were previously very limited.

4. CRISPR-based gene therapy for sickle cell disease

Sickle cell disease is a hereditary disease caused by a mutation in the HBB gene that encodes the β-chain of hemoglobin, which can cause painful vaso-occlusive attacks, anemia, and organ damage.

One of the modern gene editing strategies is exagamglogene autotemcel (exa-cel), in which the patient's hematopoietic stem cells are isolated from the body and the erythroid cell-specific BCL11A enhancer domain is edited using CRISPR-Cas9. As a result, fetal hemoglobin production is reactivated.

In the phase III CLIMB SCD-121 study, 44 patients received exa-cel. Of the 30 patients with adequate follow-up, 29 (97 percent) were free of severe vaso-occlusive attacks for at least 12 months. There were also no hospitalizations due to vaso-occlusive crises in all 30 patients for at least 12 months. PPubMed

Subsequent data show that treatment also had a positive effect on quality of life. Patients receiving Exa-cel reported clinically meaningful improvements in pain, physical and social functioning, and overall quality of life.

These results demonstrate that CRISPR-based gene editing technology can have a clinically significant impact by targeting the underlying molecular mechanism of the genetic disease.

5. Efficacy of gene therapy in beta-thalassemia

Beta-thalassemia is a hereditary blood disorder caused by a defect in the synthesis of the hemoglobin β-chain, and in severe forms, patients may require regular red blood cell transfusions. Long-term blood transfusions can lead to iron accumulation and other complications.

Betibeglogene autotemcel (beti-cel) is based on the genetic modification of the patient's hematopoietic stem and progenitor cells using a lentiviral vector. In the phase III HGB-212 study, 16 of 18 patients (89 percent) with transfusion-dependent severe beta-thalassemia achieved transfusion independence. The study defined transfusion independence as a hemoglobin level of at least 9 g/dL and no need for red blood cell transfusions for 12 months or more.

Long-term follow-up data published in 2026 further supported the stability of this result. In the phase III study group, 37 of 41 patients (90.2 percent) achieved transfusion independence, and this result was maintained until the end of follow-up. A significant proportion of patients who have achieved transfusion independence have also been able to discontinue iron chelation therapy.

These results of gene therapy in Beta-thalassemia indicate one of the main clinical problems of the disease — the need for constant blood transfusions — the possibility of long-term reduction or elimination.

Note: Different studies vary in the number of patients, follow-up period, control group, and efficacy criteria. Therefore, direct comparison of the percentages in the table requires caution.

Overall, available clinical evidence suggests that gene therapy has significant clinical efficacy in some genetic diseases. In particular, results such as motor development and survival in SMA, decreased bleeding in hemophilia, improved functional vision in retinal diseases, prevention of vasoclusive attacks in sickle cell disease, and achieving transfusion independence in beta-thalassemia confirm the clinical value of gene therapy.

However, it would be incorrect to interpret these results as a “cure-all for all genetic diseases” as a form of gene therapy. Studies have often been conducted in small patient groups, with limited follow-up periods, and there are risks associated with therapy. In addition, some treatments may require a patient to receive a high dose of the drug or pre-treatment chemotherapy to achieve efficacy. Therefore, it is necessary to assess clinical efficacy in conjunction with safety and long-term outcomes.

Safety and limitations of gene therapy

Although gene therapy has shown high therapeutic efficacy in the treatment of certain genetic diseases, the clinical application of these technologies is associated with a number of safety issues and limitations. The introduction of genetic material into the organism or direct modification of the genome can have long-term biological consequences. For this reason, in addition to assessing the effectiveness of gene therapy, an in-depth study of its short-and long-term safety is also necessary.

1. Immunological reactions

One of the most important challenges in gene therapy is the immune response of the body to the therapeutic vector or its components. In AAV-based therapies in particular, the patient may

have pre-existing antibodies against the vector capsid. Such antibodies can reduce the vector's ability to reach target cells, negatively affecting the effectiveness of therapy.

In addition, an immune system reaction to the vector or therapeutic protein may occur after gene therapy. Increased liver enzymes, inflammatory reactions, and other immunological adverse events have been reported in some clinical trials. Therefore, the use of corticosteroids or other immunomodulators may be required in some AAV-based therapies.

