The Artificial Silicon Retina Microchip for the Treatment of Vision Loss From Retinitis Pigmentosa

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Objective: To determine the safety and efficacy of the artificial silicon retina (ASR) microchip implanted in the subretinal space to treat vision loss from retinitis pigmentosa.

Methods: The ASR microchip is a 2-mm-diameter silicon-based device that contains approximately 5000 microelectrode-tipped microphotodiodes and is powered by incident light. The right eyes of 6 patients with retinitis pigmentosa were implanted with the ASR microchip while the left eyes served as controls. Safety and visual function information was collected.

Results: During follow-up that ranged from 6 to 18 months, all ASRs functioned electrically. No patient showed signs of implant rejection, infection, inflammation, erosion, neovascularization, retinal detachment, or migration. Visual function improvements occurred in all patients and included unexpected improvements in retinal areas distant from the implant.

Main Outcome Measures: Subjective improvements included improved perception of brightness, contrast, color, movement, shape, resolution, and visual field size.

Conclusions: No significant safety-related adverse effects were observed. The observation of retinal visual improvement in areas far from the implant site suggests a possible generalized neurotrophic-type rescue effect on the damaged retina caused by the presence of the ASR. A larger clinical trial is indicated to further evaluate the safety and efficacy of a subretinally implanted ASR.

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tentials of contacting retinal neurons and to simulate how light would normally activate these cells to form retinotopic visual images. Because the implant would stimulate the outer retina at an early functional stage, subsequent visual signal processing by the remaining neuroretinal networks would theoretically be possible.

In the cat, pig, and rat models, placement of the solid ASR disc into the subretinal space produced a model of outer retinal degeneration that histologically resembled that of RP.\textsuperscript{17,18,20,24,25} The immunohistochemistry of the overlying retina also showed an appearance similar to that seen in patients with hereditary retinal degeneration.\textsuperscript{20} Additionally, ASR microchips functioned within the subretinal space\textsuperscript{17,18,20} and demonstrated continued electrical activity for more than 3 years after implantation.\textsuperscript{20} Functionally, ASR microchips induced retinal and possible cortical responses in the animal models.

Because of these findings in animal models and the substantial degeneration of the outer retina in patients with late-stage RP, we believed that the placement of a small ASR microchip in the subretinal space of a patient with late-stage RP would not cause further substantial injury to the retina. Furthermore, if the ASR microchip was placed in a midperipheral retinal location, the safety and efficacy of the device could be evaluated with a minimal risk of damaging the macular area.

To determine the safety and efficacy of the ASR microchip for possible human application, we conducted a pilot clinical trial, implanting the ASR into the right eyes of patients with RP and using the left eyes as controls.

### METHODS

Between June 2000 and July 2001, Food and Drug Administration and institutional review board approval were obtained to enroll 6 patients into an ASR safety and feasibility clinical trial. Informed consent was obtained from all patients prior to entry. Eligible patients were aged 40 years and older, had RP, and were free of other significant eye or medical diseases such as uveitis, diabetes, glaucoma, or cardiac conditions. They had to have a Snellen visual acuity measurement of 20/800 OU or worse and/or diabetes, glaucoma, or cardiac conditions. They had to have a

Informed consent was obtained from all patients prior to entry. Eligible patients were aged 40 years and older, had RP, and were free of other significant eye or medical diseases such as uveitis, diabetes, glaucoma, or cardiac conditions. They had to have a Snellen visual acuity measurement of 20/800 OU or worse and/or diabetes, glaucoma, or cardiac conditions. They had to have a preoperative and postoperative using an LKC (LKC FT-1000) ophthalmic examination and complete medical examination. They were asked to describe their visual perceptions for 7 aspects of visual function and to give a comparison rating of one eye relative to the other. These perceptions included brightness, contrast, color, shape, resolution, movement, and visual field size. Because the ASR was implanted in the right eye, patients were instructed to use their left eye as the basis for comparison, to assign a fixed rating value of 10 to the left eye, and then to compare the right eye with the left. For example, if the brightness of the 2 eyes was equal, both would receive a value of 10. If the brightness of the right eye was subjectively twice that of the left, the right eye would be rated a 20; if it was half that of the left eye, the right eye would be rated a 5. If the patient had no perception, a value of 0 was assigned. In the latter case, if the left eye had perception but the right eye did not, the left would be assigned a value of 10 and the right would receive a 0. Perceptions of the 2 eyes were again compared postoperatively and were also compared with their preoperative values when possible. For example, if the right eye developed subjective perception even though it previously had none, it would be compared with the left because a ratio comparison with a preoperative value of 0 in the right eye would not be possible.

