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CHOROIDEREMIA:

Retinal Degeneration With an Unmet Need

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Abstract

Purpose: Choroideremia is an incurable, X-linked, recessive retinal dystrophy caused by loss of function mutations in the *CHM* gene. It is estimated to affect approximately 1 in 50,000 male patients. It is characterized by progressive degeneration of the retinal pigment epithelium, choroid, and photoreceptors, resulting in visual impairment and blindness. There is an unmet need in choroideremia, because currently, there are no approved treatments available for patients with the disease.

Methods: We review the patient journey, societal impact, and emerging treatments for patients with choroideremia.

Results: Its relative rarity and similarities with other retinal diseases in early years mean that diagnosis of choroideremia can often be delayed. Furthermore, its impact on affected individuals, and wider society, is also likely underestimated. AAV2-mediated gene therapy is an investigational treatment that aims to replace the faulty *CHM* gene. Early-phase studies reported potentially important visual acuity gains and maintenance of vision in some patients, and a large Phase 3 program is now underway.

Conclusion: Choroideremia is a disease with a significant unmet need. Interventions that can treat progression of the disease and improve visual and functional outcomes have the potential to reduce health care costs and enhance patient quality of life.

Keywords

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Mutations in more than 250 genes have been found to cause inherited retinal diseases, most commonly in genes expressed in photoreceptors or the retinal pigment epithelium (RPE).[1] Choroideremia is an X-linked, recessive inherited retinal disease that is currently incurable and is estimated to affect approximately 1 in 50,000 male patients.[2,3] The condition is characterized by progressive atrophy of the RPE, choroid, and photoreceptors (Figure 1).[2] Choroideremia is caused by mutations of the *CHM* gene, which encodes Rab escort protein 1 (REP1).[2,4] REP1 is important in the regulation of Rab GTPases and a key mediator of vesicle trafficking in the retina and RPE.[5,6] Mutations in *CHM* that result in choroideremia include sequence variations, translocations, point mutations, small deletions, insertions, nonsense, and frameshift mutations.[6] Nonsense and frameshift mutations account for approximately 70% of all REP1 gene alterations. The remaining 30% consists of splicing mutations.[6] Despite most disease-causing mutations in choroideremia being considered functionally null,[7] there can be variation in severity of phenotype, even within a single family with the same mutation.[8] It has not been possible to establish a clear correlation between different *CHM* mutations and disease severity.[7,9]

Although the genetic abnormalities underlying choroideremia are relatively well characterized, the pathogenesis of the disease remains poorly understood.[6] In male patients with choroideremia, night blindness and visual field loss begin in the first decade of life and progress until legal blindness develops much later in life, around the fifth to seventh decade.[2,10–12] Controversy exists regarding the sequence of pathogenic events in choroideremia. It is believed that the disease initially manifests as RPE degeneration, perhaps with independent and concurrent photoreceptor outer segment degeneration, and later choroidal atrophy.[13–15] However, there is also evidence of severe abnormalities at the photoreceptor level, particularly the outer segment, that clinically precede overt, localized RPE abnormalities.[12,16,17] Generally, carrier female patients exhibit mild disease characteristics with greater levels of variability, compared with affected male patients. Choroideremia in female patients ranges from asymptomatic to rare cases of severe disease characterized by scalloped areas of RPE degeneration with choroid loss and pigment clumping similar to choroideremia in male patients.[18] Figure 2 shows the eye examination results of a female carrier aged 58 years with a best-corrected visual acuity (VA) of 20/80 in the right eye and 20/20 in the left eye, and late-onset symptoms of choroideremia. Fundus photography reveals central and midperipheral mottling; intravenous fluorescein angiography shows areas of RPE atrophy; and optical coherence tomography (OCT) shows outer retinal loss correlating with the areas of RPE degeneration. The high variation in female carrier disease severity is believed to be due to random X-chromosome inactivation; severe choroideremia in female patients has been attributed to a skewed X-chromosome inactivation pattern.[18,19]

Clinical evaluation of patients with choroideremia involves assessment of visual function through visual field testing and full-field electroretinogram testing and assessment of retinal and RPE structure with OCT and fundus auto fluorescence (FAF). Full-field electroretinogram shows abnormal scotopic responses in such patients,[3,20–22] which correlate symptomatically with a reduction in rod-mediated night vision; it is believed that cone cell death is secondary to rod cell death, occurring much later in disease progression.[3] Optical coherence tomography reveals areas of decreased RPE reflectance and thinning of the retinal layers in the macula in the early stages of the disease and further loss of RPE

reflectivity and outer retinal tubulations followed by chorioretinal atrophy at later stages.[16] A study that conducted OCT evaluation of 21 male patients with choroideremia who spanned an age range of 7 decades reported generalized central and peripheral thinning of the retina before the fourth decade.[16] Some patients develop cystoid macular edema, mostly located in the outer retinal layers,[23] and in rare instances, observations of choroidal neovascular have also been reported.[6] Fundus autofluorescence reveals areas of chorioretinal atrophy in patients with choroideremia[3] and permits evaluation of disease progression by allowing the rate of shrinkage of intact RPE to be calculated. By combining FAF and OCT, the loss of both RPE and photoreceptors can be followed over time. Fundus autofluorescence may also be useful for detecting female carriers in childhood.[2]

