Degenerazione maculare legata all'età ed atrofia geografica: novità in tema di trattamento

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Chairman: Francesco Bandello MD,FEBO

Financial Disclosures

- Abbvie
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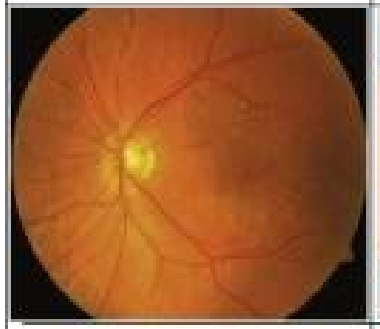
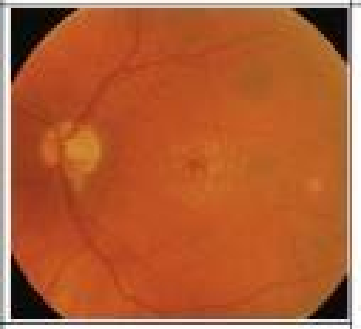
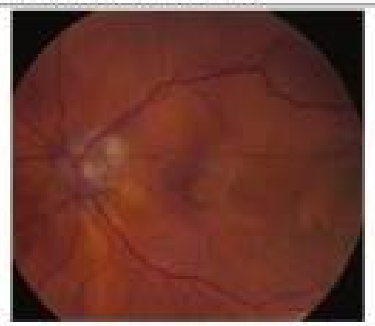
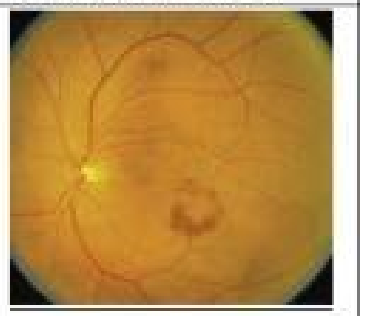
- Novartis
- SIFI
- Visufarma

Background

Age-related macular degeneration (AMD) is the leading cause of blindness in industrialised countries and the third in the world

Classified as:

Early AMD	Intermediate AMD	Advanced non-neovascular AMD	Advanced neovascular AMD
			
Several small drusen or few medium-size drusen	Many medium-sized drusen or at least one large-drusen or geographic atrophy not extending into macula	Many drusen and geographic atrophy into macula	Choroidal neovascularization

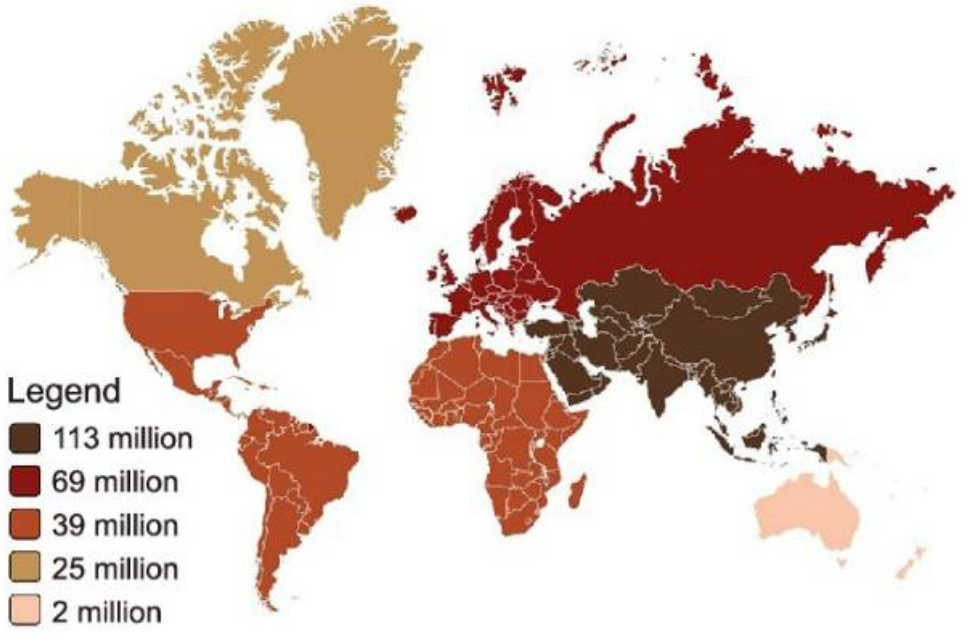
Davis MD, et al. The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS Report No. 17. Arch Ophthalmol. 2005.

AMD epidemiology

- The prevalence of all forms of the disease in subjects over 40 years is about 6-7%, while it rises up to 30% in subjects over 75 years

- **In Italy** currently **more than 800.000** people are affected by **early/intermediate AMD** and about **400.000** by **advanced AMD**

- **Global prevalence** is expected to increase in the coming years, reaching **more than 300 million affected individuals by 2040**



Wong WL, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Health. 2014.