Preoperative visual acuity testing was performed at least twice using standard back-illuminated charts from the Early Treatment Diabetic Retinopathy Study\textsuperscript{28} (ETDRS) at 0.5 m, with the patient undergoing cycloplegia (1% cyclopentolate hydrochloride, 1% tropicamide, and 2.5% phenylephrine hydrochloride) and best-corrected visual acuity testing with a retro-}

Because Humphrey visual field testing was limited by the brightness of the instrument test target (10,000 apostilbs), additional visual field light-threshold testing was conducted in 9 visual field sectors in a 3×3 grid with less than 0.1 footcandle (ft-c) of background room illumination. This was accomplished by using a 0.5-in-diameter optical fiber halogen light source placed 10 cm from the patient’s eye at the following 9 locations from the patient’s perspective: right-upper, right-middle, right-lower, middle-upper, middle-middle, middle-lower, left-upper, left-middle, and left-lower. All positions except middle-middle were located approximately 45° from the optical axis (middle-middle position). Using stacked neutral-density filters in slide holders, illuminations from 300 ft-c down to 1 e-4 ft-c in 3-dB steps were used for threshold testing. The threshold was established in each sector by crossing it at least 3 times in an ascending and descending staircase paradigm. The testing was continued until all 9 sectors were completed. Both the implanted and control eyes were tested during the sessions. In patients 1, 2, and 3, this test was implemented by 4 to 6 months postoperatively and in patients 4, 5, and 6, by 2 months postoperatively. The test is referred to as the nine-sector test.

Electroretinograms and visual evoked potentials were performed preoperatively and postoperatively using an LKC (LKC.
Technologies, Gaithersburg, Md) or Diagnosys Espion (Diagnosys LLC, Littleton, Mass) computer signal averaging system. White or infrared light (940 nm supplied by light-emitting diodes) was applied via handheld Ganzfeld stimulators (Optobionics Corporation, Naperville, Ill). The infrared handheld Ganzfeld stimulator allowed the determination of isolated implant electrical responses and patient perceptions to infrared light in the area of the implant.

The ASR (Figure 1) was implanted in the superior to superior temporal subretinal space (approximately 20° off axis from the macula) in the right eyes of all patients, who were given general anesthesia. A standard 3-port vitrectomy (irrigation cannula, light pipe, and aspiration vitreous cutter) was performed with pars plana lensectomy. A retinal bleb was created using a cannula and hydrostatic dissection. The retinotomy was extended to 2.5 mm using vitreoretinal scissors. The ASR was inserted through the retinotomy into the subretinal space, and air-fluid exchange was performed to flatten the retina. Laser or thermal cautery was not required in most patients. The scleral incisions were closed with absorbable sutures, and antibiotic steroid medication was applied. Postoperative follow-up examinations were conducted according to the study protocol. Patients visits were scheduled as follows: postoperative days 1, 2, and 4; weeks 1, 2, 4, 6, and 8; and months 3, 4, 6, 9, 12, 15, 18, 21, and 24. Fluorescein angiograms were performed at 6 months, and electroretinograms were done at multiple visits, including 1 year postoperatively.

**RESULTS**

Fifteen patients with RP were screened for our investigation. Thirteen patients were able to perceive phosphenes, and 6 were selected for ASR implantation. Patient 1 had isolated RP without a significant family history. Patient 2 had an extensive vertical autosomal dominant family history with multiple affected family members. Patient 3 had autosomal dominant RP with an affected brother and daughter. Patient 4 had type 2 Usher syndrome with no family history of this condition. Patients 5 and 6 were brothers who had autosomal dominant RP and a vertical family history.

In the immediate postoperative period, the most common adverse effect requiring intervention was elevation of the intraocular pressure (IOP) to higher than 25 mm Hg.
This occurred in patients 1, 5, and 6. The IOP elevation generally occurred toward the end of the first week. This elevation was believed to be related to the steroid contained in the postoperative antibiotic steroid drops (dexamethasone with either tobramycin, neomycin sulfate, or polymyxin B sulfate) because the IOP decreased rapidly when treatment with the drops was stopped but increased when their administration was restarted. Elevated IOP was treated with IOP-lowering medication and steroid tapering. After approximately 3 weeks, when the steroid antibiotic drops regimen was stopped, the IOP returned to preoperative values. Scratchiness in the eye that was operated on was noted by several patients and resolved after approximately 6 weeks when the external absorbable sutures dissolved. Patient 5 noted aniseikonia between his aphakic ASR-implanted eye and his unoperated on eye when using glasses. A subsequent anterior chamber intraocular lens relieved those symptoms. Another patient noted syneresis of images seen from the implanted eye, which was believed to be related to syneresis of a previously implanted posterior chamber intraocular lens. These symptoms substantially improved after replacement of the syneretic posterior chamber intraocular lens with a stable anterior chamber intraocular lens.