Natural history studies aim to shed light on the pathogenesis of choroideremia, which will provide insights relevant to patient management and clinical trial design. Although natural history data are available for choroideremia, they mainly comprise retrospective analyses[9,11,24] or prospective cross-sectional snapshots of a representative choroideremia population.[12] The Natural History of the Progression of Choroideremia Study (NIGHT; NCT03359551) is an ongoing, 2-year prospective, natural history observational study of around 300 patients with choroideremia who are more than 18 years of age. This study aims to provide important evidence on the disease state and rate of disease progression in patients with choroideremia who are not receiving treatment. Initial baseline and 12-month data have indicated that mean visual acuity change is slow, but this is heterogenous and a considerable proportion of patients experience decline over a 12-month period; furthermore, visual acuity becomes asymmetrical in late-stage disease.[25,26] The potential of such studies is further highlighted by a recent analysis that used patients enrolled in NIGHT and aimed to validate anatomical or physiologic clinical outcomes measures for use in clinical trials of potential treatments for choroideremia. Two reproducible methods for quantifying anatomical outcome measures have been identified: preserved RPE area using FAF images and ellipsoid zone areas using OCT.[13] Further analyses of data from natural history studies will provide evidence that will improve diagnosis, predict the likely course of disease, characterize the burden of disease, and help assess the impact of treatment interventions.

The Patient Journey

In patients with choroideremia, vision loss is progressive and inevitably leads to blindness. Typically, boys affected by the disease report difficulty seeing at night in their first or second decade of life, and in their 20s become aware of loss of peripheral vision. Most patients show a slow degeneration of peripheral vision, whereas central vision is preserved until later in life, resulting in tunnel vision. Men in their 40s with choroideremia may have good visual acuity but only a small visual field; one study found the median age for retaining 20/20 vision was 39 years.[27] Later, around 50 to 70 years of age, the central vision is also lost, resulting in severe vision loss and often complete blindness.[2,6,11,12]

Unless there is a known family history, in which case testing would have been expedited, the first interaction with a health care professional (often a primary care doctor or ophthalmologist) occurs when nyctalopia develops in the patients' teenage years. Clinical characterization of choroideremia usually includes a fundus examination, visual fields,

electroretinogram, OCT, FAF, and an evaluation of family history.[2,3] Fundus examination is often the first evaluation completed and typically reveals patches of chorioretinal atrophy and RPE degeneration in the midperiphery,[6] corresponding to peripheral visual field deficits. Patients with suspected choroideremia are then referred to retinal specialists. A family history consistent with X-linked inheritance helps to further support diagnosis, which can be confirmed with the identification of a pathogenic variant in the *CHM* gene. In the early stages of disease, and en face near-infrared reflectance may show increased visualization of the pericentral choroidal vasculature[12] and a mottled pattern reflecting fine pigmentary changes on fundus photography (Figure 1A).[6] Examination using spectral domain OCT may generally appear normal but with evidence of photoreceptor outer segment shortening and cell loss, which becomes more apparent over time; however, one study demonstrated severe outer nuclear layer thinning on OCT and clear depigmented lesions within the central retina on fundus examination in all enrolled patients younger than 15 years.[12] Over time, ocular degeneration in patients progresses more centrally to encompass more of the choroid and RPE.[6] This manifests as residual, scallopedged islands of relatively normal RPE pigmentation surrounded by the depigmented RPE and choroid observed on en face near-infrared reflectance.[12] The areas of choroidal atrophy correspond to the areas of visual field lost.[6] In late-stage choroideremia, some patients may have a small residual island of the RPE with severe retinal thinning such that the vessels of the choroid may be visualized (Figure 1, E and F).[12] One study estimated a 10-fold decrease in FAF every 25 years, equating to a 7.7% reduction in residual retinal area every year.[28] This contrasts with an approximate mean loss of 0.5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters per year.[25]

There are several challenges associated with the diagnosis of choroideremia. First, particularly in the early stages, choroideremia often manifests as non-specific retinal degeneration.[6] Second, the clinical phenotype of the disease can have features that overlap with other retinal dystrophies, such as gyrate atrophy and rare variants of X-linked retinitis pigmentosa (RP), Usher syndrome Type 1, cone-rod dystrophy,[29] Kearns-Sayre syndrome,[6] and dystrophies caused by autosomal dominant *RPE65* and *NRL* mutations.[30–32] Finally, if severe and diffuse enough, autoimmune retinopathies can mimic certain features of choroideremia, for example, bilateral diffuse uveal melanocytic proliferation.[33] Features that distinguish RP from choroideremia include the retinal pigment migratory pattern; the extent of pigment migration into the retina, which is characteristic of RP, is not observed in patients with choroideremia.[6,34] In addition, owing to the relatively low prevalence of choroideremia, many ophthalmologists, even retinal specialists, do not have experience with the condition. The rarity and clinical overlap of choroideremia with other retinal dystrophies mean that it is frequently misdiagnosed, prolonging the time to correct diagnosis and impact on subsequent monitoring and treatment.

