Retinal Degeneration: Retinal Prosthesis

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Retinitis Pigmentosa

• Heredofamilial group of disease

• Characterized by
  - progressive VF loss
  - progressive nyctalopia
  - progressive ERG abnormalities
Retinal Dystrophy

- Histopathology shows shortening of the outer segments of rods and cones occurs first even before symptoms. (Milam et al. Prog Retin Eye Res 1998;17:175-205.)
- OCT offers a “live biopsy” of these eyes
- OCT confirms outer retinal preponderance of findings
OCT: Normal vs. Dystrophy

Normal control with boundaries overlaid on OCT image (left).

45 % decrease in ORL vs. 11 % decrease in IRL

Retinal dystrophy patient shows that the OPL is not clearly seen.

Rod Cone Dystrophy: Early

31 y/o, 20/20 OU, depressed ERG

The retinal thickness profile demonstrates mORL thinning despite the good central visual acuity. This mimics the histopathology in early disease, where thinning and loss of photoreceptors is seen early on without visual acuity being affected.

Rod Cone Dystrophy: Advanced

46 y/o, 20/100 OD, 20/400 OS

Horizontal OCT scan shows corresponding hyperreflectivity of the choroidal layer with overlying marked retinal and RPE thinning

Thinning involves foveal area

Visual Prostheses

• Cortical

• Epiretinal
  • Second Sight, Argus II

• Subretinal
  • Optobionics

JI Lim, MD
Epiretinal Visual Prosthesis

- Requires image processing to relay spatiotemporal information to ganglion cells
- Requires functional inner retinal network: ganglion cells
- Groups:
  - Humayun and colleagues
  - Rizzo and colleagues

Argus II System

• Humanitarian device

• FDA approval for electrical stimulation of the retina to induce visual perception in blind patients with severe to profound retinitis pigmentosa and bare light or no light perception in both eyes.

• Effectiveness for this use has not been demonstrated.
The Argus® II System Components

Argus II Glasses
- Miniature video camera captures a scene
- Sends video to VPU

Argus II Implant
- Smallest, highest density neurostimulator ever approved
- 55 enabled electrodes
- Implant is MR Conditional for use in 1.5 and 3.0 Tesla MRI Systems

Video Processing Unit (VPU)
- Processes and transforms videos into instructions transmitted into implant
Video Processing

Video Camera:
Analog NTSC format with a $49^\circ \times 39^\circ$ field of view. An $18^\circ \times 11^\circ$ region of interest is sampled, matching the retinal area covered by the implant.

Signal Conversion:
From the sampled analog NTSC signal, a digital image with a resolution of 240 pixels is generated.

Image Processing of Digital Image:
System architecture supports menu of three downloadable image processing strategies. Patient selects preferred software “filter” for a given task.
Filter Algorithms:

- **Basic Subsampling** applies a two-dimensional spatial low pass filter to the 20x12 image and then samples every second pixel horizontally and vertically in order to create the 10x6 stimulation pattern.

- **Contrast Enhancement** increases the contrast by performing a histogram stretching on the 20x12 image prior to the low pass filtering and the sub-sampling to 10x6 pixels.

- **Edge Detection** applies a two-dimensional edge enhancement algorithm based on Different of Gaussians (DOG) on the 20x12 image. The algorithm works by subtracting two different Gaussian blurs, with a different blurring radius for each.
Inductive RF Link

Wireless Communication

- **Power Transfer** to the implant is accomplished by short range (~1”) inductive coupling from an RF source on the glasses, operating in the 3MHz range.

- **Forward Telemetry** data is transferred to the implant by amplitude modulated biphasic mark encoding of the MHz power carrier signal. Data transfer bit rate in the kHz range.

- **Back Telemetry** data from the implant is transferred by frequency modulation of a carrier in the 0.5MHz range. Data transfer bit rate in the kHz range.
Implanted Device

Case

Coil

Array

Band

Tack
Neural Excitation

Electrodes:

**Stimulation Pulses** are delivered at frequency, amplitude, pulse width and interphase gap settings customized to each patient. Bi-polar, square wave pulse parameters are constrained to ensure charge balance and to remain within safe charge density limits.

Ganglion Cells:

Action Potentials are induced in response to the electrical stimulus. Complex spatial signal summation occurs due to large number of neurons beneath each electrode. Signals are transmitted to visual cortex.
Results from the Argus II clinical trial

• Outcomes varied from patient to patient
  – Each patient did see something
  – Quality and usefulness of the vision varied
  – Unable yet to predict who will respond well and who will not
Functional Vision Assessment

Outcomes

• Performed in the clinic

• Significant improvement for:
  – Object detection and localization
  – Identifying the direction of motion of an object
  – Identifying large high contrast letters and words

• Over ¼ of patients regained measurable visual acuity
Visual Function - Square Localization

- The Argus II System improved subjects’ ability to locate an object
The Argus II System improved subjects’ performance on a spatial vision task.
Visual Function
Grating Visual Acuity

Best score was 1.8 logMAR (20/1262)

- About ¼ of subjects regained a measurable visual acuity

<table>
<thead>
<tr>
<th></th>
<th>% of Subjects Whose Visual Acuity Improved to Better than 2.9 LogMAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>System ON</td>
<td>27% (n=8)</td>
</tr>
<tr>
<td>System OFF, Implanted Eye</td>
<td>0% (n=0)</td>
</tr>
<tr>
<td>System OFF, Fellow Eye</td>
<td>0% (n=0)</td>
</tr>
</tbody>
</table>
Visual Function - Character Recognition