No patient experienced infection, prolonged inflammation or discomfort, undesirable visual symptoms, intraocular or retinal hemorrhage, neovascularization, implant rejection, migration, or erosion through the retina.

Patients 1, 3, and 6 were pseudophakic before ASR implantation. Preoperatively, patient 2, who had bare to no LP, had a 3+ posterior subcapsular cataract (<20/200 view in the affected eye). Patient 4, who had a visual acuity of HM at 1 ft, had a 1+ anterior subcapsular cataract, 1+ nuclear sclerosis, and 1+ posterior subcapsular cataract (20/30 view in the affected eye). Patient 5, who had a visual acuity of counting fingers at 1 to 2 ft, had a 1 to 2+ anterior subcapsular cataract, 1+ posterior cortical cataract, and 0 to 1+ nuclear sclerosis cataract (20/30 view in the affected eye). To facilitate viewing of the implant during the procedure, the cataracts were removed from patients 2, 4, and 5 during the ASR operation. Patients 2 and 4 were left aphakic, and patient 5 underwent secondary anterior chamber intraocular lens implantation approximately 1 month after ASR implantation.

CLINICAL CHARACTERISTICS

The Table summarizes the clinical characteristics and results. At the last follow-up visit, there were no ASR-related complications. The retina overlying the implant remained clear with patent vessels (Figure 2). Fluorescein angiograms showed no signs of neovascularization, vascular dropout, disruption, or leakage. In all patients, the anterior and posterior segments of the eye appeared quiet. All devices were functioning electrically, as demonstrated by electoretinographic recordings of ASR electrical spikes to infrared stimuli (Figure 3A).

Before implantation, only 2 (patients 5 and 6) of 6 patients were able to read ETDRS letters in either eye at 0.5 m. Preoperatively, patient 5 read 16 to 25 letters OD and 24 to 28 letters OS, and patient 6 read 0 letters OD and 0 to 3 letters OS. These 2 patients demonstrated postoperative improvements in the total number of ETDRS letters read (Figure 3B) that were consistent with their subjective impression of improved central perception of contrast, shape, and resolution. Six months after implantation surgery, patient 5 read 35 to 41 letters OD and 21 to 28 letters OS, and patient 6 read 25 to 29 letters OD and 0 letters OS. The smallest letters read in the right eye improved from a Snellen equivalent of approximately 20/800 to 20/200 OD for patient 5 and from worse than 20/1600 (no letters read) to approximately 20/400 OD for patient 6. Patient 3 was unable to read any of the ETDRS letters preoperatively (<20/1600) in either eye but postoperatively was able to see some of the largest letters with the right eye only (approximately 20/1280-20/1600 OD) at 12 to 18 months (Figure 3B). On multiple tests, positive responses from preoperative central Humphrey visual field testing with the size V white static target could be obtained consistently only for patients 5 and 6. Postoperatively, only patient 5 demonstrated improved central and paracentral visual fields (30-2) in the right eye on multiple tests (Figure 4).
Compared with the unoperated on eye, 2 eyes (patients 1 and 3) with the ASR showed improvement on the 9-sector test at 6 months to 1 year after surgery. In patient 1, threshold sensitivity improved by approximately 1000% to 1500% in all sectors and was consistent with the patient’s impression that his entire visual field was brighter in the eye with the implant compared with the same eye before surgery as well as the unoperated on eye (Figure 5). In patient 3, threshold sensitivities in the right-middle, right-lower, and middle-lower sectors of the 9-sector test improved at 18 months by approximately 5000% to 10000% (Figure 5). These visual field areas of improvement on the 9-sector test were consistent with the patient’s subjective impression that his best vision for objects directly in front of him was achieved when he elevated his chin and used his inferior visual fields to look straight ahead. Patient 2 showed consistent LP in multiple sectors of the operated eye on the nine-sector test compared with her subjective bare to no LP in those same sectors preoperatively. These perceptions were in keeping with the patient’s postoperative impression that she developed consistent LP in the right eye and noticed shadows of people given the proper lighting conditions. This patient’s 9-sector thresholds did not improve further beyond 1 year after surgery.

