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The Impact of Gene Therapy on the Treatment of Hypertrophic Cardiomyopathy – A Literature Review

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Abstract

Introduction: Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disorder. HCM is defined by increased left ventricular (LV) wall thickness or mass not attributable solely to abnormal loading conditions. It is chronic, heterogeneous in terms of its clinical presentation, ranging from absence of symptoms in fenotype to severe left ventricular hypertrophy, sudden cardiac death and end-stage heart failure at young age.

Aim of the Study: This study aims to explore the potential of gene therapy as a novel therapeutic approach for HCM, including the advancements, ongoing clinical trials, and associated challenges.

Materials and methods: More than 55 articles were analysed. They were found using the PubMed search engine focusing on studies investigating gene therapy techniques, including gene replacement, allele-specific silencing, and genome editing with CRISPR/Cas9.

Results: Gene therapy has shown promising results in preclinical models. Early clinical studies are currently underway, aiming to assess the safety and efficacy of gene therapy on humans. Additionally, techniques such as allele-specific silencing and CRISPR-Cas9 present new opportunities in gene therapy. Despite the successes observed in preclinical research, it is crucial to evaluate the safety profile on humans and to address challenges such as off-target effects and the immune response to the introduced molecules.

Conclusions: Gene therapy is emerging as a promising innovation in the treatment of HCM, enabling targeted correction of the genetic causes of the disease. Despite recent advancements, further long-term studies are still necessary to confirm its safety, efficacy, and potential for broad application before it can become a standard therapeutic option.

Key words: hypertrophic cardiomiopathy (HCM); genetic HCM; miosin binding protein C3 (MYBPC3); gene therapy; CRISPR/Cas9; adeno-associated virus (AAV); transgene expression; clinical trials in cardiomyopathies;

Introduction

According to the European Society of Cardiology (ESC), cardiomyopathies are a group of diseases involving structural and functional abnormalities of the myocardium, often accompanied by changes in the pericardium, endocardium, or other organs. Types of cardiomyopathies include dilated (DCM), restrictive (RCM), arrhythmogenic right ventricular (ARVC), non-dilated left ventricular (NDLVC), and hypertrophic cardiomyopathy (HCM). HCM is a condition characterized by an increased thickness or mass of the LV myocardial wall, which cannot be explained solely by abnormal loading conditions. 30% of HCM cases result from single-gene mutations within sarcomeric genes, most commonly inherited in an autosomal dominant manner, with 8 of these mutations recognized as pathogenic(1). These include mutations in the beta-myosin heavy chain (MYH7), alpha-tropomyosin (TPM1), cardiac troponin T (TNNT2), myosin-binding protein C (MYBPC3), essential myosin light chain (MYL3), alpha-cardiac actin (ACTC1), regulatory myosin light chain (MYL2), and cardiac troponin I (TNNI3), collectively accounting for approximately 75% of known mutations.

Cardiomyopathies are characterized by variable expression influenced by the specific mutation, age, presence of arterial hypertension, and physical activity (2). HCM occurs in individuals of all ages and is estimated to affect 1 in 500 people (3).

The clinical presentation of HCM is highly variable. HCM may be asymptomatic, but its first clinical manifestation can also be sudden cardiac arrest, most often due to ventricular fibrillation. The course of HCM depends on the degree of myocardial hypertrophy, the magnitude of the left ventricular outflow tract (LVOT) gradient, and the propensity for arrhythmias, particularly atrial fibrillation (AF). HCM may lead to the systolic heart failure (4).

The most commonly reported symptom in HCM is exertional dyspnea. Additionally, patients may experience anginal pain, palpitations, dizziness, and syncope. On physical examination, a systolic murmur is often detected along the left sternal border, which may radiate to the apex of the heart and the upper edge of the right sternal border.

In electrocardiography (ECG), findings may include signs of left ventricular hypertrophy (LVH), absence of R-wave progression in leads V1-V3, a left axis deviation, signs of biatrial enlargement, or left bundle branch block (LBBB) (5).

The diagnosis of HCM is primarily based on imaging studies, particularly transthoracic echocardiography (TTE) using 2D and Doppler techniques. Since hypertrophy can occur in any region of the heart, it is essential to document the presence, distribution, and severity of hypertrophy according to specific criteria. During the initial assessment, echocardiography should be performed at rest and during the Valsalva maneuver in the sitting, semi-recumbent, and standing positions if a pressure gradient was not previously provoked (6).