Choroideremia and Associated Vision Loss Have a Significant Societal Burden and Impact on Patient Quality of Life

Patient quality of life—A PubMed search conducted in March 2018 did not reveal any studies that evaluated quality of life (QoL) in patients with choroideremia. This highlights the relative neglect of choroideremia as a serious condition and emphasizes the need for further research in the area. The importance of vision loss to QoL was supported in a recent

U.S. nationwide survey of more than 2,000 people that found that vision loss was considered to be the worst possible health outcome.[35] Of the possible consequences of vision loss, reduced QoL was ranked as the top concern, followed by loss of independence. The impact of vision loss on patients' health-related QoL manifests as functional disabilities, such as difficulty with walking and driving.[36,37] A study of more than 5,000 participants from the 2005 to 2008 National Health and Nutrition Examination Survey evaluated the relationship between the severity of visual field defects and vision-related and physical functional disability. Participants with greater severity of visual field defects had greater difficulty with vision-related activities, particularly daytime driving in familiar places and noticing objects off to the side when walking.[36] Accordingly, patients' mobility and independence have been shown to worsen as visual impairment increases.[38] The QoL lost because of vision impairment and blindness has been estimated to be 215,000 quality-adjusted life-years in those younger than 40 years in the United States in 2012.[39]

Given the paucity of QoL data for choroideremia, other similar conditions could serve as "surrogates" in QoL assessment. In the case of choroideremia, RP may provide insight as a chronic progressive degenerative disease of the eye that may also be asymptomatic in the initial stages of disease but can progress from irreversible visual field loss with maintenance of visual acuity to gradual visual acuity loss and eventual blindness.

The 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) is a measure of vision-related health-related QoL from the patients' perspective. The questionnaire provides an overall score as well as subscale scores that focus on content related to the impact of visual difficulties in everyday life, including psychosocial domains such as role difficulty, social function, and mental health.[40] Studies using the NEI-VFQ-25 have shown that patients with RP have impacted health-related QoL and that the impact of the disease on patients' QoL is likely to increase with greater levels of vision loss.[40–42]

A number of studies have investigated the impact of vision loss caused by different conditions on patients' mental health. One study of 144 patients with RP found that the prevalence of depression in these patients is much higher than the prevalence reported in the general population.[42] These findings were supported in a longitudinal, prospective cohort study of 540 older adults from the Netherlands with vision impairment (48% macular degeneration, 15% glaucoma, and 13% cataract) who were followed for 24 months. The study showed that these patients were more vulnerable to developing symptoms of anxiety and depression and that annual cumulative incidence of subthreshold anxiety was 9.5% and subthreshold depression was 21.3%, which were much higher than levels reported in the general older population.[43] The likely impact of vision loss on patients' mental health highlights the need for monitoring of patients with vision impairment and the need for novel therapies.

Economic burden—As with patient QoL, no studies evaluating the economic burden of choroideremia were identified. Studies of patients with visual impairments, including patients with RP, have reported significant economic and social disadvantage in affected individuals, their families, and society generally.[39,44–46] Patients with visual deficiencies have more frequent medical visits, may need assistance to perform everyday activities, and

may have difficulties maintaining employment. Studies have reported that there are significant differences between patients with RP and the general population in terms of education level and income[44] and that patients with RP use more inpatient, outpatient, and emergency department services and prescription drugs.[45] A systematic review of the literature regarding the economic burden of visual impairment and blindness reported high indirect costs primarily related to lost productivity, changes in employment, loss of income, premature mortality, and excess financial burden on society. All identified costs correlated with the degree of visual impairment, and the highest level of expenditure was associated with blindness. Annual estimates for lost productivity and absenteeism due to visual impairment and blindness were approximately five billion U.S. dollars, and the annual cost related to the overall decrease in workforce participation in the United States was estimated at more than seven billion U.S. dollars.[46] According to another estimate from an econometric and statistical analysis of U.S. survey, commercial claims, and census data from participants younger than 40 years, total indirect costs related to vision loss and eye disorders were 13 billion U.S. dollars, most of which ($12.2 billion) were due to productivity losses.[39] Although only a proportion of these will be due to choroideremia, in light of its low prevalence, these data highlight the societal costs of retinal dystrophies, and the disproportionately higher burden of these in the younger patient population.