No patient was able to perceive or discriminate color on preoperative pseudoisochromatic plate color testing. Postoperatively, patient 5 reported substantial improved color perception of his environment such as seeing the green and white of highway signs, red and white of stop signs, red and white checks on a tablecloth, green grass, and multiple colors in his environment. These perceptions were consistent with his ability to correctly identify the blue and orange dots of the control isochromatic plate and the red and green dots of the test plate using the operated on eye. The unoperated on control eye was never able to perceive colors in the pseudoisochromatic plates.

**COMPARATIVE SUBJECTIVE VISUAL FUNCTION CHANGES AFTER ASR IMPLANTATION**

In the first group of 3 patients, at 18 months after surgery, their impressions were that visual function improvements had stabilized. In the second group of 3 patients, at 6 months after surgery, the impressions of 2 patients (patients 5 and 6) were that their visual function changes had generally stabilized, but patient 4 reported continuing improvement. Patient 1 had LP in both eyes before surgery. The preoperative right-left self-reported comparison ratio for
brightness was 5:10, and for visual fields it was 2:10. Postoperatively, the ratios stabilized at 7:10 and 15:10, respectively, at 18 months. The visual field size in the right eye was subjectively about 750% larger compared with the same visual field before surgery. Functionally, the patient reports not having to turn his head to see light coming from the right side.

Patient 2 had bare to no LP in the right eye with LP in the left eye before surgery. Preoperatively, only the left eye had subjective perceptions of brightness, contrast, shape, and visual field size. Postoperatively, she is still unable to read any letters on the ETDRS chart. However, she subjectively reports substantial visual function improvement in the right eye, particularly in the inferior nasal visual field, that has persisted at 18 months. The self-reported postoperative right-left ratios were as follows: brightness, 8:10; contrast, 10:10; shape, 10:10; and visual field size, 8:10. Functionally, this patient reports being able to see shadows of people with her right eye.

Patient 3 had a visual acuity of HM to LP OU before surgery. At 18 months after surgery, the patient noted that preoperatively the right-left ratios had been 7:10 for brightness and 10:10 for shape, resolution, movement, and visual field size. He indicated that postoperatively these ratios were 30:10, 35:10, 50:10, 50:10, 50:10, and 50:10, respectively. Functionally, the patient reports regaining the ability to use nightlights for navigation at night and can now see movement on television.

Patient 4 had a visual acuity of HM OU before surgery. Preoperatively, the self-reported right-left ratios were 10:10 for brightness, contrast, shape, and visual field size. Postoperatively, the ratios were variable but improved in the right eye compared with the left: 15:10, 17:15, 17:
that he can more easily discern denominations of paper
lights are on at night in his house.

Figure 4. Results of Humphrey central visual field tests with the V white static spot size for patient 5, demonstrating consistently improved central and paracentral visual fields in the right eye postoperatively compared with the preoperative measurements. Whereas almost all of the visual field outside the 15° radius in both
eyes was preoperatively less than a 0-dB threshold (unrecordable with threshold sensitivity >10000 apoticls) (A, top, and B, top), large portions of the visual
field in the right eye were recordable postoperatively at 0 dB or better (A, middle and bottom). The Humphrey visual field test results of the unoperated on left eye
were substantially unchanged (B, middle).

10, and 13:10, respectively, for brightness, contrast, shape, and visual field size. Postoperative perception of movement was noted to be 2:10 relative to what the patient remembered from his youth. Subjectively, this patient indicates that when both eyes are used, his overall visual function is substantially improved from a rating of 10 preoperatively to approximately 25 after surgery. Functionally, the patient reports now being able to navigate his yard without a cane and that he can readily tell which lights are on at night in his house.

Patient 5 had a visual acuity before surgery of approximately counting fingers at 1 to 2 ft OU, with the smallest ETDRS letters recognized translating to a Snellen equivalent of approximately 20/800 OU. He noted equal visual function in both eyes in all perceptions (10:10) preoperatively. Postoperatively, the right-left ratios were as follows: brightness, 17:10; contrast, 30:12; color, 17:10; shape, 15:10; resolution, 35:10; movement, 13:10; and visual field size, 11:10. Functionally, the patient reports that he can more easily discern denominations of paper money, sees well enough to use eating utensils, and rec-
ognizes faces again, something he has not been able to do for approximately 10 years.

Patient 6 had a preoperative visual acuity of HM OU and noted equal visual function in both eyes in all perceptions (10:10) before surgery. Preoperatively, he recognized no ETDRS letters with the right eye (<20/1600 OD) and a maximum of 3 letters with the left (20/1600 OS). Postoperatively, the right-left ratios were variable between days but appeared to maximize as follows: brightness, 20:10; contrast, 25:10; color, 20:10; shape, 20:10; resolution, 20:10; movement, 20:10; and visual field size, 18:10. Functionally, the patient reports that he can sometimes recognize denominations of paper money. At times, he is able to differentiate the color of traffic lights. He also sees well enough to locate cars in the street and to find his coffee cup at meals.

