PERSPECTIVE

Communicating the Promise for Ocular Gene Therapies: Challenges and Recommendations

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• PURPOSE: To identify challenges and pose solutions for communications about ocular gene therapy between patients and clinicians as clinical research progresses.
• DESIGN: Literature review with recommendations.
• METHODS: Literature review of science communication best practices to inform recommendations for patient-clinician discussions about ocular gene therapy.
• RESULTS: Clinicians need to employ communications about ocular gene therapy that are both attentive to patient priorities and concerns and responsive to other sources of information, including overly positive news media and the Internet. Coverage often conflates research with therapy—clinical trials are experimental and are not risk free. If proven safe and efficacious, gene therapy may present a treatment but not a cure for patients who have already experienced vision loss. Clinicians can assist patients by providing realistic estimates for lengthy clinical development timelines and positioning current research within models of clinical translation. This enables patients to weigh future therapeutic options when making current disease management decisions.
• CONCLUSIONS: Ocular gene therapy clinical trials are raising hopes for treating a myriad of hereditary retinopathies, but most such therapies are many years in the future. Clinicians should be prepared to counter overly positive messaging, found in news media and on the Internet, with optimism tempered by evidence to support the ethical translation of gene therapy and other novel biotherapeutics. (Am J Ophthalmol 2015;160(3):408–415.

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RECENT SUCCESSES IN OCULAR GENE THERAPY CLINical trials have revitalized hopes for a field that was previously marked by high-profile disappointments.[1] Pioneering clinical trials to address mutations of the *RPE65* gene that cause Leber congenital amaurosis (LCA) established safety and demonstrated improvements in visual function.[2–4] These studies were celebrated by the research community and the media,[5] igniting hopes for gene therapies for related retinopathies. Our goal here is to identify challenges and pose solutions for communications about ocular gene therapy between patients and clinicians as clinical research progresses. Although we focus on gene therapy, similar considerations apply to other experimental biotherapeutics.

The discussion is timely. One research group at the University of Pennsylvania reports that positive safety and efficacy results from the LCA trials have been sustained over time in adults and children[6]; readministration in the second eye of 3 adult patients was both safe and efficacious after previous exposure to the vector.[6] A fully enrolled phase III pediatric clinical trial is underway and expected to report in late 2015 (NCT00999609). The pediatric trial is crucial because LCA studies suggest a therapeutic window for visual gain, with earlier application leading to more dramatic responses.[7]

Although these results appear promising, studies in dogs suggest that degenerative processes may continue after the gene therapy intervention, if such degeneration has already commenced.[8] In humans, a second research group reported that gene therapy improves vision for at least 3 years, but photoreceptor degeneration also continues at the same rate as in the natural course of the disease.[9] Long-term follow-up (4.5-6 years) from 3 treated patients indicated progressive diminution of the areas of improved vision.[10] Similar results were reported by a team from the United Kingdom: retinal sensitivity improved after gene therapy but diminished after 12 months.[11] Gene therapy may therefore not offer a permanent treatment, and most benefit is likely if the intervention occurs prior to the onset of retinal degeneration.[8] Some patients may require a second round of gene therapy, and gene therapy may best be used in combination with other medications, if and when these are developed.[12] Research continues to improve gene therapy

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TABLE. Completed or Active Ocular Gene Therapy Clinical Trials Registered in ClinicalTrials.gov by May 2015 and Associated PUBMED Publications