If left ventricular outflow tract obstruction (LVOTO) is detected and the underlying mechanism remains unclear, transesophageal echocardiography (TEE) should be considered (7). Additionally, cardiac magnetic resonance imaging (CMR) plays an important diagnostic role, particularly in patients suspected of having apical or lateral wall hypertrophy, as well as in those with an apical aneurysm of the LV(8).

The diagnostic criteria for HCM are defined as left ventricular wall thickness ≥15 mm in any segment of the myocardial muscle, which cannot be solely explained by conditions that burden the heart. In first-degree relatives, HCM is diagnosed when the left ventricular wall thickness is ≥13 mm. Given the genetic basis of HCM, it can also occur in children, where left ventricular wall thickening must be more than 2 standard deviations above the normal value (9).

The treatment primarily focuses on symptom management, improving physical capacity, and preventing complications, with the use of beta-blockers, calcium channel blockers, and, in some cases, antiarrhythmic drugs (10). In certain patients with left ventricular dyssynchrony, cardiac resynchronization therapy (CRT) is applied. To prevent sudden cardiac death, the use of an implantable cardioverter-defibrillator (ICD) is indicated in high-risk patients (11).

This article will discuss one of the emerging therapeutic options for HCM: gene therapy, including its achievements, ongoing clinical trials, and associated challenges. Despite a history spanning over 40 years, gene therapy remains in the developmental phase. However, it demonstrates significant potential in the treatment of genetically determined cardiovascular diseases(12).

Gene replacement

Mutations in the MYBPC3 gene represent the most common genetic defect associated with HCM. These mutations predominantly result in haploinsufficiency, a state in which one of the two alleles in the diploid genome fails to produce sufficient protein levels to meet physiological demands. In this context, only approximately 60% of the normal protein levels are synthesized. Given the mechanism described above, gene therapy targeting the MYBPC3 gene primarily focuses on replacing the defective gene. This approach involves delivering a full-length wild-type MYBPC3 complementary DNA via a vector, which is subsequently translated into functional protein, effectively compensating for the defective counterpart. Lentiviruses were initially used as vectors in gene therapy. In in vivo studies on mice harboring homozygous loss-of-function mutations in MYBPC3, significant restoration of myofilament function and improvement in cardiac performance were demonstrated (13). At present, adeno-associated virus type 9 (AAV9) is the most frequently employed vector in studies on HCM. AAV9 is a small, non-enveloped virus that carries single-stranded DNA (ssDNA) and has the capacity to deliver up to 4 kb of foreign DNA(14).

In a study by Marianiani et al., AAV9 was employed as a vector. One-day-old neonatal mice with severe HCM were administered a copy of the MYBPC3 gene via the AAV9 vector. Thirty-four weeks post-delivery, a dose-dependent increase in MYBPC3 messenger RNA (mRNA) expression and levels of Cardiac Myosin Binding Protein C (cMyBP-C) was observed. This intervention successfully prevented myocardial hypertrophy and cardiac dysfunction (15). Further studies were conducted on cardiomyocytes derived from human-induced pluripotent stem cells (hiPSCs) harboring naturally occurring mutations in the MYBPC3 gene. In these models, the delivery of a full-length MYBPC3 gene during the differentiation phase effectively prevented cardiac hypertrophy and functional impairment (16)

Tenaya Therapeutics, a biotechnology company based in the United States, performs a non-randomized Phase 1b of clinical trial titled "MyPEAK-1" (NCT05836259). This trial evaluates the safety and efficacy of the MYBPC3 gene therapy candidate in humans for the first time. Eligibility criteria include patients aged 18–75 years with HCM caused by a MYBPC3 mutation, New York Heart Association (NYHA) functional class II or III heart failure, NT-proBNP levels ≥160 pg/mL, and left ventricular ejection fraction (LVEF) ≥45%. One of the key exclusion criteria is the presence of high titers of pre-existing antibodies against AAV9 (17). In the "MyPEAK-1" trial, eligible patients receive a single intravenous dose of MYBPC3 gene on AAV9 vector called TN-201. Participants are stratified into two dosing cohorts: Group 1 is