This pilot clinical trial supports the hypothesis that ASR retinal prosthetic chips can be safely and consistently
implanted into the subretinal spaces of patients with RP. The microchips were well tolerated without discomfort, and patients showed no signs of rejection, infection, inflammation, neovascularization, vessel disruption, retinal detachment, migration, or erosion of the implant through the retina. These results are consistent with previously reported findings from animal studies showing similar biocompatibility of the implant materials (silicon, silicon oxide, titanium, and iridium oxide). The continued electrical activity of the ASR microchip is also consistent with similar observations from animal studies.

Regarding subjective responses, 4 of 6 patients (patients 2, 3, 4, and 5) indicated perception of light sensation to infrared light in the projected visual field of the implant during testing. Typically, the first test of a session resulted in perception of light but not subsequent tests. This response may be associated with an electrical capacitive block in the retina that results from the initial monophasic electrical stimulus, which prevents repeated acute responses (the repetitive light flashes observed by all patients preoperatively as a result of external contact lens electrical stimulation were caused by biphasic stimulation, which would prevent a capacitive block).

Figure 5. Results of 9-sector testing. A, The right eye of patient 1 showed improvement in light thresholds of 1000% to 1500% in all sectors. No persistent changes were noted in the control (left) eye. B, The right eye of patient 3 demonstrated an improvement in light thresholds of 5000% to 10000% in the right-middle, right-lower, and middle-lower sectors. No persistent changes were noted in the control (left) eye. The threshold improvements in the indicated sectors of the right eye in patient 3 were consistent with this patient’s subjective impressions.
Substantial and persistent visual function improvements were noted in all patients who underwent implantation with the ASR. These improvements spanned subjective impressions, lifestyle and quality-of-life changes, task performance, ETDRS letter recognition, color recognition, Humphrey visual field testing, and the custom 9-sector test of visual fields. The retinal areas and levels of improvement, however, were greater than those expected from a small ASR chip implanted in the superior to superior temporal retina and stimulating a small portion of the retina. Although phosphenes were perceived in the visual fields corresponding to the ASR in 4 of 6 patients, improvements in visual function also occurred in retinal visual fields distant from the implant, including the macular region. These improvements were first noted about 1 week to 2 months after surgery and continued until approximately 6 to 12 months postoperatively.

The mechanism of visual function improvement in the retinal areas distant from the implant is unlikely to be caused by direct ASR electrical stimulation from the pixels to the retinal cells. The improved perceptions of contrast, color, resolution, movement, and visual field size are too great and too complex to be explained by a direct electrical effect of the implant. A possible explanation of this improvement may be that it is due to an indirect, generalized neurotrophic effect on the retina from ASR electrical stimulation.

Consistent with this theory is the observation that visual function improvements did not appear immediately. Improvements began from 1 week to 2 months after ASR implantation and continued for approximately 1 year. Patients 3 and 5 complained of worsened vision during the first month after surgery before improvement was noted. Patient 2, who had no subjective LP before surgery, noted inconsistent LP during the first week after surgery and then a “quarter-size” light at several feet in the projected visual field of the implant. In the succeeding weeks, the spot of light increased to a vertical oval that covered the left and middle visual fields.

Data from other studies have suggested growth and neurotrophic effects from electrical stimulation. The application of electrical currents to a variety of organ systems may promote and maintain certain cellular functions. These functions include bone growth,29,30 neurite outgrowth of retinal ganglion cells and to in-}

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plantation exerts a neurotrophic effect, would earlier implantation in specific types of retinal degenerative disease be more effective? Finally, would patients with other forms of outer retinal degeneration, such as age-related macular degeneration, also benefit?

In summary, ASR microchips containing approximately 5000 microelectrode-tipped microphotodiodes were implanted into 6 eyes of 6 patients in a pilot safety and feasibility study. After 6 to 18 months of follow-up, all ASRs functioned electrically, and no patient showed signs of implant rejection, infection, inflammation, erosion, neovascularization, retinal detachment, or migration. Visual function improvements occurred in all patients and included unexpected vision improvements in retinal areas distant from the implant. Further study is required to verify these findings, to assess the optimal settings for ASR stimulation, and to determine the groups of patients most likely to benefit from ASR implantation.

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Dr A. Chow has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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