Disease	Intervention	Phase	Enrollment	Age Group	Start Year - End Year	Status	Sponsor	Clinical Trial Identifier
Choroideremia	AAV2-hCHM	I/II	10	A,S	2015–2021	R	Spark Therapeutics[a]	NCT02341807
	rAAV2 REP1[b]	II	30	A,S	2015–2018	NYR	University of Oxford	NCT02407678
	rAAV2.REP1[b]	I/II	12	A,S	2011–2015	R	University of Oxford	NCT01461213[c]
	rAAV2.REP1[b]	I	6	A,S	2015–2018	R	University of Alberta	NCT02077361
Leber congenital amaurosis	AAV2-hRPE65v2	III	24	C,A,S	2012–2029	ONR	Spark Therapeutics[a]	NCT00999609
	AAV2-hRPE65v2	I/II	12	C,A,S	2010–2026	ONR	Spark Therapeutics[a]	NCT01208389
	AAV2-hRPE65v2	I	12	C,A,S	2007–2024	ONR	Spark Therapeutics[a]	NCT00516477[d]
	rAAV2-CB-hRPE65	I/II	12	C,A,S	2008–2027	ONR	Applied Genetic Technologies[a]	NCT00749957
	rAAV 2/2.hRPE65p.hRPE65	I/II	12	C,A	2007–N/A	ONR	University College, London	NCT00643747[e]
	rAAV2-CBSB-hRPE65	I	15	C,A,S	2007–2026	ONR	University of Pennsylvania	NCT00481546[f]
	rAAV2/4.hRPE65	I/II	9	C,A	2011–2014	Com	Nantes University Hospital	NCT01496040
	rAAV2-hRPE65	I	10	C,A,S	2010–2017	R	Hadassah Medical Organization	NCT00821340
Leber hereditary optic neuropathy	scAAV2-P1ND4v2	I	27	A	2014–2019	R	John Guy, University of Miami	NCT02161380
	rAAV2-ND4	N/A	6	C,A	2011–2013	R	Bin Li, Huazhong University of Science and Technology	NCT01267422
Neovascular age-related macular degeneration	rAAV.sFlt-1	I/II	40	A,S	2011–2015	ONR	Lions Eye Institute, Australia	NCT01494805
	AAV2-sFLT01	I	34	A,S	2010–2018	ONR	Genzyme, a Sanofi Co[a]	NCT01024998
	RetinoStat	I	21	A,S	2011–2015	ONR	Oxford BioMedica[a]	NCT01301443
	RetinoStat	I	21	A,S	2012–2027	R	Oxford BioMedica[a]	NCT01678872
	AdGVPEDF.11D	I	N/A	A,S	N/A	Com	GenVec[a]	NCT00109499
Retinitis pigmentosa	rAAV2-VMD2-hMERTK	I	6	C,A,S	2011–2023	R	Fowzan Alkuraya, King Khaled Eye Specialist Hospital	NCT01482195
Retinoschisis	rAAV2tYF-CB-hRS1	I/II	27	C,A,S	2015–2020	NYR	Applied Genetic Technologies[a]	NCT02416622
	AAV-RS1	I/II	100	A,S	2014–2017	R	National Eye Institute	NCT02317887
Stargardt macular degeneration	StarGen	I/II	46	C,A,S	2011–2017	R	Sanofi[a]	NCT01367444
	StarGen	I/II	28	A,S	2012–2022	R	Sanofi[a]	NCT01736592
Usher syndrome	UshStat	I/II	18	A,S	2012–2017	R	Sanofi[a]	NCT01505062[g]
	UshStat	I/II	18	A,S	2013–2022	R	Sanofi[a]	NCT02065011

A = adult; C = child; Com = completed; N/A = not available; NYR = not yet open for participant recruitment; ONR = ongoing, but not recruiting participants; R = recruiting/enrolling by invitation; S = senior.

[a]Industry sponsor.

[b]NightstaRx AAV2-REP1 product.

[c]Results published by Seitz et al[13] (PubMed ID 25744334) and MacLaren et al[14] (PubMed ID: 24439297).

[d]Results published by Melillo et al[15] (PubMed ID: 22812667), Maguire et al[7] (PubMed ID: 19854499), and Maguire et al[4] (PubMed ID: 18441370).

[e]Results published by Bainbridge et al[11] (PubMed ID: 25938638) and Bainbridge et al[2] (PubMed ID: 18441371).

[f]Results published by Jacobson et al[10] (PubMed ID: 25936984), Cideciyan et al[16] (PubMed ID: 25537204), and Jacobson et al[17] (PubMed ID: 21911650).

[g]Results published by Zallocchi et al[18] (PubMed ID: 24705452).