Busted myth I

Looking at available treatments and investments, we are led to believe that **neovascular subtype is the most important form of AMD**

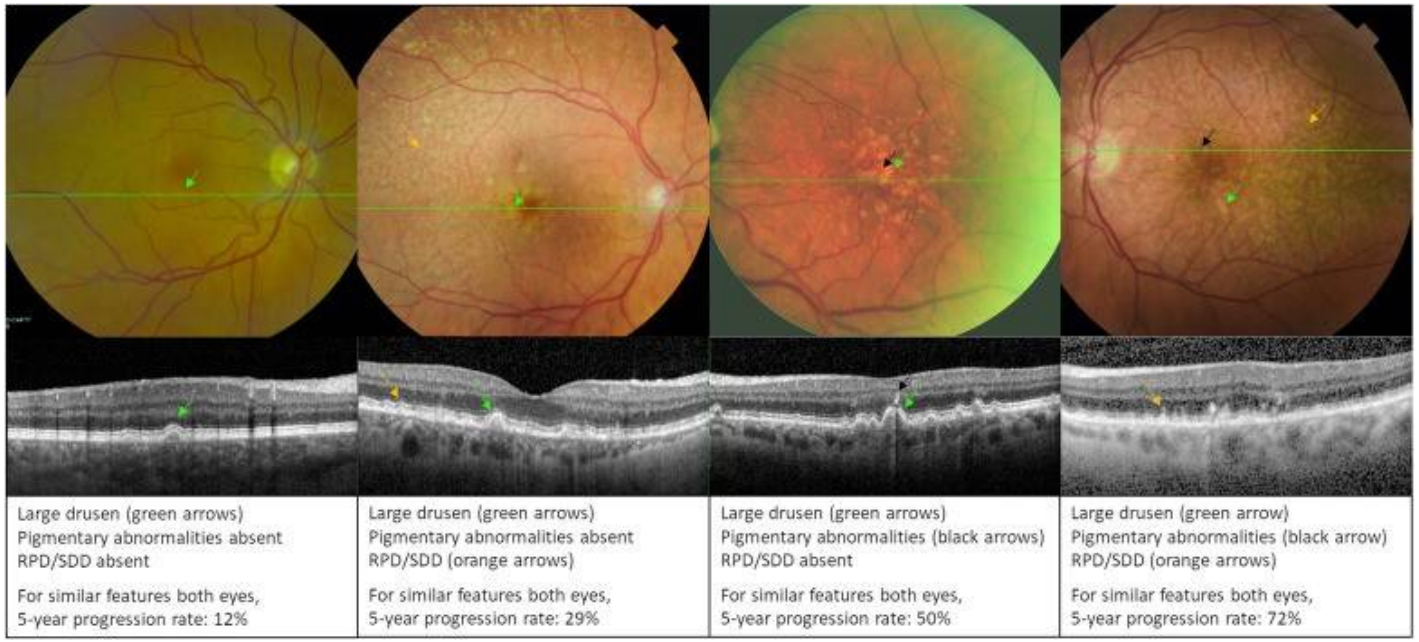
Dry AMD accounts for at least 85% of all AMD cases!

Li JQ, et al. Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis. Br J Ophthalmol. 2020.

Busted myth II

Intermediate AMD represents only one stage of the disease

Several intermediate AMD phenotypes exist, characterized by different risk of progression!

