Gene Therapy for Choroideremia

Subjects: Others

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Choroideremia (CHM) is an X-linked recessive chorioretinal dystrophy caused by mutations involving the *CHM* gene. Gene therapy has entered late-phase clinical trials, although there have been variable results.

Keywords: choroideremia ; gene ; therapy ; clinical trials ; stem cells ; ataluren ; small molecules

1. Introduction

Choroideremia (CHM) (MIM #303100) is a rare X-linked recessive disorder resulting in progressive degeneration of the photoreceptors, retinal pigment epithelium (RPE), and choroid [1][2]. It has a prevalence of 1 in 50,000–100,000 and is caused by mutations in the CHM gene on chromosome Xq21.2 [3]. It encodes Rab escort protein 1 (REP1), which binds to Rab proteins [4][5], facilitating lipid modification through the addition of a geranyl-geranyl group to their C-terminus (known as prenylation). The prenylated Rab protein is then escorted by REP1 and delivered to the target intracellular compartment [4]. Despite CHM being ubiquitously expressed, the primary site of the disease is the retina, as certain Rabs prefer to be prenylated by REP1 over the isoform REP2 [6].

Due to the X-linked inheritance, males are predominantly affected, demonstrating signs of poor night vision that becomes apparent between the ages of 5 and 25 years [7]. The best corrected visual acuity (BCVA) declines slowly with age, and the mean onset of moderate visual impairment occurs in the fifth decade, and, when the macular involvement is evident, visual acuity (VA) becomes asymmetrical [8]. In some patients with preserved central macula, VA can be maintained until late stages of the disease [7][8][9]. Reduction of VA is associated with patchy peripheral visual field loss, which firstly manifests as a mid-peripheral ring scotoma, with later evolution to the complete loss of the peripheral field [10]. Despite retaining good central VA until advanced stages, early change in color vision is reported [11]. The tritan discrimination is predominantly detected using the Cambridge Colour Test [12]. This defect is easy to explain due to the density reduction of S cones located parafoveally compared to M and L cones located centrally [12][13]. In the early stages, fundus examination shows peripheral pigmentary clumping at the level of the RPE that evolves into areas of chorioretinal atrophy [14]. This degenerative process begins at the equator following a centripetal and centrifugal distribution [15]. The same degenerative process is also noted around the optic disc, while a central island of relatively preserved retinal tissue remains even in advanced stages [16].

In order to investigate these retinal changes, several structural and functional tests have been used [17][18][19][20][21][22][23][24][25]. Fundus autofluorescence (FAF) can monitor the progressive concentric loss of autofluorescence, retaining a residual retinal island at the macula of preserved autofluorescence (PAF) [21]. FAF reflects lipofuscin distribution and the signal originating from the RPE (with the photoreceptors contributing in part) [21][26]. The most common pattern is characterized by decreased FAF with sharp demarcated borders of increased signal from residual degenerating retinal tissue [14][16]. The rate of FAF loss was estimated to be 7.7% per year [21]. Areas of PAF have been reported to be vertically expanded and favoring the central and the temporal side of the macula [20]. Spectral domain optical coherence tomography (SD-OCT) reveals attenuation of the ellipsoid zone, [18][22] reduction of outer nuclear layer thickness [22], and outer retinal tubulations due to primary RPE dysfunction [18][23]. In CHM children until the fourth decade, an asymptomatic increase in central retinal thickness without other signs of retinal edema has been described [16]. In CHM adults, macular cystic edema was also identified [11][18][27] and correlated with progressive decrease in VA and poor prognostic outcomes [18]. OCT angiography (OCTA) [24][28] has shown the ability to detect vascular changes in retinal and choroidal circulations noninvasively in CHM, highlighting decreased vascular density [17][19] that precedes photoreceptor loss [20]. Confocal adaptive optics scanning light ophthalmoscopy (AOSLO) is able to provide effective photoreceptor cellular structure characterization [23][25]. A cone density reduction around the fovea was recognized as the early pathogenic effect of CHM mutation on cellular function [29]. Pathological features were identified as normal foveal cone distribution with peripheral abnormalities or increased foveal cone spacing with normal cone mosaic in retinal eccentricities [23]. Those features are associated with pathological retinal loci and are likely indicative of advanced disease stages [30][31]. Microperimetry highlighted cone and rod system dysfunction sensitivity [21][32][33], with the rod-mediated measurements being more

severely affected. Nasal retinal sensitivity appeared to decline earlier than temporal retina, which mirrors a similar pattern of FAF island shrinkage reported previously [21]. Abnormal dark adaptation with a rod intercept time longer than 20 min has been reported [20].