Another aspect of immunological problems is the limitation of the possibility of re-administration of the same AAV serotype. Neutralizing antibodies formed after the first treatment can render the subsequent dose ineffective. This is a particularly important issue in cases where retreatment is required for long-term effects.

2. Off-target effects in gene therapy

One of the important safety concerns with CRISPR-Cas9 and other gene editing technologies is the possibility of off-target effects, i.e., changes occurring in unintended regions of the genome. In theory, such changes could affect normal cell function or pose long-term biological risks.

Off-target editing was one of the main problems in the early generations of CRISPR-Cas9 technology. Currently, there are significant advances in identifying and reducing such risks using high-resolution Cas proteins, improved guide RNA design, and genome-wide sequencing methods.

Additionally, genome editing is not limited to small point mutations, but can also cause large deletions or other unexpected genomic changes in some cases. For this reason, extensive testing of gene editing accuracy and genomic safety is required before clinical application.

3. Vector-related security problems

The effectiveness of gene therapy largely depends on the vector that delivers the therapeutic material to the target cells. Each type of viral vector has its own advantages and risks.

Although AAV vectors have relatively low pathogenicity, immunological reactions, hepatic toxicity, and other adverse effects may occur when administered at high doses. Additionally, the limited genetic payload capacity of AAV poses a problem in delivering large genes.

An important feature of lentiviral vectors is the integration of the therapeutic gene into the cell genome. This can provide long-term gene expression, but theoretically carries the risk of altering the normal function of the gene, depending on the integration site. Therefore, modern lentiviral vectors used in clinical practice are specially designed to increase safety.

4. Long-term maintenance of the therapeutic effect

Another important issue of gene therapy is how long the therapeutic effect after treatment lasts. Certain gene therapies can have long-term effects after single administration. However, in all therapies, such a result is not guaranteed.

For example, in some AAV-based therapies, the therapeutic gene is not permanently integrated into the genome and is present in the cell in an episomal form. The number of copies of the therapeutic gene may decrease as a result of cell division. This is particularly important in rapidly growing patients, such as children.

Also, in some gene therapies, the expression of the therapeutic protein may decrease over time. For this reason, in clinical studies, it is considered important to observe patients for several years or even longer.

5. High cost and availability of gene therapy

One of the biggest economic challenges in the clinical use of gene therapy is its high cost. Although many modern gene therapies are designed as one-time treatments, their cost can be very high. This is due to the complex manufacturing process, high level of biological control, the need to modify individual patient cells, and long-term safety monitoring.

Especially in ex vivo gene therapies, obtaining cells from the patient, their genetic modification in the laboratory, quality control and re-Administration to the patient requires a complex infrastructure. As a result, the possibility of using gene therapy can be limited to economically and technologically advanced medical centers.

Therefore, in the future development of gene therapy, it is important not only to improve clinical efficacy, but also to make treatment more economically feasible.

6. Patient selection in gene therapy

The effectiveness of gene therapy may not be the same in all patients. The patient's age, stage of the disease, type of genetic mutation, immunological status, and the degree of persistence of target cells affect the outcome of treatment.

For example, in some neurodegenerative genetic diseases, it may be difficult to fully restore lost function with gene therapy once motor neurons or other target cells have been irreversibly damaged. Therefore, in some diseases, gene therapy may be more effective if used before symptoms appear or in the early stages of the disease.

In addition, in AAV-based therapies, the presence of neutralizing antibodies against the vector in the patient may be one of the criteria for treatment failure. Therefore, it is important to screen patients molecularly and immunologically before therapy.

7. Ethical and legal issues

Gene therapy raises not only medical but also ethical issues. The distinction between somatic and germline gene editing is particularly important. In somatic gene therapy, changes are made only in the cells of the patient being treated and are not usually passed on to the next generation.

Germline cell or embryo genome editing can also affect future generations. Therefore, germline genome editing raises very high ethical, legal, and safety concerns. The main focus of current clinical gene therapy is on somatic cell therapy.

While gene therapy has shown high clinical efficacy in some hereditary diseases, its safety and long-term effects are still being actively studied. Issues such as immunological reactions, genomic safety, effective delivery of the therapeutic gene, high cost of treatment, and proper patient selection are the main factors hindering the widespread use of gene therapy. However, the development of new generation vectors, precise gene editing technologies, and improved delivery systems is gradually reducing these limitations.