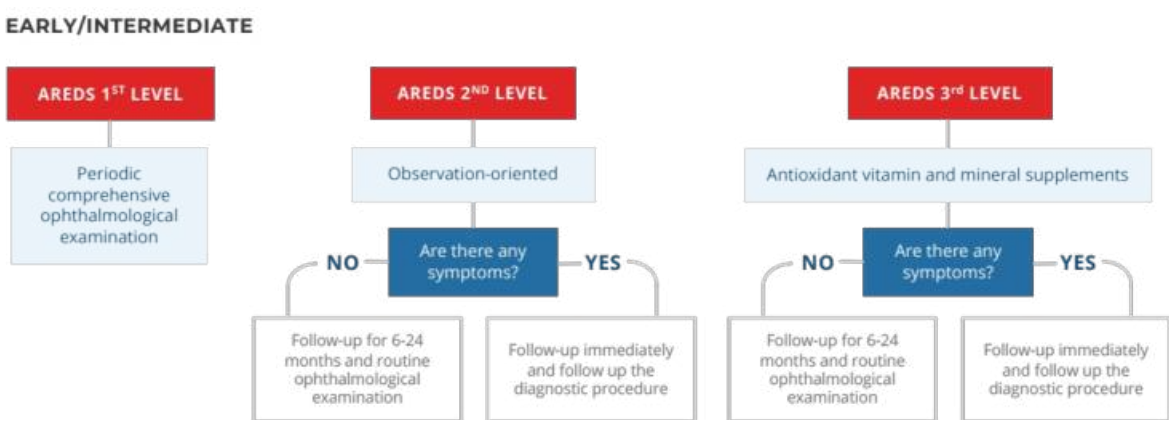


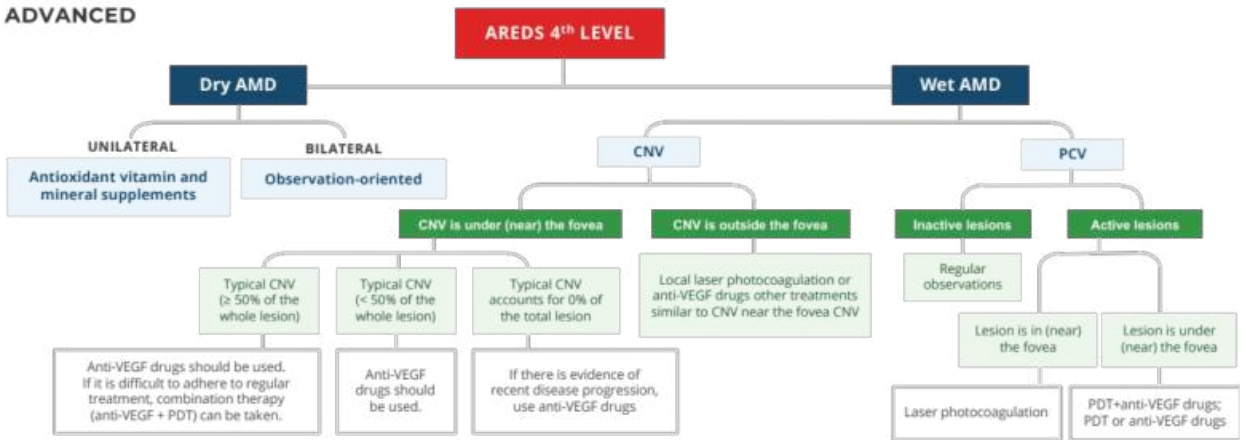
Large drusen (green arrows) Pigmentary abnormalities absent RPD/SDD absent For similar features both eyes, 5-year progression rate: 12%	Large drusen (green arrows) Pigmentary abnormalities absent RPD/SDD (orange arrows) For similar features both eyes, 5-year progression rate: 29%	Large drusen (green arrows) Pigmentary abnormalities (black arrows) RPD/SDD absent For similar features both eyes, 5-year progression rate: 50%	Large drusen (green arrow) Pigmentary abnormalities (black arrow) RPD/SDD (orange arrows) For similar features both eyes, 5-year progression rate: 72%

Agrón E, et al. An Updated Simplified Severity Scale for Age-Related Macular Degeneration Incorporating Reticular Pseudodrusen: Age-Related Eye Disease Study Report Number 42. Ophthalmology. 2024.

Busted myth III

There are no treatments for dry AMD. We can only "wait and see"



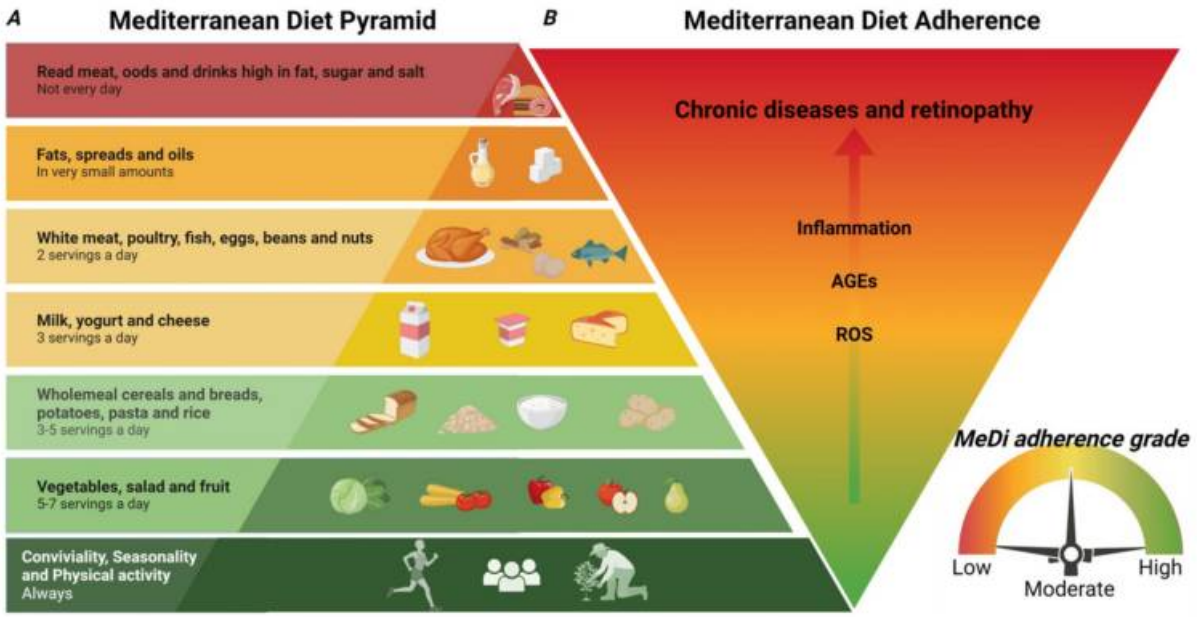


Several therapeutic options are already available both for intermediate AMD and geographic atrophy (GA)!