Treatment Options

Aims of treatment—To date, there are no approved treatments for choroideremia. Physicians treating patients with choroideremia should refer patients for low vision consultation and evaluation, so that patients may be provided with the most appropriate adaptive technology and assistance. In addition, regular visits with a retinal specialist are important, so disease progression can be monitored and comorbidities (including cataracts, cystoid macular edema, or choroidal neovascularization) can be identified and treated. The lack of available treatment options for choroideremia is in itself likely to reduce the motivation for patients and physicians to maintain regular appointments, and thus increase the risk of disease complications. Owing to the degenerative nature of choroideremia, patients are frequently seen by a health care professional for the first time in a moderately advanced disease state where the patient has good central but little peripheral vision. Therefore, preservation of vision (i.e., halting decline) is often a realistic aim of treatment. However, preliminary gene therapy studies have suggested that it may not only be possible to halt disease progression but also to reverse the loss of visual acuity experienced at later stages of disease progression.[10] Although there are currently no treatment options available for patients with choroideremia, several approaches to managing the disease and its progression are under investigation.

Adeno-associated virus–mediated gene therapy.—Gene transfer of functional *CHM* into patients with choroideremia is currently being explored. A number of adeno-associated virus (AAV) vector-based gene therapies are in clinical development by several entities, including Nightstar Therapeutics, Spark Therapeutics, and Roche/4D Therapeutics. There are several factors that make choroideremia an attractive target for gene therapy. First, the slow rate of disease progression provides a potentially large therapeutic window in which patients can be treated, although an extended follow-up would be required to assess

treatment efficacy.[3] Second, the eye is relatively easy to access surgically, allowing for direct delivery of the vector to the target tissue.[47] Finally, the availability of a range of imaging techniques facilitates noninvasive monitoring and evaluation after treatment.[47] Adeno-associated virus gene-replacement therapies are being explored in a number of diseases, including other retinal dystrophies, and AAV serotype 2-based therapies have been shown to be well tolerated and effective for use in humans long term.[3] In December 2017, LUXTURNA (voretigene neparvovecrzyl; Spark Therapeutics, Philadelphia, PA) became the first gene therapy for pharmacologic treatment for an inherited retinal disease (biallelic *RPE65* mutation-associated retinal dystrophy), and the first AAV vector gene therapy to be approved in the United States.[48,49]

Preclinical studies using animal and in vitro models showed restoration of REP1 expression and function after delivery of healthy *CHM* by recombinant AAV.[50–52] The first clinical data from gene therapy in patients with choroideremia were published in 2014.[10] The study was a multicenter clinical trial of 6 male patients aged 18 years or older with a clinical phenotype of choroideremia and predicted null mutation in the *CHM* gene who were treated with AAV2-REP1 (vector supplied by Nightstar Therapeutics, London, United Kingdom). Patients enrolled had a best-corrected visual acuity of at least 20/200 Snellen and visible active disease within the macula. To assess whether there is an optimum treatment window for choroideremia gene therapy, adult patients with disease at different stages of foveal involvement (but all with severely constricted visual fields) were included, representing a cross-section from normal foveal architecture to complete foveal loss, as assessed using fundus examination and FAF. Exclusion criteria included a history of amblyopia, retinal surgery, or uveitis in the study eye; an inherited retinal disease other than choroideremia; grossly asymmetric disease; or any ocular morbidity that confounded use of the fellow eye as a long-term comparator. The ideal patient for a choroideremia gene therapy clinical trial likely differs from the ideal patient to receive gene therapy that has already been shown to be well tolerated and effective in the treatment of choroideremia. In the early stages, the clinical trial design accounts for enrollment of patients with severe disease to determine whether the treatment is tolerated. Inclusion criteria of subsequent clinical trials allow for enrollment of patients with better remaining vision, with the goal of demonstrating not only tolerability at increasing doses but ultimately efficacy. One eye of each patient was injected with the vector construct, while the other eye acted as a control and did not receive intervention.[10,53] Six months after treatment, the mean improvement in visual acuity was 3.8 ETDRS letters.[10] Retinal sensitivity at the location of maximal sensitivity, as assessed by microperimetry, increased by a mean of 2.3 dB (95% confidence interval: 0.8–3.8) and mean retinal sensitivity increased by 2.5 dB (SE 1.1) 6 months after surgery in the 5 eyes that were administered the full dose of the vector but fell by 2.3 dB in 1 eye that was administered a reduced dose.[10] As enrolled patients were at different stages in their disease, subgroups based on disease stage were evaluated for treatment efficacy. The two patients with advanced choroideremia who had low baseline visual acuity (Patient 1 and Patient 4) gained 21 letters and 11 letters in their treated eyes, and 11 and −1 letters in their control eyes, respectively, at 6 months.[10] These two patients also reported subjective improvement in vision of their treated eye after 6 months.[10] Importantly, in this slowly progressing disease, the clinically meaningful improvement in visual acuity in these 2 patients was sustained at 3.5 years after

