

Argon Laser Photocoagulation for Senile Macular Degeneration¹ (1979-1982)

Purpose

- Primary research question(s): Is argon laser photocoagulation useful in preventing severe visual loss in eyes with evidence of macular degeneration and a symptomatic choroidal neovascular membrane outside the fovea?
- Primary outcome: Change in best-corrected visual acuity from baseline; severe visual acuity loss defined as 6-line loss from baseline.
- Secondary outcome: Complications of laser treatment including foveal hemorrhage, retrobulbar hemorrhage, perforation of Bruch's membrane.
- Perceived clinical importance: The trial was the first of its kind to show that laser photocoagulation could be effective in decreasing vision loss related to macular degeneration. The trial allayed fears that laser treatment would only damage central vision, and galvanized efforts to further explore laser treatment for related ophthalmologic disorders.

Background and Context

- In 1979, senile macular degeneration (SMD) was the leading cause of new blindness in the United States, accounting for 14% of new blindness in persons 65 years old and older. SMD is now referred to as age-related macular degeneration (AMD). The SMD trial was the first in a series of studies on particular diseases wherein vision may be threatened by a patch of abnormal blood vessels (neovascular membrane) leaking into the macula and emanating from the choroid, a blood vessel layer just behind the retina. The treatment was controversial in that clinicians were wary about aiming a laser near the foveal avascular zone. Prior to the initiation of the study, clinicians had suggested that destroying the neovascular membrane with a laser beam might be of benefit in preventing further loss of vision. However, the treatment also destroyed the retina in the treated area, sacrificing some present vision for a better long-term outcome. The trial was an opportunity to provide proof supporting the concept of laser treatment with the potential of transforming treatment.

Date and Place Conducted

- 1979-1982

- Johns Hopkins University, The Wilmer Ophthalmological Institute, Baltimore, Maryland (Coordinating Center)
- Twelve participating clinical centers

Principal Investigators

- Stuart Fine, M.D., Study Chair
- Argye Hillis, Ph.D., Director of the Coordinating Center
- Macular Photocoagulation Study Group

Sponsored by/source of funding

- National Eye Institute, National Institutes of Health

Size and Design

- Number of participants: 224
- Participant characteristics:
 - Age 50 or older
 - Angiographic evidence of choroidal neovascular membrane at distance of 200 to 2500um from center of foveal avascular zone
 - Best corrected visual acuity of 20/100 or better
 - Symptoms related to neovascular membrane
 - No prior photocoagulation in the study eye
 - No other ocular disease that could independently affect visual acuity
- Design: Multi-centered, randomized controlled trial
 - After meeting criteria and receiving informed consent, patients were randomized into either the “treatment” group or “no treatment” group
 - Treatment group patients received argon laser photocoagulation
 - Follow-up visits were scheduled for all patients at three and six months after enrollment, and at six-month intervals thereafter
 - Treatment group patients were examined between three and nine weeks post procedure to insure that the new vessel membrane had been obliterated and that no additional laser treatment was required
 - The trial had an independent Data and Safety Monitoring committee that was appointed by the Director of the National Eye Institute. The committee included experts in retinal diseases and biostatistics, a representative from the National Eye Institute, and an ethicist. In

addition, the Study Chair and members of the Coordinating Center served as non-voting members of the DSMC

Issues Encountered During the Trial

- After 18-months, it became evident through accumulated data that laser treatment was effective in preventing severe visual loss in the SMDS trial (60% of untreated vs. 25% of treated eyes had severe visual loss).
- The study results also indicated that patients with choroidal neovascularization secondary to macular degeneration often experienced a rapid course of visual degeneration, remaining treatable for only a short window of time because the new vessels typically enlarged to occupy an area beneath the fovea.
- After critical review of the data, the data and safety monitoring committee recommended to halt recruitment and randomization in the trial, to continue following all patients, and to offer laser treatment to patients originally assigned to the “no treatment” group if they were still eligible for laser treatment.
- The timeline in which these recommendations were implemented is important to note. In March 1982, the data and safety monitoring committee met with the clinical investigators to discuss the initial findings. By the end of March, all the changes to the protocol had been implemented, all study participants had been informed, and the findings were written and submitted for publication. On May 2, 1982, the investigators sent copies of the yet to be published article to the ophthalmological community, and on May 6, 1982, the NEI announced the findings in a press conference.

Findings

- 60 % of untreated vs. 25% of treated eyes had lost six or more lines of vision after 18 months of follow-up
- Twice as many treated eyes had a visual acuity better than 20/40 (20.3% treated vs. 12.6% untreated)
- More than twice as many untreated eyes had a visual acuity of less than 20/200 (4% treated vs. 12.2% untreated)
- Treated eyes were two times as likely to be in the result group that showed improvement (61% treated vs. 30.6% untreated)
- SMDS demonstrated that treatment reduces the risk of severe visual loss for eyes with evidence of senile macular degeneration and a well circumscribed symptomatic choroidal neovascular membrane at least 200um from the center of the FAZ.

Impact

- The senile macular degeneration trial had a major impact on both clinical practice and in public health implications for the prevention of new blindness, particularly in older adults. In addition, the change in protocol after the data indicated benefits of treatment had a major impact on the ethical conduct of randomized controlled trials in ophthalmology, and demonstrated the importance of data and safety oversight.

Unresolved issues

- No unresolved issues with the trial

Summary

Senile macular degeneration (now known as age-related macular degeneration or AMD) is a major cause of new blindness and vision impairment. The argon laser photocoagulation trial was the first randomized controlled trial using laser photocoagulation, establishing laser treatment as an effective intervention for preventing further vision loss due to macular degeneration in selected patients. The treatment was controversial in that clinicians were wary about aiming a laser near the foveal avascular zone. The treatment also destroyed the retina in that area, sacrificing present vision for a better, long-term outcome. The trial was an opportunity to provide proof supporting the concept of laser treatment with the potential of transforming treatment.

The trial demonstrated that treatment reduces the risk of severe vision loss in eyes with evidence of senile macular degeneration, but it also illustrates the importance of data and safety monitoring in ophthalmology trials. During the course of the trial, initial results indicated that laser treatment was effective after the first 18 months of follow-up. This finding resulted in a change in protocol: the investigators immediately ended recruitment, offered treatment to those in the “no treatment” group who were still eligible for treatment based on the location of the neovascular membrane, and continued to follow all those who enrolled.

This trial was the first randomized clinical trial to demonstrate the effectiveness of any treatment for choroidal neovascularization in AMD. Moreover, this trial provided natural history data from the untreated control arm and data regarding the incidence of CNV in initially unaffected fellow eyes and risk factors for the development of CNV. These data were of importance in the design of later clinical trials of other therapeutic and preventive treatments for CNV in AMD.

References

1. Argon laser photocoagulation for senile macular degeneration. Results of a randomized clinical trial. Arch Ophthalmol. 1982;100(6):912-8.

2. Changing the protocol: a case report from the Macular Photocoagulation Study. Macular Photocoagulation Study Group. Control Clin Trials. 1984;5(3):203-16.

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