Treatments for Intermediate AMD

Treatment 1 Assumption: Lack of essential compounds

- The basis of the Mediterranean Diet (MeDi) pyramid includes the Mediterranean lifestyle, with conviviality, daily moderate physical activity, and balanced diet
- The worst is the adherence to MeDi pyramid, the highest is the risk of onset and progression of chronic diseases and retinal diseases
- Patients with AMD are known to have low level of essential compounds for the retina



Sbai O, et al. Effect of the Mediterranean Diet (MeDi) on the Progression of Retinal Disease: A Narrative Review. Nutrients. 2024.

Treatment 1 Solution: Nutraceuticals

- Nutraceuticals are foods (or part of a food) that provide medical or health benefits, including the prevention and/or treatment of a disease

Study	Daily dose
AREDS1	
Vitamin C	500 mg*
Vitamin E	273 mg/400 IU*
Beta-carotene	15 mg*
Zinc	80 mg*
Copper	2 mg
AREDS2	
Vitamin C	500 mg*
Vitamin E	273 mg/400 IU*
Zinc	25 mg*
Copper	2 mg
Lutein	10 mg
Zeaxanthin	2 mg

*Maximum acceptable daily dose according to the Italian Ministry of Health: vitamin C: 1000 mg; vitamin E: 60 mg; beta-carotene: 7.5 mg; zinc: 15 mg (adults), 7.5 mg (children). AREDS = The Age-Related Eye Disease Study.

AREDS reports

Nutraceuticals: an evolving approach

Although AREDS and AREDS2 formulations are currently the most effective, many other molecules are under investigation:

- Citicoline and Coenzyme Q10 -> Neurodegeneration
- Omega-3 fats EPA and DHA -> Cellular damage + inflammation + angiogenesis dysregulation
- Troxerutin -> Apoptosis + inflammation + angiogenesis dysregulation
- Vitamin B12 and Folic Acid -> Hyperhomocysteinemia (Apoptosis + inflammation + angiogenesis dysregulation)
- Lycopene -> Inflammation + angiogenesis dysregulation
- Saffron -> Apoptosis + inflammation + angiogenesis dysregulation
- Berries -> Apoptosis + inflammation + angiogenesis dysregulation

- Many other molecules under investigation…

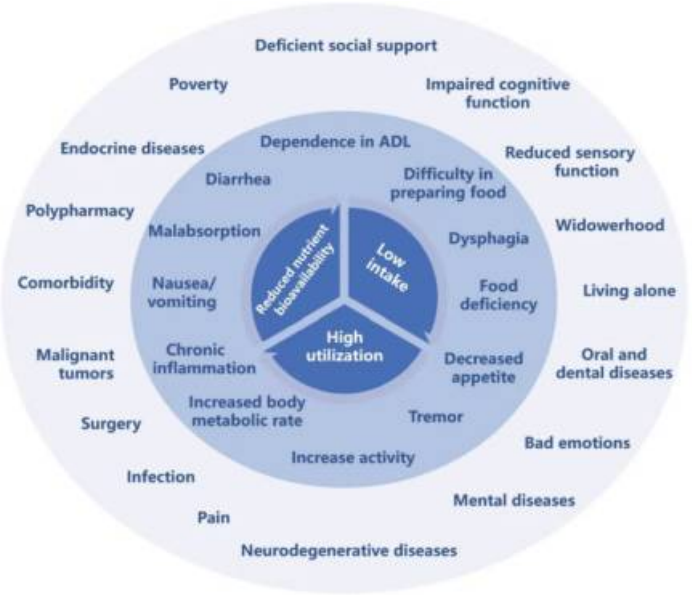
Do we need Nutraceuticals?

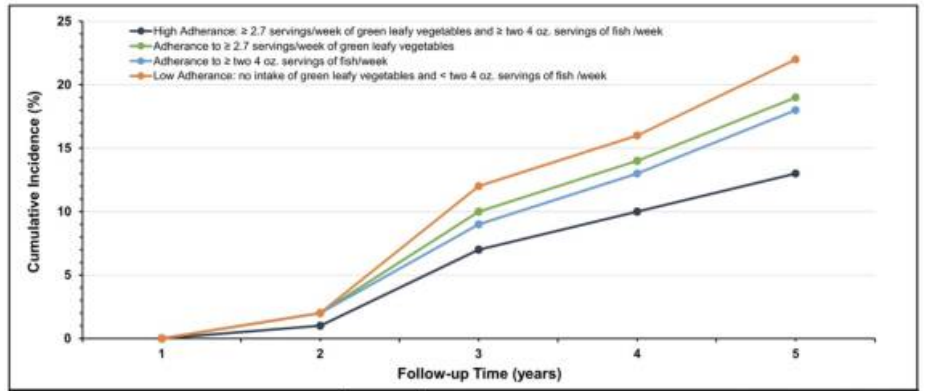
Older adults are vulnerable to malnutrition due to age-related physiological decline, reduced access to nutritious food, money, and comorbidity

