

CORRESPONDENCE

Visual Acuity after Retinal Gene Therapy for Choroideremia

TO THE EDITOR: Two recent clinical reports of retinal gene therapy with adeno-associated virus (AAV) vectors in patients with Leber's congenital amaurosis showed initial gains in visual function that subsequently declined.^{1,2} We previously reported early improvement in visual acuity in two of six patients who received retinal gene therapy in one eye (the study eye) to treat choroideremia,³ a disease that is characterized by atrophy of the choriocapillaris and retinal pigment epithelium and involves vision loss that leads to blindness.

Choroideremia is caused by loss-of-function mutations in the gene *CHM*. We delivered non-mutated *CHM* in an AAV vector (AAV.REP1) by subfoveal injection into the vicinity of the retinal pigment epithelium and photoreceptor cells, the dysfunction of which is presumed to be a contributing factor in vision loss. Here we report that the early improvement that we observed in two of the six patients was sustained at 3.5 years after treatment, despite progressive degeneration in the other eyes (the control eyes). The control eyes did not receive the intervention, and visual acuity in the control eyes was better than the visual acuity in the study eyes at baseline.

The best corrected visual acuity was reported as the number of letters correctly read by the patient on an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart at 4 m. Two patients (Patients 1 and 4) had advanced disease, and the visual acuity in the study eyes at baseline in these patients was several lines below normal (each line contains 5 letters) on the ETDRS chart (Table 1). By 3.5 years, visual acuity in the treated study eye had increased by 21 letters (>4 lines) from baseline on the ETDRS chart in Patient 1 and by 18 letters (>3 lines) in Patient 4. In contrast, over the same period, visual acuity in the control eyes decreased by 18 letters in Patient 1 and by 6 letters in Patient 4.

A cataract developed in the study eye in Patient 4 at 2 years. This cataract was subsequently removed, but the removal was not the primary reason for the gain in visual acuity recorded at

3.5 years. The visual acuity at 3.5 years was similar to the level recorded 12 months after surgery, before the cataract was clinically significant.

The other four patients had good visual acuity at baseline and therefore a limited scope for improvement. Patient 3, the youngest patient, had the largest area of surviving retina and the best pretreatment visual acuity — 20/16 (89 ETDRS letters). This visual acuity returned to the baseline level 12 months after the administration of gene therapy and was sustained until the last follow-up. No loss of visual acuity was observed in the untreated control eye during this time, probably because the disease was still in the early stages. However, the treated eye of Patient 3 did show improvement on an electrophysiological study. This test measures a global macular response and may therefore be more relevant in younger patients with larger areas of surviving retina (Fig. S3 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

The levels of visual acuity in the study eyes in Patients 2, 5, and 6 all returned to baseline levels by 6 months after treatment, but by the 3.5-year follow-up, the visual acuity of the study and control eyes in Patient 6 had declined by 29 and 18 letters, respectively. Patient 6 received a lower total vector dose than the other patients in the trial; we speculate that the loss of visual acuity in this patient was caused by progressive degeneration of cells in the fovea rather than a toxic effect of the vector. In contrast, at the 3.5-year follow-up, the visual acuity in the injected eyes in Patients 2 and 5 remained close to that at baseline, whereas the visual acuity of the control eye was lower by 10 and 11 letters, respectively.

Best corrected visual acuity is a reliable marker of visual function. In contrast to Leber's congenital amaurosis, in which visual acuity is generally profoundly affected early in life, choroideremia and most types of retinitis pigmentosa are characterized by progressive loss of the visual field, with visual acuity remaining close to normal levels until the very late stages of disease.

Table 1. Visual Acuity in Patients with Choroideremia Who Received Retinal Gene Therapy.*

Patient No.	Vector Dose†	Visual Acuity, Baseline		Visual Acuity, 2 Yr		Visual Acuity, 3.5 Yr		Change in Letter Score, Baseline to 3.5 Yr		Change in Letter Score, Study Eye vs. Control Eye, 3.5 Yr
		Study Eye	Control Eye	Study Eye	Control Eye	Study Eye	Control Eye	Study Eye	Control Eye	
	vg	letter score								
1	1×10 ¹⁰	23	58	41	62	44	40	21	-18	39
2	1×10 ¹⁰	79	82	73	77	77	72	-2	-10	8
3	1×10 ¹⁰	89	85	94	85	90	86	1	1	0
4	1×10 ¹⁰	53	76	61	70	71	70	18	-6	24
5	1×10 ¹⁰	79	83	76	78	83	72	4	-11	15
6	6×10 ⁹	84	88	69	84	55	70	-29	-18	-11

* The best corrected visual acuity was reported as the number of letters correctly read by the patient on an Early Treatment of Diabetic Retinopathy Study chart at 4 m. Patients 2, 4, 5, and 6 underwent cataract surgery after the 2-year follow-up visit. Cataracts developed in all patients, and they reported subjective vision change. Ocular hypertension in both eyes also developed in Patient 3. Additional details are provided in Table S1 in the Supplementary Appendix.

† The injection volume of AAV.REP1 was 0.1 ml in Patients 1 through 5 and 0.06 ml in Patient 6. The abbreviation vg denotes vector genomes.

Therefore, in some patients, the effect of preserving visual acuity with the use of retinal gene therapy may take several years to become apparent.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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