Disease-specific differences in the effectiveness of gene therapy

Analyzed clinical studies show that the effectiveness of gene therapy is not the same in different genetic disorders. For example, early-onset gene therapy in spinal muscular atrophy shows particularly high results. Children treated in the presymptomatic stage had a higher chance of

maintaining motor development and preventing progression to a severe clinical form of the disease. This suggests that the timing of treatment is very important in gene therapy.

In the case of SMA, because it is difficult to restore lost motor neurons once the disease has reached a clinically severe stage, it is important to compensate for the genetic defect as early as possible. Therefore, the effectiveness of gene therapy depends not only on the molecular properties of the drug, but also on the time at which the disease is detected and treatment is initiated. Modern reviews of central nervous system diseases also highlight effective delivery to target cells and treatment time as key factors in clinical success.

In hemophilia, the main criteria for assessing effectiveness are a reduction in the number of bleeding episodes and the endogenous production of the missing clotting factor. In this disease, gene therapy can reduce the need for regular factor replacement by ensuring the production of factor VIII or IX in the patient's body for a long period of time. Thus, the clinical value of gene therapy in hemophilia is determined not only by the improvement in laboratory parameters, but also by the reduction in the patient's daily treatment burden.

In hereditary retinal diseases, the effectiveness of gene therapy can be assessed by changes in visual function. The anatomical features of the eye allow for the direct delivery of the therapeutic gene to the target tissue. This is one of the factors that explains why gene therapy has a faster clinical effect in some tissues than in others.

2. Comparison of ex vivo and in vivo approaches

The results of the analysis show that ex vivo and in vivo forms of gene therapy have unique advantages in different clinical situations.

In ex vivo therapy, a patient's cells are removed from the body, genetically modified in the laboratory, and then returned to the patient. The main advantage of this approach is the ability to control the modified cells before they are administered to the patient. Examples include therapies for beta-thalassemia and sickle cell disease based on hematopoietic stem cells.

In vivo therapy, on the other hand, involves directly delivering the therapeutic gene or gene editing tool to the patient's body. This method does not require extracting and re-transplanting cells from the body. However, delivering the therapeutic material to the exact tissue may be more difficult. Therefore, tissue-specific and high-precision delivery systems will be of particular importance in the future development of gene therapy.

3. Clinical significance of AAV and CRISPR technologies

AAV vectors are an important platform for current clinical gene therapy. They can be effective in delivering a therapeutic gene to patient cells and are particularly useful in targeting liver, muscle, eye, and certain nerve tissues. However, the limited genetic payload capacity of AAV and immunological issues prevent it from becoming a universal vector.

CRISPR-Cas9, on the other hand, has a different mechanism: it allows for targeted modification of a specific part of the existing genome. Therefore, CRISPR technology creates the possibility of directly modifying the genetic cause in some cases, rather than simply compensating for the disease.

However, editing accuracy remains a major issue in CRISPR-based therapies. Additionally, safely and effectively delivering editing components to the desired cells is another major challenge in clinical applications. Therefore, it is expected that the joint improvement of gene editing

technology and high-precision delivery systems in the future will be an important direction in improving the effectiveness of gene therapy.

4. Balance between efficacy and safety

One of the most important aspects of gene therapy is ensuring safety while achieving high therapeutic efficacy. While the potential for long-term clinical benefit from a single treatment is a significant advantage, it is precisely this long-term effect that complicates safety assessment.

For example, immune reactions associated with viral vectors, liver toxicity, or off-target changes in genome editing require long-term follow-up. Modern Regulator comments that the number of gene therapy products is increasing, but some uncertainties about their long-term safety and efficacy will be resolved over time.

In this context, high clinical efficacy is not enough to automatically consider a therapy safe. Long-term monitoring after gene therapy, monitoring outcomes in real clinical practice, and identifying late-onset adverse effects are important. Due to the unique mechanisms of gene therapies, long-term safety and efficacy monitoring is particularly required.