CHM is amenable to gene therapy treatment because it is a monogenic disease, and the cDNA (1.9 kb) is within the size capacity of adeno-associated virus (AAV) vectors (4.7 kb) [34][35]. Lentivirus vectors were used to introduce CHM cDNA in a mouse model, but they showed limited affinity to photoreceptors [36][37]. AAV vectors were able to restore REP1 expression and prenylation function in cell cultures of fibroblasts and lymphocytes derived from CHM patients [38] and improve phagocytosis and trafficking defects in cell cultures of nonhuman primates [39]. Tolmachova and colleagues developed an AAV2 vector (AAV2/2–CBA–REP1) and successfully achieved CHM transgene expression in human and mouse photoreceptors and RPE cells [40]. The advances in preclinical studies lead to the first-in-human gene therapy clinical trial for CHM (NCT01461213) using an adeno-associated virus Rab escort protein 1 (AAV2.REP1) vector in 2011 and from then several multicenter clinical trials worldwide. The aim of this review is to give a summary on the outcomes of CHM gene therapy trials in phase I/II.

2. Discussion

Gene therapy for CHM has reached phase III clinical trials, providing real promise for patients. Review of the ongoing trials has shown that 40 patients have been treated so far with an AAV2-REP1 vector. The most common AEs were subconjunctival hemorrhage, blurred vision metamorphopsia, and a post-operative IOP reduction. The most AE was acute localized foveal thinning, retinal stretching, and intraocular inflammation (vitritis and choroiditis) in three patients. However, overall increased vision with an average gain of 3.1 ETDRS letters (−14 to 18 ETDRS letters) has been ascertained.

Despite the promising results, in order to prolong the long-term transgenic potential and the need for repeat treatments, several challenges remain to be addressed, such as defining the ideal therapeutic window, ensuring that the necessary cell types are adequately transduced, and minimizing viral toxicity. Many of these questions will be answered by ongoing clinical trials, such as the REGENERATE trial phase II (Oxford and Moorfields Eye Hospitals, UK), the GEMINI trial phase II (Tubingen, Germany), and a phase III international multicenter gene therapy STAR trial. Up to now, results have not yet been published for these trials.

Regarding viral toxicity, the vector used for RPE65 retinal dystrophy (Luxturna, Spark Therapeutics Inc., USA) included a strong ubiquitous promoter that targets multiple cell types, including the RPE and the photoreceptors. The solution was adjusted to pH 7.3 and subjected to removal of empty capsids [41][42]. Several strategies are being used to optimize AAV vectors, ranging from the addition of exogenous agents for immune evasion to genetic manipulation of the viral capsid. Continued work in these areas should be followed in order to improve targeting, transgene expression, and immune evasion improving the translational success [43]. The vector construct used, AAV2-CAG-CHM-WPRE-polyA, is identical to the vector used in Luxturna, except for the CHM transgene. In order to reduce post-injection inflammation, all trials used a systemic steroid treatment that included 1 mg/kg/day of prednisolone for 10 days (beginning 2 days prior to gene therapy, on the day of surgery, and for 7 days afterward), followed by 0.5 mg/kg/day for 7 days, 0.25 mg/kg/day for 2 days, and 0.125 mg/kg/day for 2 days. The NCT02671539 (Tubingen) trial also reported a combination of moxifloxacin and dexamethasone eye drops for 21 days. In order to improve the safety profile of the gene therapy and to reduce the risk related to sub-retinal injection, 4D Molecular Therapeutics (4DMT) optimized the AAV vector and designed a new drug: 4D-100 (Roche Pharma AG) comprises an AAV capsid variant carrying a transgene encoding a codon-optimized human CHM gene to be delivered by intravitreal injection. Due to its optimized vector, 4D-110 is a novel gene therapy approach that shows promise in safely treating a broad region of the retina and a broad range of patients. The clinical trial (NCT04483440) was designed to assess the preliminary safety, tolerability, and biological activity of a single intravitreal injection of 4D-110. Up to now, 15 patients were enrolled, and the estimated study completion date is May 2023.

2.1. Small Molecule Drugs for CHM

In addition to gene therapy, there are several alternative strategies under development with a potential to treat CHM. About 30% of CHM cases are related to in-frame nonsense mutations, resulting in premature termination codons (PTCs) [44][45]. Small molecule drugs based on aminoglycosides can promote ribosomal read-through of PTCs during translation through competitive binding of near-cognate aminoacyl-tRNAs (tRNAs) instead of eukaryotic release factors (eRFs) [44][46]. In order to halt the progression of recessive disease, 20–25% of wild type levels of functional protein need to be restored [46].

Among the compounds with proven read-through activity are traditional aminoglycosides (gentamicin, paromomycin and geneticin (G418)), the less toxic next-generation designer aminoglycoside-derivatives (NB84, NB74, and NB124), non-aminoglycoside small molecule drugs (PTC124 and PTC414), and small molecule read-through (SMRT) compounds (RTC13, RTC14, GJ071, and GJ072) [46][47]. PTC124 (also known as ataluren or Translarna) has received NICE (National Institute for Health and Care Excellence) approval for Duchenne muscular dystrophy treatment caused by nonsense mutations in the dystrophin gene [48].

