Promising gene therapies for ocular conditions

BY AMEER KHAMISE

Gene therapy, a pivotal advancement in modern medicine, particularly shines in ophthalmology. By targeting defective genes with engineered vectors, this approach promises significant strides in treating inherited retinal diseases. This article reviews the top five gene therapies in late-stage trials, highlighting their innovative potential and inherent challenges [1].

ADVM-022 for wet age-related macular degeneration

ADVM-022, developed by Adverum Biotechnologies, is an innovative gene therapy aimed at treating wet age-related macular degeneration (AMD). This therapy employs a novel approach by using an adeno-associated viral vector to deliver a gene encoding for a protein like aflibercept, a drug commonly used to treat wet AMD by inhibiting vascular endothelial growth factor (VEGF) [2].

The significance of ADVM-022 lies in its potential to provide long-lasting VEGF inhibition with a single intravitreal injection, contrasting sharply with the frequent injections currently required in standard treatments. Data from the ongoing LUNA phase 2 trial demonstrates annualised reduction in anti-VEGF injection rates of greater than 90% across the two-dose cohorts (2E11 and 6E10). Additionally, patients in both treatment arms showed an improvement in central subfield thickness sustained after 26 weeks and required no rescue injections during this period, illustrating both efficacy in reducing retinal fluid and maintaining visual acuity over extended periods [2].

Adverum Biotechnologies plans to initiate a phase 3 trial in 2025 to further evaluate the efficacy, safety, and durability of ADVM-022, offering hope for a more permanent solution for patients burdened by frequent treatment schedules.

OCU400 for retinitis pigmentosa

OCU400, a novel gene therapy developed by Ocugen, is aimed at treating retinitis pigmentosa (RP), a group of rare genetic disorders that result in progressive vision loss. This gene therapy employs a unique gene-agnostic approach by using a recombinant adeno-associated virus to deliver the NR2E3 gene, which plays a critical role in maintaining retinal cell health [3].

The phase 3 clinical trial of OCU400 has commenced, marking a significant advancement in treating RP. Following the promising results from phase 1/2 trials, OCU400 demonstrated a good safety profile and notable efficacy. Specifically, the studies reported a measurable improvement in the visual function tests that assess the ability to navigate under dim lighting, with all participants showing some degree of functional vision enhancement [3].

This ongoing study is crucial as it explores a gene-agnostic approach, potentially revolutionising the treatment landscape for various genetic disorders of the retina [3].

GS030: An optogenetic approach to retinitis pigmentosa

GS030, developed by GenSight Biologics, represents a groundbreaking approach in the treatment of RP through optogenetics, coupling a gene therapy vector (GS030-DP) with a wearable device (GS030-MD). This therapy transforms retinal ganglion cells into light-sensitive cells by delivering the gene for the light-sensitive protein ChrimsonR via an intravitreal injection [4].

The pivotal phase 1/2a PIONEER trial has provided significant insights into the efficacy and safety of GS030. Specifically, a remarkable outcome was observed in a 58-year-old male patient treated with 5.0×10^10 vector genomes (vg) of GS030-DP, who demonstrated partial recovery of functional vision. This included the ability to locate and count objects, a critical step towards practical vision restoration. Safety data from the trial indicates good tolerance of the therapy across three different dosing cohorts – 5×10^10, 1.5×10^11, and 5.0×10^11vg per eye – showing its potential for higher-dose applications without significant adverse effects [4].

Botaretigene Sparoparvovec for X-linked retinitis pigmentosa

Botaretigene Sparoparvovec, being developed by Janssen Pharmaceuticals, is a significant gene therapy aimed at treating X-linked retinitis pigmentosa (XLRP). This form of RP disproportionately affects males due to its X-linked inheritance pattern [5].

This gene therapy employs an adeno-associated virus vector to deliver a correct copy of the RPGR gene, which is commonly mutated in XLRP patients. The correct gene aims to restore the function of the retinal cells that are responsible for vision.

In phase 1/2 trials, Botaretigene Sparoparvovec has shown promising results, with the intermediate dose group achieving a statistically significant increase in mean retinal sensitivity of 1.05dB (CI 0.81, 1.29) and an improvement in the Central 30° Hill-of-Vision (V30) by 1.26dB-sr (CI 0.65, 1.86) at 12 months [5].

These findings suggest that the therapy not only helps in slowing down the progression of vision loss but may also improve visual functions in patients who have already experienced significant vision impairment. The significant improvements in static perimetry and mesopic microperimetry documented in the trials underline the therapy's efficacy in enhancing visual function under low light conditions, crucial for daily activities [5]. A phase 3 trial (LUMEOS) is currently underway with the study completion expected towards the end of 2024 [5].

QR-421a for Usher syndrome and non-syndromic retinitis pigmentosa

QR-421a, developed by ProQR Therapeutics, is an innovative gene therapy targeting Usher syndrome and non-syndromic RP

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due to USH2A gene mutations. By using antisense oligonucleotides to skip exon 13, QR-421a enables the production of a functional, albeit slightly shortened, usherin protein, aiming to slow or halt retinal degeneration associated with these conditions [6].

Phase 1/2 trials of QR-421a have shown encouraging results, with the therapy demonstrating a concentration-dependent increase in exon 13 skipping in patient-derived photoreceptor precursors. In a zebrafish model, a single intravitreal injection of QR-421a restored retinal function, as evidenced by significantly improved electroretinogram b-wave amplitudes compared to untreated mutants ($p<0.001$). In human cell models, QR-421a achieved up to 63% exon skipping at higher concentrations, indicating significant potential for therapeutic effect [6].

The ongoing phase 2/3 trials, Sirius and Celeste, aim to further validate these findings in patients with advanced and early to moderate vision loss, respectively. These trials focus on key endpoints such as best-corrected visual acuity and retinal sensitivity over an 18-month period. Preliminary results are promising, suggesting that QR-421a could become a viable long-term treatment option for USH2A-related RP [6].

This review underscores the transformative potential of gene therapies in ophthalmology, showcasing top advancements in phase 3 trials. While promising, these therapies face technical and biological challenges that require careful navigation to ensure efficacy and safety, pointing towards a hopeful yet cautious future in ocular treatment strategies [5].

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