The overall prevalence is between 3-28%, mainly associated with overall status

Poor health behaviours significantly associated with the incidence of AMD

The degree of malnutrition correlates with the risk of increasing disease severity in AMD



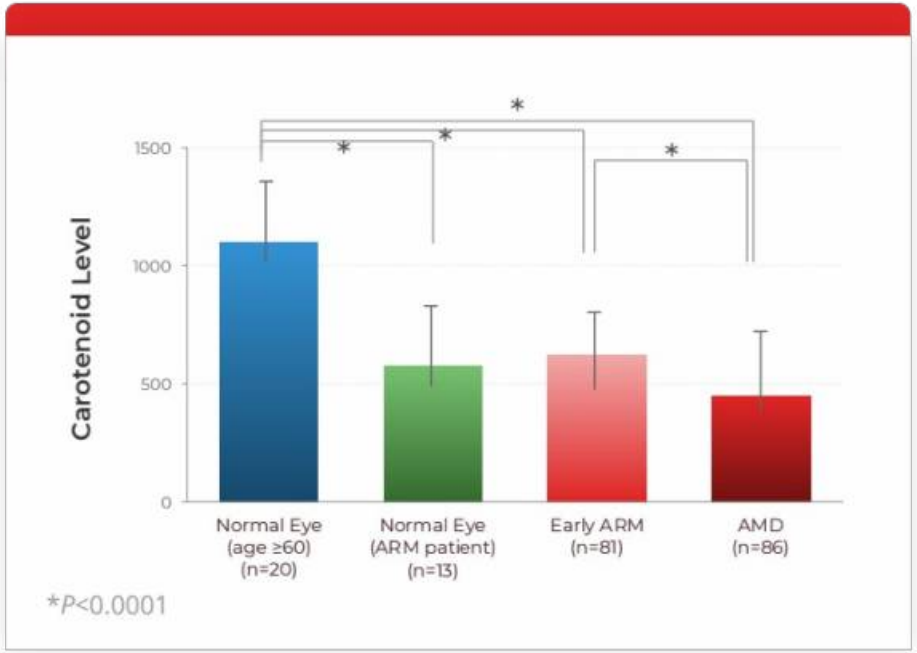


Adherance to green leafy vegetables and/or fish	N (%)	Cumulative Incidence of eyes transitioning to higher AMD severity, (%)				
		Year 1	Year 2	Year 3	Year 4	Year 5
High Adherance: ≥ 2.7 servings/week of green leafy vegetables and ≥ two 4 oz. servings of fish /week	295 (11)	0%	1%	7%	10%	13%
Adherance to ≥ 2.7 servings/week of green leafy vegetables	245 (9)	0%	2%	10%	14%	19%
Adherance to ≥ two 4 oz. servings of fish/week	776 (29)	0%	2%	9%	13%	18%
Low Adherance: no intake of green leafy vegetables and < two 4 oz. servings of fish /week	1381 (51)	0%	2%	12%	16%	22%

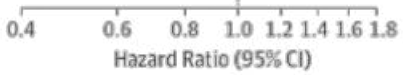
Seddon JM, et al. The role of nutritional factors in transitioning between early, mid, and late stages of age-related macular degeneration: prospective longitudinal analysis. Am J Clin Nutr. 2024.

Treatment 2 Assumption: The importance of Lutein

Macular carotenoids are decreased in AMD patients



	Lutein/ Zeaxanthin		No Lutein/ Zeaxanthin			
	No. of Eyes	No. of Events	No. of Eyes	No. of Events	Favors Lutein/ Zeaxanthin / Favors No Lutein/ Zeaxanthin	P Value
Late AMD						
All eyes	3451	940	3440	1000	0.90 (0.82-0.99)	.04
Large drusen OU	2688	576	2742	667	0.87 (0.77-0.95)	.04
Late AMD in 1 eye	763	364	698	333	0.96 (0.83-1.11)	.59
Neovascular AMD						
All eyes	3461	607	3440	655	0.89 (0.79-1.00)	.05
Large drusen OU	2688	322	2742	407	0.80 (0.68-0.95)	.01
Late AMD in 1 eye	763	285	698	248	1.02 (0.86-1.21)	.79
Central geographic atrophy						
All eyes	3451	367	3440	390	0.92 (0.78-1.07)	.27
Large drusen OU	2688	274	2742	301	0.94 (0.78-1.13)	.51
Late AMD in 1 eye	763	93	698	97	0.85 (0.64-1.13)	.27



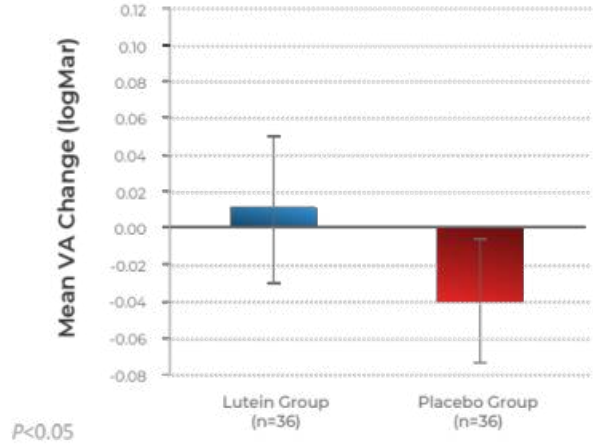
Many studies support the benefit of Lutein supplementation in AMD

Age-Related Eye Disease Study 2 (AREDS2) Research Group. JAMA Ophthalmol. 2014;132(2):142-149.