On average, Argus II System improved subjects’ ability to identify large letters. Median percent correct with the System ON was approximately 50% higher than with the System OFF. ON and OFF sig. different for each group, p>0.001, Wilcoxon signed rank test.
Visual Function Assessment

• How does the vision help in everyday life?
• Improved
  – Orientation and mobility
  – Activities of daily living
Subjects were better at finding a door with the Argus II System ON. 6 tests per visit.
Subjects were better at following a line with the Argus II System ON. 6 tests per visit – success is defined as staying within 1 feet of the line’s center.
Activities of Daily Living

- Subjects performed significantly better on sock sorting task
- Subjects performed significantly better on sidewalk tracking
- Subjects performed significantly better on identifying the direction of someone walking

Sock Sorting n=28

Mean # of out of bounds

<table>
<thead>
<tr>
<th></th>
<th>System ON</th>
<th>System OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felt cover</td>
<td>4.9 ± 2.6</td>
<td>6.9 ± 3.0</td>
</tr>
<tr>
<td>Bare table</td>
<td>6.9 ± 3.0</td>
<td>9.0 ± 2.7</td>
</tr>
</tbody>
</table>

p<0.01, t-test assuming unequal variance

Sock Sorting n=28

Direction of Walking n =27

p<0.05, two-tailed binomial distribution

- p<0.05, Paired t-test
Quality of Life Assessment

- 77% of patients received a meaningful benefit
- None had a negative impact
Part 2: Observer-rated tasks:
Performed at or near subjects’ homes
FLORA Results

n = 26 subjects

Effect of Argus II System on subjects’ functional vision/quality of life:

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Mild positive</th>
<th>Prior positive</th>
<th>Neutral</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>% subjects (n)</td>
<td>35% (9)</td>
<td>27% (7)</td>
<td>15% (4)</td>
<td>23% (6)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Overall:

- Positive: 77% (20)  
- No positive effect: 23% (6)

- Argus II System improved subjects’ functional vision and/or well-being
Safety

Adverse events did occur – some of them serious

- No permanent impairment
- No loss of residual native vision
- Events were resolved using standard treatment methods
- In 45 patients implanted worldwide since approval, 4 patients (8.9%) have had SAEs compared with 13 (43%) in the clinical trial
# Patients | Clinical Trial | Post-Approval
---|---|---
Implant Duration (Years)
Average | 5.4 | 1.0
Range | 1.2 – 6.8 | 0.1 – 2.4
Serious Adverse Events (SAEs)*
# Patients with an SAE | 13 (43.3%) | 4 (8.9%)
# SAEs | 28 | 6
# Patients with Device Explant | 3 | 0
# Patients with Device Failure | 2 | 0

* Device- or procedure-related SAEs.
### Clinical Trial vs. Post-Approval SAEs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Trial</th>
<th>Post-Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>Conj Erosion</td>
<td>4 (13.3%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Hypotony</td>
<td>4</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Presumed endophthalmitis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>RRD</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Re-Tack</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>TRD, serous RD</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sclerotomy leak</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ERM, uveitis, retinal tear, K melt*/K opacty*/keratitis*</td>
<td>1 each</td>
<td>0</td>
</tr>
</tbody>
</table>

* Infective
**SAEs In the First 6 Months: Clinical Trial vs. Post-Approval**

<table>
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<th></th>
<th>Clinical Trial</th>
<th>Post-Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients with ≥ 6 Mo Follow-Up</td>
<td>30</td>
<td>31*</td>
</tr>
<tr>
<td># SAEs in first 6 Months</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td># SAEs/Patient</td>
<td>0.4</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Includes one patient who had an SAE but who is currently 2 months post-implant
Study Conclusions

- Benefit evaluated using 9 different assessments that targeted 3 key domains:
  - Visual Function
  - Functional Vision
  - Quality of Life

- The data demonstrate the substantial clinical improvement the Argus II System provided to subjects in all 3 domains and that this probable benefit outweighed the risk to health
There are 4 steps in the therapy process

1. Determining eligibility
2. Surgery to implant device
3. Programming of device
4. Low-vision rehabilitation
Inclusion Criteria

- Adults, ≥ 25 years old
- *Bare light or NLP in both eyes*
- Previous history of useful form vision.
- Aphakic or pseudophakic. (Phakic will require lens removal during implant procedure.)
- Patients able to comply with post-implant clinical follow-up, device fitting, and visual rehabilitation.

The Argus II implant is intended to be implanted in a single eye, typically the worse-seeing eye.
Surgery requires 2-4 hours (under general anesthesia)

- Similar to scleral buckling
- Retinal tack fastens device to posterior pole
Fitting and Training

• After surgery the system needs to be custom programmed

• Programming
  • ~3 sessions (2 hours each), starting at week 1
  • System can be used at home when programming/training is complete
Low-vision Rehabilitation

Once the fitting is complete, learning how to use the device is important for a successful outcome

• Patient ‘kit’ to take home to help patient practice using the device
• Rehabilitation from trained experts, 5-15 one hour sessions
Cost of Procedure

• Cost of device is covered by Medicare
• Surgery covered by Medicare
• $140,000
Product Development

• Short-term
  – The external system can be upgraded (both hardware and software) to take advantage of advances in cameras, computers, and image processing
  – Changes are relatively easy to implement because there is no need to change the implant
  – Areas of focus: zoom, color vision, and virtual electrodes
  – Also focusing on improving the aesthetic appearance and providing more options
Product Development

• Medium-term (5 – 7 years)
  – An implant with 4 times as many electrodes has been developed
  – Pre-clinical testing in process
  – At some point, adding more electrodes will not improve the outcome any further (law of diminishing returns)
Thank you!