administered 3E13 vector genomes per kilogram (vg/kg), and Group 2 is administered 6E13 vg/kg. All patients receive active treatment. During the follow-up period, several key outcomes will be evaluated, including NT-proBNP levels, changes in NYHA functional class, LVEF and echocardiographic parameters. Additionally, periodic endomyocardial biopsies will be performed to confirm gene delivery and assess the expression of the encoded protein. The main objective of the "MyPEAK-1" trial is to assess the frequency and severity of adverse events (AEs) over a 5-year follow-up period, as well as to evaluate the incidence of serious adverse events (SAEs) directly related to the investigational therapy. At this stage, the study includes a limited number of participants; however, there are plans to expand the trial to other countries in the future (18).

Allele-Specific Silencing in Hypertrophic Cardiomyopathy

In cases of mutations within the MYBPC3 gene, allele-specific silencing techniques are also being explored. RNA interference (RNAi) leverages the natural mechanisms of microRNAs and long non-coding RNAs, which precisely bind to complementary RNA base pairs.

This approach involves designing small interfering RNAs (siRNAs) that, once introduced into cells, specifically bind to the mutated mRNA. This binding triggers its degradation, effectively reducing the production of the abnormal, mutant protein. By targeting only the mutated allele, this method aims to mitigate the pathological effects while preserving the expression of the wild-type protein. This technique is utilized in cases where only one allele in a given pair carries the defective copy of the gene (19). An experimental study was conducted to evaluate exon skipping of exon 6 in the MYBPC3 gene in mice possessing a homozygous guanine (G)-to-adenine (A) transition at the final nucleotide of exon 6, resulting in the production of defective mRNAs. This approach was implemented using antisense oligonucleotides (ASOs) delivered via an AAV vector. The study demonstrated improvements in cardiac function and a reduction in the progression of left ventricular hypertrophy. However, due to the transient effects of this approach, its utility remains currently limited (20).

Allele-specific silencing techniques were also employed to demonstrate the suppression of mutant MYH6 alpha-myosin heavy chain gene expression in mice carrying the R403Q mutation. This was achieved through RNAi delivered to mouse cardiomyocytes via an AAV9 vector. A

25% reduction in the mutant protein levels was shown to attenuate the progression of myocardial fibrosis and hypertrophy. Researchers highlight the therapeutic potential of partial silencing of mutant transcripts in managing genetic cardiomyopathies(21)

Genome Editing

Another technique being explored for the treatment of HCM is genome editing using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas). This powerful technology enables the correction of both gain-of-function and loss-of-function mutations by directly modifying the cell's natural genomic sequence(22). CRISPR/Cas9 is composed of a guide RNA (CRISPR) that specifically aligns with the target gene and Cas9, an enzyme that induces double-stranded breaks (DSBs) in the DNA. The repair of DSBs can occur through homology-directed repair (HDR), a precise mechanism that restores the damaged DNA sequence. However, HDR is effective only in dividing cells, a limitation that is strategically utilized in this technology.

CRISPR/Cas9 is a versatile tool that allows precise editing of the genome by removing, adding, or altering specific sections of the DNA sequence. This technology offers immense potential for addressing genetic mutations, including those associated with HCM, by targeting and correcting the underlying genomic defects(23).

With the advent of genome editing technologies, research into their application for treating HCM has begun. One of the pioneering studies focused on utilizing CRISPR/Cas9 to correct MYBPC3 mutations in preimplantation human embryos.

In this study, human sperm carrying a pathogenic 4-base-pair deletion in MYBPC3 was co-injected with the Cas9 genome editing machinery into oocytes possessing a normal MYBPC3 allele. By modulating the cell cycle stage, DSBs were induced, resulting in high-efficiency correction. This process produced homozygous embryos carrying the wild-type MYBPC3 gene with no detectable off-target mutations. The researchers highlighted the potential of CRISPR/Cas9 for correcting inherited mutations in human embryos, suggesting that this technique could complement preimplantation genetic diagnosis (PGD) in mitigating the transmission of genetic diseases(24).

In a subsequent study, researchers generated a rat model of HCM carrying a Mybpc3 premature termination codon mutation (p.W1098X). In 3-day-old rats, the CRISPR/Cas9 system was delivered via a single dose of adeno-associated virus serotype 9 (AAV9) particles to correct the mutation through homology-directed repair (HDR). At the 6-month follow-up, the correction

of only 3.56% of all Mybpc3 mutations was achieved. This partial correction restored MYBPC3 protein expression by 2.12% and resulted in a reduction in myocardial hypertrophy (25).