treatment (Patient 1 had gained 21 letters, and Patient 4 had gained 18 letters by the end of follow-up), despite progressive degeneration in control eyes (Patient 1 lost 18 letters, and Patient 4 lost 6 letters).[53] The other 4 patients (Patients 2, 3, 5, and 6) had near normal baseline visual acuity (better than 6/9 Snellen equivalents) and had marginal losses of 1 to 3 ETDRS letters at 6 months after treatment.[10] At the 3.5-year follow-up, visual acuity in the treated eye of Patient 2 and Patient 5 was close to baseline values, whereas the control eye was lowered by 10 and 11 ETDRS letters, respectively.[53] Patient 3 experienced no change in visual acuity in either eye, whereas Patient 6 had reduced visual acuity in both eyes of 3 and 2 letters in treated and control eye, respectively.[53] Although all but 2 patients followed over 3.5 years experienced gains in visual acuity less than the 15 ETDRS letters commonly accepted as clinically significant, the potential to maintain or gain a small amount of visual acuity is an encouraging prospect for patients who would otherwise experience inevitable vision loss and likely blindness.

The fovea is vulnerable to mechanical damage because of its single cell layer structure and choroideremia disease pathology, and the volume of the target tissue is consistently shrinking. Therefore, the volume and site of injection are important considerations. For patients with early-stage choroideremia, in which there is a large treatable area of retina, intravitreal vector delivery may be beneficial, so that a large area can be targeted.[54] Younger patients with 20/20 vision may also opt for intravitreal treatment to avoid possible damage to the fovea. Conversely, subretinal delivery of the vector may be a preferred approach for the treatment of more advanced stages of choroideremia, in which the area of treatable retina is localized, as the residual cells are targeted specifically.[54] However, subretinal injection increases the risk of mechanical damage to the fovea, which had been a concern in a preclinical animal study[55] and other subretinal gene therapy clinical trials.[56,57] In the first clinical trial, involving *RPE65* deficiency, a decrease in foveal thickness of 80.3 μm from before treatment to 90 days after treatment was observed in one of 3 eyes. The authors speculated that abnormal foveal architecture before treatment may have affected the outcome after treatment but nevertheless concluded that strategies involving near-fovea retinotomy may impact foveal structure.[56] In a follow-up of this study, short-term foveal thinning was observed in 2 of 15 eyes, which was retained after long-term follow-up in 1 eye. A third eye showed significant foveal thinning in the long term but not the short term. In a further two eyes of patients who underwent foveal detachment, short-term photoreceptor damage was observed, which later recovered. Based on these observations, the authors speculated that short-term foveal thinning was due to a complication of subfoveal injection, whereas long-term foveal thinning represented the natural progression of *RPE65*-Leber congenital amaurosis disease.[57] Foveal thinning was not reported in any of the patients in a Phase 3 study of *RPE65*-Leber congenital amaurosis disease, although full-thickness macular hole, which spontaneously resolved to macular thinning, was reported in one of 20 eyes.[48]

In addition, a recent study in healthy primate eyes found no clinically significant outer nuclear layer thinning after subretinal injection of an AAV vector not involving the fovea.[58] Finally, in the Phase 1/2 choroideremia gene therapy study (analysis supported by Nightstar Therapeutics), the mean thickness of the retina in the 6 patients was similar before and 6 months after the surgery.[10] The study continues to monitor the patients to provide long-term

outcome data. Although subretinal injection has the potential to cause damage to the fovea, this must be weighed against the potential benefit of gene therapy for a disease in which the fovea will undergo inevitable damage if untreated.

A pooled analysis of the 4 Phase 1/2 open-label trials of AAV2-REP1 including a total of 32 adult patients with choroideremia showed that microperimetry and anatomical outcomes were preserved and 16% had achieved 15-ETDRS letter improvements at 1 year (analysis supported by Nightstar Therapeutics).[59] Based on these findings, a Phase 3 study of AAV2-REP1 in adult patients with choroideremia (STAR; NCT03496012; Nightstar Therapeutics) began in March 2018.[60] There is an additional ongoing Phase 1/2 trial in patients with choroideremia using a second vector, AAV2-hCHM (NCT02341807; Spark Therapeutics). In preliminary 6-month safety data from the AAV2-hCHM study, which enrolled nine adult patients, visual acuity returned to baseline in all but one patient, who gradually returned to within 20 ETDRS letters of baseline by Month 6.[61] In this patient, foveal thinning to approximately 80% of baseline was observed; indeed, mild foveal thinning due to shortening or loss of photoreceptor outer segments was seen in all patients. This individual also experienced foveal sensitivity loss, and the investigators suggest that these observations show the potential for non-vector-related individual vulnerability to the subfoveal injection procedure.[61] Mean sensitivity, as assessed by light-adapted perimetry, remained unchanged in both operated and control eyes; microperimetry demonstrated short-term increases in light sensitivity; and two-color dark-adapted perimetry showed nonsignificant increases in cone-mediated sensitivity for some locations in the treated eye of three patients.[61] One additional pipeline gene therapy reagent for choroideremia is 4D-110 (4D Molecular Therapeutics/ Roche, Emeryville, CA).[62] Limited information on the vector construct is available, and clinical trials have not yet commenced; however, 4D-110 will be administered by intravitreal injection.