The effects of Lutein supplementation

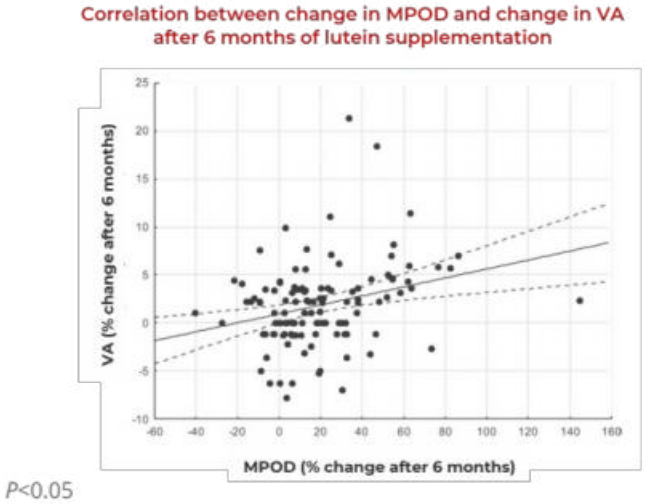
- Preserve visual acuity –> VA was stable in the lutein group and declined significantly in the placebo group

Murray IJ, et al. Invest Ophthalmol Vis Sci. 2013;54(3):1781-1788.



- Increase macular pigments concentration –> significant correlation was found between the increase in MPOD and the increase in VA

Weigert G, et al. Invest Ophthalmol Vis Sci. 2011;52(11):8174-8178.



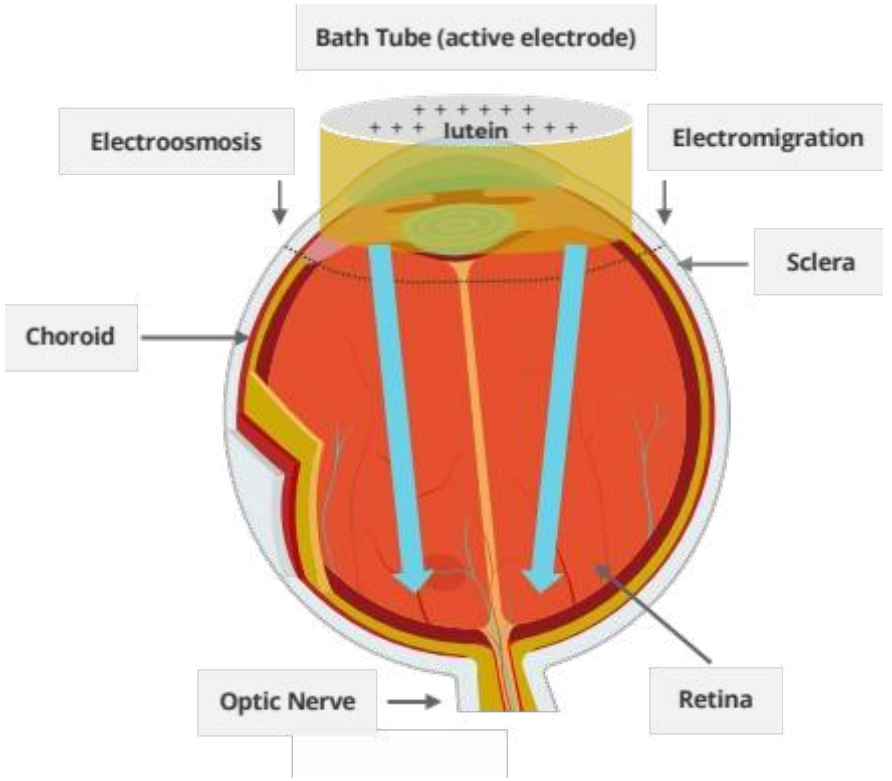
Is it possible to optimize Lutein supplementation?