CRISPR/Cas9 technology has also been employed in studies targeting a missense mutation in the MYH7 gene, utilizing a mouse model with the human MYH7 c.1208G>A variant. An optimal variant of adenine base editor (ABE) and guide RNA (gRNA) was identified. The study focused on homozygous mice, which typically survive only about one week due to the development of severe HCM. Delivery of ABE and gRNA to cardiomyocytes resulted in a 35% increase in normal protein production, extending the lifespan of these mice by an additional two weeks. Heterozygous mice were also treated, achieving suppression of left ventricular hypertrophy and cardiac remodeling for up to 16 weeks, demonstrating the therapeutic potential of base editing in addressing HCM-associated genetic mutations(26).

In preclinical studies, Clustered Regularly Interspaced Short Palindromic Repeats and their associated protein 13 (CRISPR-Cas13) were also utilized. A high-precision variant of CRISPR-Cas13 (hpCas13d) was developed, and its efficacy was validated through in vitro testing. Next, hpCas13d molecules were delivered via AAV9 to cardiomyocytes in two mouse models carrying single heterozygous single nucleotide variants (SNVs) in MYH7. It was demonstrated that hpCas13d can precisely recognize and suppress the pathological MYH7 variant sequences, effectively preventing myocardial hypertrophy(27).

Modulation of the Signaling Pathway

The molecular mechanisms leading to cardiac dysfunction in HCM are not well understood. Increased sensitivity of the myocardium to Ca2+ has been observed, which contributes to pathogenic remodeling of the cardiac muscle(28). It has been hypothesized that early intervention in Ca2+ regulation may prevent pathological hypertrophy and improve cardiac function which is characterized by increased myofilament sensitivity to Ca2+ and diastolic dysfunction. Increased I_{NaL} appear to play a leading role in HCM and may represent a selective target for pharmacological prevention of arrhythmias in (29)

Modulating the signaling pathway is one of the potential therapeutic approaches for treating the aggressive form of hypertrophic cardiomyopathy (HCM) caused by the D166V mutation in the regulatory light chain of myosin (RLC), encoded by the MYL2 gene. The D166V mutation in the RLC prevents phosphorylation, which is essential for the proper functioning of the cardiac muscle. A study was conducted using AAV9 to deliver a phosphomimetic human RLC variant

with a serine-to-aspartic acid substitution at the Ser15 phosphorylation site (S15D-RLC) into the hearts of humanized HCM-D166V mice. This approach aimed to mimic phosphorylation at this critical site. The study demonstrated an increase in the contractile force of cardiac papillary muscles and enhanced actomyosin activity. Phosphorylation of myosin RLC may have significant translational implications for the treatment of HCM caused by mutations in the MYL2 gene (30).

Nucleosome Occupancy and Methylome Sequencing (NOMe-seq)

Effective treatment methods and a deeper understanding of the mechanisms underlying myocardial remodeling in HCM are still being sought. NOMe-seq enables the detection of nucleosome positioning and DNA methylation, providing valuable insights into epigenetic regulation in HCM(31). It has been demonstrated that, compared to controls, cardiac tissues from patients with HCM exhibit significant differences in the transcriptome (reversion to a fetal gene program), DNA methylome (identification of hypermethylated and hypomethylated differentially methylated regions), and chromatin accessibility (alterations in various genomic elements). These findings provide a high-resolution multi-omics map of HCM cardiac tissues and highlight the potential for therapeutic interventions targeting the process of fetal gene reprogramming in HCM(32).

Ethical Considerations

Ethical issues are a significant challenge in the implementation of gene therapy, highlighting the necessity for legal regulations prior to standardizing this type of treatment. These regulations should incorporate input from experts in biological, social, and medical sciences. Before consenting to therapy, it is essential to establish a process that enables patients to fully understand the procedure, its potential benefits, and any associated risks or complications. Such measures are critical to ensure informed decision-making and uphold ethical standards in gene therapy applications.