There are a number of challenges that remain and will need to be overcome before AAV-mediated gene therapy can be used as a treatment for choroideremia. First, the safety and durability of effect should be demonstrated in a larger number of patients with choroideremia and over the long term. Further study is also required to identify predictive factors (such as disease stage) for treatment success, so that patients who will likely experience the greatest benefit from treatment are targeted. So far, only adult patients with advanced choroideremia disease have been enrolled in clinical trials because of risk–benefit considerations. Ultimately, once safety has been confirmed, it may be desirable to include younger individuals to more fully explore whether the intervention can prevent disease progression and determine whether affected carrier female patients could also benefit from treatment. Administration-specific factors are also critically important for the success of gene therapy treatments. Sharing of best practice and novel techniques to maximize surgical precision will be key in treatment success and minimization of risks and adverse events associated with the procedure. Finally, it will be beneficial to understand any potential treatment effects on the second (untreated) eye and the effects of bilateral treatment.

Nonsense bypass therapy.—Nonsense mutations result in the premature introduction of a termination codon in the mRNA transcript and consequently the generation of a truncated, often dysfunctional peptide. For patients whose choroideremia is a result of a nonsense

mutation, translational readthrough-inducing drugs are cited as a possible treatment.[63] Readthrough agents (ataluren and its analogue PTC-414; PTC Therapeutics, South Plainfield, NJ) have shown promise as treatments in a zebrafish model of choroideremia caused by a nonsense mutation, in which they prevented the onset of retinal degeneration and increased REP1 production and function.[64]

Preclinical studies suggest that this therapeutic approach warrants further investigation. However, the use of readthrough agents to treat choroideremia has a number of disadvantages compared with the other potential treatments discussed in this article. For example, bypass therapy targets choroideremia caused by nonsense mutations only, which means that the target population is reduced, there is a theoretical risk of off-target effects, and the early stage of development of the therapy means that clinical application is distant.

Retinal prosthesis systems.—Retinal prosthesis systems (RPS) provide long-term retinal stimulation in patients with late-stage outer retinal degenerative disease and aim to salvage rudimentary vision, such as light perception. They consist of a surgically implanted electrode array that delivers electrical stimulation to the retinal surface. The electrical signals are initiated by an external unit consisting of a video-processing unit and eyeglass-mounted camera.[65] A number of RPS are in clinical development (IRIS II [Pixium Vision Paris, France], Suprachoroidal Retinal Prosthesis [Bionic Vision Australia]) or have been approved for use in patients with RP (Argus II [Second Sight, Sylmar, CA], Alpha IMS [Retina Implant AG, Reutlingen, Germany]). Although trials of RPS have been predominantly performed in patients with RP-related blindness, a trial of Argus II included one patient with choroideremia,[66,67] and ongoing trials of IRIS II permit patients with choroideremia to be included (NCT02670980; Pixium Vision). Data from the Argus II RPS clinical trial in patients with RP and choroideremia demonstrate that the device results in improved visual function with an acceptable safety profile up to 5 years after implantation.[67] In addition, assessment of visual function tasks showed improvements in daily activities and QoL in patients with a functioning Argus II device.[68]

Remaining challenges regarding the optimization of RPS treatment include identifying suitable patients; mastering the surgical technique and avoidance/management of surgery-related adverse events; ensuring patients are supported throughout the rehabilitation process; understanding the effects of chronic implant, improving the level of visual function that can be achieved; ensuring device longevity; and appropriate cost and reimbursement.[65,67] The extent to which RPS will be safe and effective in the treatment of choroideremia has yet to be determined.

Cell-based therapy.—For patients with advanced choroideremia disease, in whom the RPE and/or photoreceptor tissue has been lost, gene therapy will likely not be an option; replacement or regeneration of the lost tissue may be necessary.[69] In clinical trials, early studies of autologous RPE transplantation produced beneficial results in patients with choroidal neovascularization secondary to age-related macular degeneration.[70–72] Human embryonic stem cell–derived RPE transplantation has been demonstrated more recently in two Phase 1/2 studies in patients with Stargardt macular dystrophy (n = 9) and atrophic age-related macular degeneration (n = 9). The safety findings were encouraging, and the

improvement or maintenance in best-corrected visual acuity reported in 17 of 18 eyes after a median of 22 months of follow-up was not matched in the fellow untreated eyes.[73] In conditions that result in photoreceptor cell loss, such as RP, photoreceptor replacement would be needed.[69,74] Although there are currently no published data reporting stem cell–derived photoreceptor transplantation in humans, transplantation of rod precursors into a mouse model of end-stage RP with no rod function demonstrated continued development to mature rod cells and restoration of visual function.[74]