Treatment 2 Solution: Lutein Scleral Iontophoresis

- During iontophoresis, lutein, in the form of liposome aggregates, passes through the sclera and the ciliary body and reaches the peripheral retina

- Once lutein is delivered to the peripheral retina, it diffuses through the tissue's components towards the macular region (blue arrows)

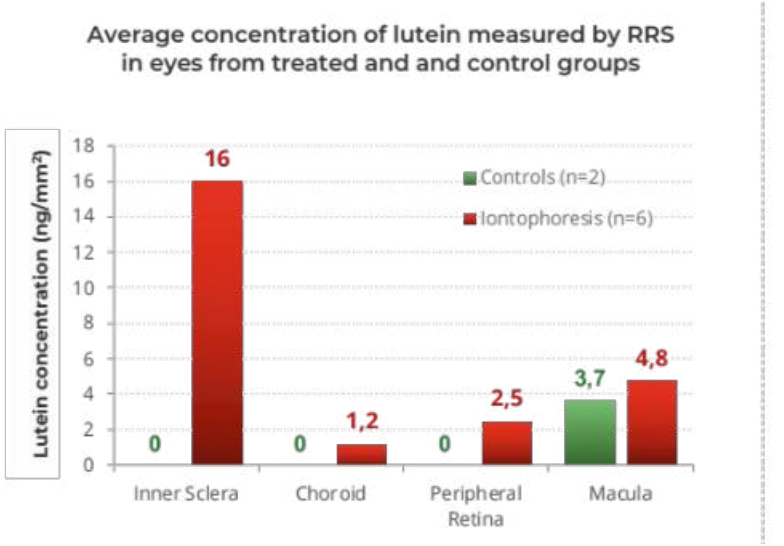
- Electric mobility (2.5 mA for 4 minutes) facilitates transport of lutein toward the macula

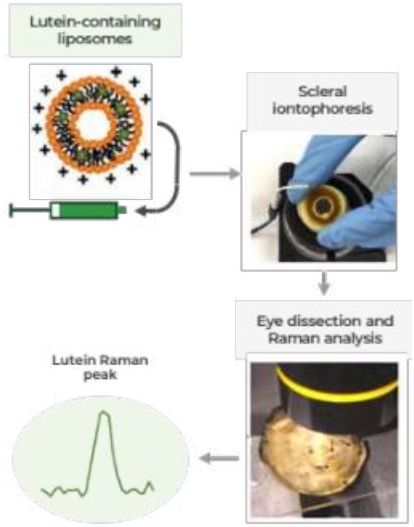


Lombardo M, et al. J Biophotonics. 2018;11(3):10.1002/jbio.201700095

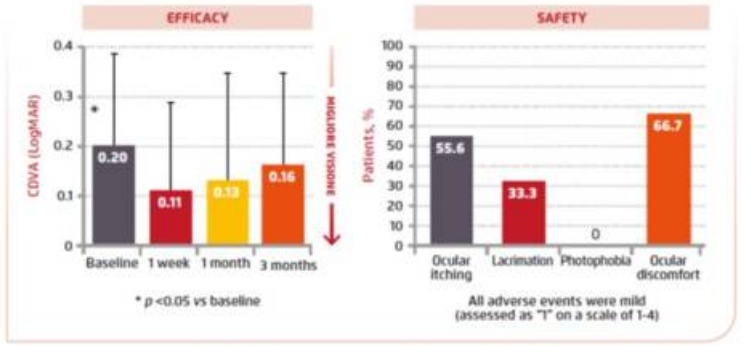
Does Lutein scleral iontophoresis really work?

- Transscleral iontophoresis was shown to be effective for in-situ delivery of lutein to the retina of human donor eyes
- 40 minutes after treatment, RRS measurements demonstrated that lutein greatly enriched the inner sclera, choroid, and retina of all treated samples





- Preliminary findings show that treated patients undergo VA and retinal sensitivity improvements
- High safety profile
- Multicenter clinical trial ongoing…



CDVA improved significantly (p=0.01) at 1 week postoperatively, and then returned toward preoperatively value during follow-up **(5 ETDRS letters).**

The 1-mm EDTRS sector retinal thickness did not change during follow-up (from 263 µm at the baseline to 262 µm at 3 months [p=0.52]).