5. Economic challenges of gene therapy

Despite the high clinical efficacy of gene therapy, its widespread use is severely hampered by economic factors. Many gene therapies are designed as single-dose treatments and require highly complex biological manufacturing processes. As a result, the initial cost of therapy can be very high compared to traditional medications.

In addition, the implementation of gene therapy requires specialized clinical centers, qualified specialists, genetic diagnostics, cell processing laboratories, and long-term monitoring systems. Therefore, when assessing the cost-effectiveness of gene therapy, it is necessary to take into account not only the cost of the drug, but also the reduction in the need for other treatments throughout the patient's life.

According to Nature Reviews Genetics, while the clinical success of gene and cell therapies is increasing, high one-time costs and manufacturing complexity remain a major challenge to their sustained widespread use.

6. Future prospects for gene therapy

The future development of gene therapy is associated with several key areas. First, the goal is to more accurately deliver therapeutic material to the desired cells by creating new generation AAV capsids and non-viral delivery systems. Second, more precise genome editing technologies, such as base editing and prime editing, are being developed alongside CRISPR-Cas9.

Third, the adaptation of gene therapy to the genetic characteristics of an individual patient, i.e., personalized gene therapy, is one of the promising areas. Developments in 2025–2026 are demonstrating the clinical potential of individualized gene editing approaches in some very rare genetic diseases.

New delivery platforms, including lipid nanoparticles and extracellular vesicles, are also being developed as alternatives or complements to viral vectors. Such technologies may enable the delivery of large or diverse therapeutic payloads, reduce immunogenicity, and increase tissue selectivity.

Overall, the results of the analysis suggest that gene therapy can provide clinically significant and sometimes long-term benefits in some genetic diseases. However, efficacy depends on the molecular mechanism of the disease, the time of initiation of treatment, the type of gene therapy chosen, the delivery system, and the individual characteristics of the patient. Therefore, the future success of gene therapy depends not only on the development of new gene editing tools, but also on their safe delivery, long-term monitoring, and economic feasibility.

Conclusion: Gene therapy is one of the most promising areas of modern medicine, allowing direct impact on the mechanisms of genetic diseases. This article analyzes the basic mechanisms, modern technologies, clinical efficacy, safety, and existing limitations of gene therapy.

Analyzed clinical studies have shown that gene therapy has high efficacy in certain monogenic diseases. Specifically, gene therapy in spinal muscular atrophy is helping to maintain motor functions and improve patient survival rates. In hemophilia, gene therapy can provide long-term production of clotting factors in the body, significantly reducing the number of bleeds and the need for regular factor drugs. In hereditary retinal diseases, improvement in visual function has been observed. CRISPR-Cas9-based gene editing technologies have demonstrated the potential for targeted genome modification in the treatment of sickle cell disease and other inherited diseases.

However, it is too early to consider gene therapy as an absolute and universal treatment method. Immunological reactions, limited vector capabilities, off-target genetic changes, long-term maintenance of treatment effects, high economic costs, and the presence of complex clinical processes in some therapies are the main factors hindering its widespread use. The issue of long-term genomic safety, especially in gene editing technologies, requires special attention.

The results of the study show that the effectiveness of gene therapy depends on the type of disease, the nature of the genetic mutation, the age of the patient, the stage of the disease, and the selected delivery technology. In some diseases, starting treatment before symptoms appear can lead to better outcomes. Therefore, genetic diagnostics, newborn screening, and early disease detection are important in improving the clinical effectiveness of gene therapy.

In the future, improvements in AAV and other next-generation vectors, increased precision of CRISPR-Cas9, base editing, and prime editing technologies, the development of effective and safe gene delivery systems, and the reduction of therapy costs may allow for the wider use of gene therapy. In addition, the development of personalized gene therapy, tailored to the individual genetic characteristics of the patient, creates new opportunities for rare genetic diseases for which treatment options are currently limited.

In conclusion, gene therapy is a new therapeutic paradigm that allows us to address the molecular cause of certain genetic diseases rather than temporarily controlling their effects. Although current clinical evidence supports its effectiveness, issues of long-term safety, cost-effectiveness, and equitable access for all patients have not yet been fully resolved. Therefore, the future success of gene therapy depends on its development into a safe, long-term, cost-effective, and widely available treatment, in addition to improving clinical efficacy.

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