In the case of genome editing using CRISPR/Cas9, unintended genomic alterations, known as "off-target effects," may occur. These can lead to potentially harmful mutations in critical genes, such as tumor suppressor genes and genes involved in genomic stability, posing significant safety concerns(33). The immune response to AAV vectors can lead to inflammation. One of the CRISPR-associated vectors, 5'-triphosphate gRNA (5'-ppp gRNA), produced in vitro, has

been shown to induce cytotoxicity. This can be mitigated by replacing it with chemically synthesized single guide RNA (sgRNA) containing a 5'-hydroxyl group, which avoids triggering innate immune responses. However, such scenarios still pose potential health risks and highlight the need for careful evaluation of immunogenicity and toxicity in CRISPR-based therapies(34). Incomplete genome editing may result in the development of so-called "cardiac mosaicism," where only a subset of cells is edited. This heterogeneity could potentially lead to complications such as arrhythmias(35).

The introduction of gene therapy for the treatment of HCM raises the possibility of genome editing in the germline. This approach could prevent the transmission of the condition to future generations, offering a long-term solution to hereditary HCM(36)However, this presents a significant bioethical challenge, akin to human species cultivation (eugenics), as well as issues regarding from whom and how informed consent should be obtained. Additionally, CRISPR-Cas9 may pose risks to the environment, agriculture, and animal husbandry(37).

Another issue for consideration is the potential inequality in access to advanced treatments. The high cost of such therapies may limit availability to individuals with sufficient financial resources. Poor socioeconomic conditions are associated with psychological distress and a lower quality of life, which can lead to multimorbidity and poor adherence to medical recommendations (38). The development of a "policy for expanded access to gene therapy" is of critical importance. This approach represents a potentially one-time treatment that could prevent future costs associated with managing the disease as it progresses(39). Economic models developed based on clinical studies in hemophilia have demonstrated that gene therapy is financially advantageous in the management of this condition(40).

Technical challenges

AAV are widespread in the environment and, although not highly immunogenic, can elicit both humoral and cellular immune responses. A significant proportion of patients possess neutralizing antibodies against AAV vectors. Even very low levels of AAV antibodies can prevent effective transduction in target organs, posing a significant challenge to the success of gene therapy. New variants of AAV with different immunological profiles are being developed, chemical vectors are being modified, and strategies such as immunosuppression and plasmapheresis are being employed. These approaches increase the likelihood of successfully applying gene therapy to a larger group of patients(41). Attempts are also being made to

administer very high doses of AAV; however, this approach carries the risk of dose-dependent vector toxicity. Such toxicity can manifest as myocarditis, hepatotoxicity, or thrombotic microangiopathy (TMA)(42).

There are interspecies differences in sensitivity to AAV, and despite positive outcomes in preclinical studies using AAV9 in small animals, these results should not be directly extrapolated to humans. It is essential to evaluate AAV variants for their tropism toward human cardiac muscle and transduction efficiency. Solutions are being developed to improve AAV tropism for specific tissues, including optimization of AAV capsid selection, strategies to overcome immune responses against AAV, and vector genome design. These advancements reduce dose-dependent immunogenicity, which is both biologically advantageous and economically beneficial(43).

AAV-based gene therapy is also being used for other diseases. While there is substantial evidence supporting its safety, cases of fatalities have been reported. Notably, two deaths due to acute liver failure were documented in patients undergoing treatment for spinal muscular atrophy (SMA) (44). Additionally, a fatal case was reported in a patient treated for Duchenne muscular dystrophy. The patient developed mild cardiac dysfunction and pericardial effusion, followed by acute respiratory distress syndrome (ARDS) and cardiac arrest six days after transgene treatment. The patient died two days later. ARDS is not typically observed as a complication of AAV-based therapy, indicating that both host factors and the inherent characteristics of the vector contributed to the unexpectedly high levels of vector genomes in the lungs, which ultimately resulted in the patient's death(45). These situations highlight the critical importance of carefully evaluating and making informed decisions regarding the inclusion of patients in gene therapy.

Conclusion

Advances in understanding the genetic basis of HCM have driven the search for precise and personalized treatment approaches. Gene therapies represent a rapidly evolving alternative for the treatment of HCM. Although preclinical data and early studies are promising, further long-term research is necessary to establish the safety, efficacy, and scalability of this therapy before it can become a standard therapeutic option. Advances in this field have the potential to significantly enhance the quality of life for patients with HCM and open the door to curative interventions.

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