In choroideremia, as well as many other retinal diseases, the inter-reliant nature of the choriocapillaris, photoreceptors, and RPE means that all three tissues are often affected by late-stage disease.[69] In terms of using stem cell therapy for the treatment of patients with choroideremia, to the best of our knowledge, no studies have yet been conducted. However, preclinical work is being undertaken to create an RPE–photoreceptor bilayer patch using induced pluripotent stem cells that can be transplanted into retinas of eyes with choroideremia, thus replacing degenerated tissue with healthy cells.[75]

Conclusion

Choroideremia is a disease with a significant unmet need. Interventions that can treat progression of the disease and improve visual and functional outcomes have the potential to reduce health care costs and enhance patient QoL. Adeno-associated virus–mediated gene therapy has shown promise as a disease-modifying treatment for choroideremia. Gene replacement of healthy *CHM* may lead to preservation, or even improvement, of visual outcomes. Results from Phase 2 and Phase 3 clinical trials of *CHM* gene therapy in patients with choroideremia will provide further data on this subject.

Acknowledgments

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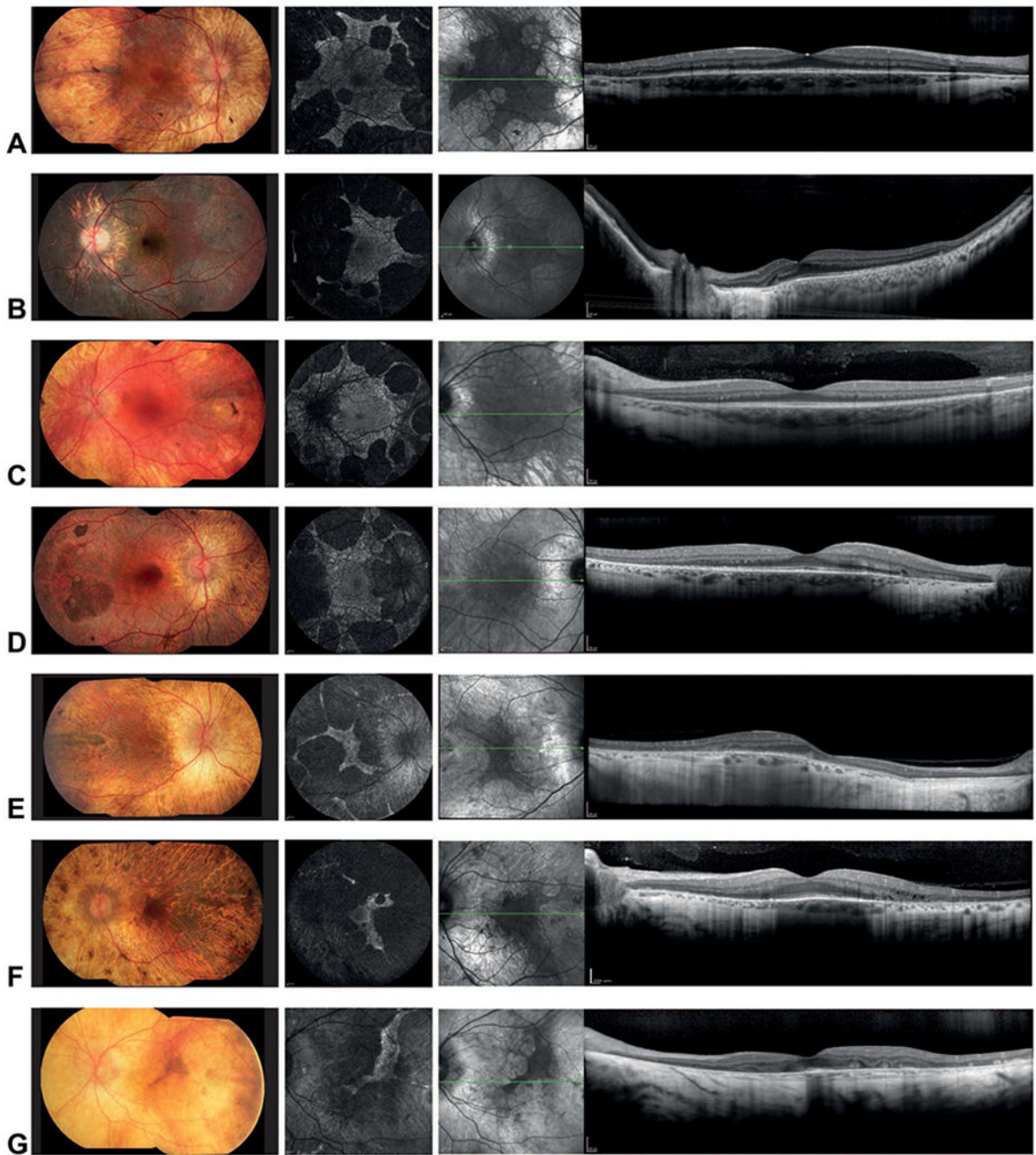
Fig. 1.
Progression of choroideremia as visualized by fundus photography (Column 1), FAF (Column 2), near-infrared reflectance (Column 3), and OCT (Column 4) in a (**A**) 17-year-old male, (**B**) 24-year-old male, (**C**) 30-year-old male, (**D**) 35-year-old male, (**E**) 44-year-old male, (**F**) 50-year-old male, and (**G**) 71-year-old male.
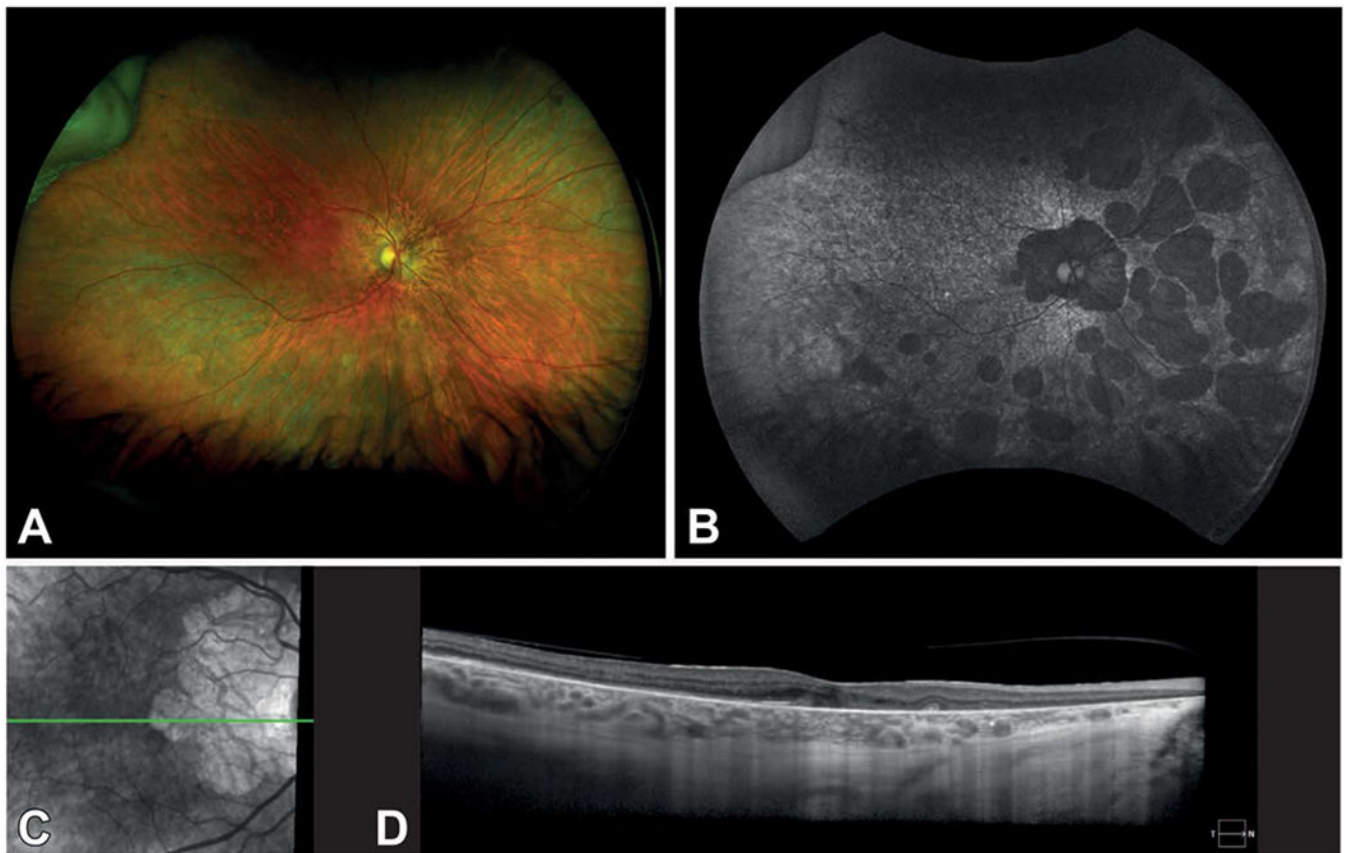
Fig. 2.
Choroideremia as visualized by (**A**) fundus photography, (**B**) FAF, (**C**) near-infrared reflectance, and (**D**) OCT in the right eye of a 58-year-old female carrier with a best-corrected visual acuity of 20/80.