In vitro and in vivo preclinical testing of ataluren in models of CHM has led to some promising results with improved REP1 expression [49]. Limitations in the evolution of this treatment are the lack of suitable ocular preparations for targeted drug delivery, the lack of specificity for the gene of interest, hence risk of overriding other random PTCs in the genome, and the decreased availability of transcripts due to nonsense-mediated decay (NMD), thus reducing the substrate for the drug action [46]. It is possible that combining read-through agents with NMD pathway inhibitors (e.g., caffeine, NMDI1, VG1) or dual action agents (amlexanox) could enhance therapeutic benefit [47][50][51][52].

2.2. Stem Cell Therapies

Stem cell regenerative approaches are an alternative future treatment for CHM, but there is still a need to identify the correct cell type and the adequate stem cell system in order to achieve tissue regeneration. In addition, the delivery method and the therapeutic window need to be assessed [36].

Skin fibroblast-derived induced pluripotent stem cell (iPSC) technology has been used to differentiate RPE cells, which have been used in clinical trials for treating wet age-related macular degeneration (AMD) in Japan, and retinal progenitor cells were injected intravitreally in a Phase IIb clinical trial for retinitis pigmentosa (NCT02320812) [53]. Recently, hESC-derived RPE cells layered on synthetic membrane have been reported to improve visual acuity (visual acuity gain of 29 and 21 letters, respectively) in two patients with acute wet AMD and rapid deterioration in visual acuity [54]. Further research is required for inherited retinal diseases because, being a chronic disease, they may have long-term structural changes with atrophy that may prevent this form of therapy from being successful.

2.3. Neuroprotection Agents

Neuroprotectants are being investigated, such as antioxidants and lutein supplements. They have been found to delay disease progression and result in visual acuity improvement in retinitis pigmentosa [55][56]. Lutein is a xanthophyll carotenoid found in high quantities in green leafy vegetables; it is able to augment macular pigment function through short-wavelength filtration and reactive oxygen species stabilization [57]. Oral supplementation with lutein for 6 months has been studied in CHM patients but there was no measurable benefit in terms of foveal sensitivity and central visual acuity [57].

Reactive oxygen species (ROS) underlie the pathophysiology of diverse neurodegenerative diseases. To control the oxidation process, cells need to activate and deploy endogenous antioxidant defenses. Oxidative stress is caused by an imbalance between the antioxidant defense system and the production of ROS. In the retina, the source and impact of ROS are different depending on the pathology. RPE is particularly susceptible to ROS formation due to its high consumption of oxygen, high proportion of polyunsaturated fatty acids, and constant exposure to light, inducing an increase of photoreceptor cells apoptosis [58]. However, in most inherited photoreceptor degenerations (IPDs), it is suggested that photoreceptors death may be mechanistically different [59]. One possible source of oxidative stress in IPDs is oxygen toxicity in the outer retina due to reduced consumption by photoreceptors mitochondria [60].

Mutations in the glyoxalase 1 (GLO 1) enzyme, involved in the detoxification of a cytotoxic byproduct of glycolysis, were identified in a Sicilian family affected with retinitis pigmentosa (RP). This mutation was suggested to be associated with a faster progression of the retinal disease [61]. At least five other RP causative genes (KLHL7, RDH11, CERKL, AIPL1, and USH1G) suggested a tight connection between induced oxidative stress and RP onset with faster progression [62].

Zebrafish are a well-described CHM model that has been successfully used to highlight the efficient read-through of aminoglycosides and small molecule drugs and their toxic effects. High levels of oxidative stress were associated with *chm*^{ru848} eyes, but once treated with PTC-derived small molecules, the ROS were significantly reduced [49]. Oxidative stress can play a negative role in CHM eyes, and its reduction may be beneficial. Discovering new treatments to counter ROS formation will be a step forward in preventing or slowing down the progression of CHM. Enhancing the production of antioxidant enzymes to reduce ROS or to promote cytoprotective signaling pathways may be a worthy strategy to pursue [63].

2.4. Electronic Implants

Electronic retinal implants are an alternative treatment for the final stage of CHM [64]. CHM patients with no light visual perception have been enrolled in several clinical trials testing a 44-channel suprachoriodal bionic eye device (NCT03406416) in Melbourne, Australia, and testing the Intelligent Retinal Implant System (IRIS) V1 (NCT01864486) and V2 (NCT02670980) (Pixium Vision SA). The IRIS II has demonstrated reasonable safety at 6 months with a comparable adverse effect profile compared to the Argus II implant that reaches more than 5 years of follow-up. The IRIS had an increased number of electrodes compared with the Argus II, providing better visual acuity; however, future studies will be needed to further elucidate that result [65].

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