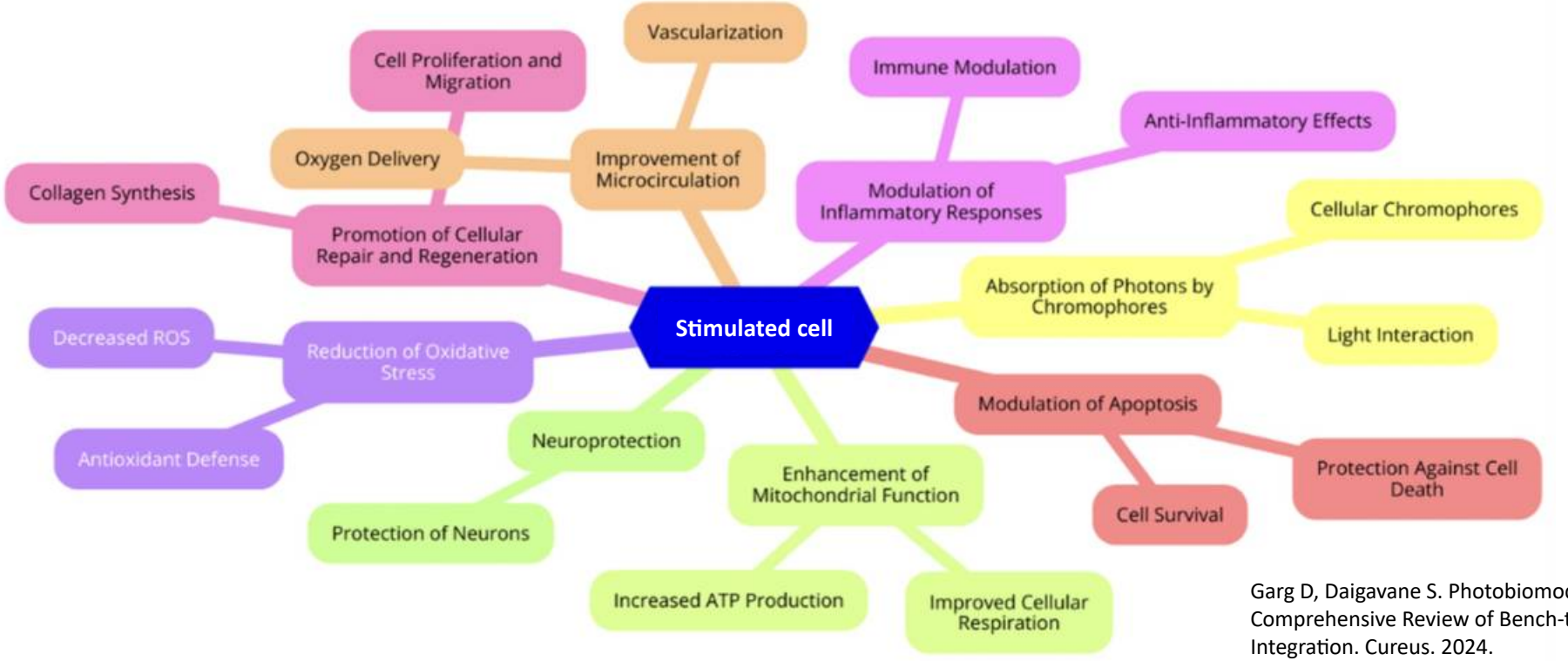
The patients did not complain of pain or discomfort during the treatment.

At 1 week, the patient outcome report score for tolerability was low for all symptoms.

Treatment 3 Assumption: A stimulated cell does not die

Apoptosis and metabolic dysregulation are major pathogenic mechanisms in AMD

Retinal cells in AMD are known to have decreased intracellular and mitochondrial activities



Garg D, Daigavane S. Photobiomodulation in Ophthalmology: A Comprehensive Review of Bench-to-Bedside Research and Clinical Integration. Cureus. 2024.

Treatment 3 Solution: Photobiomodulation

Photobiomodulation therapy is based on delivering wavelengths of light at 590 nm (yellow), 660 nm (red) and 850 nm (NIR)

Lightsite studies I, II, III showed clinical benefits

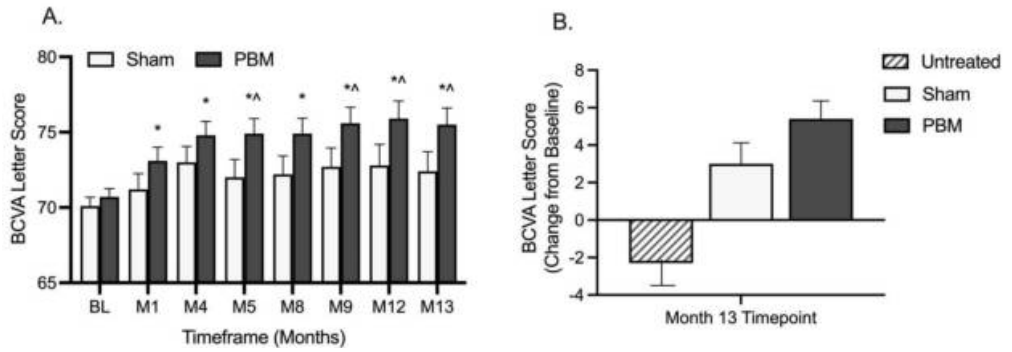
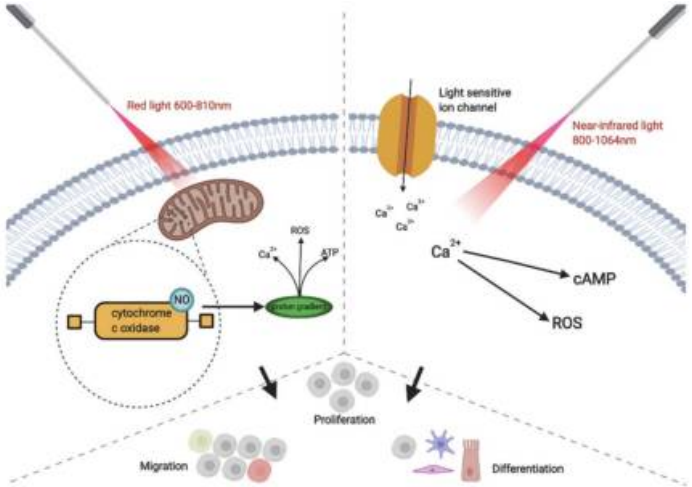
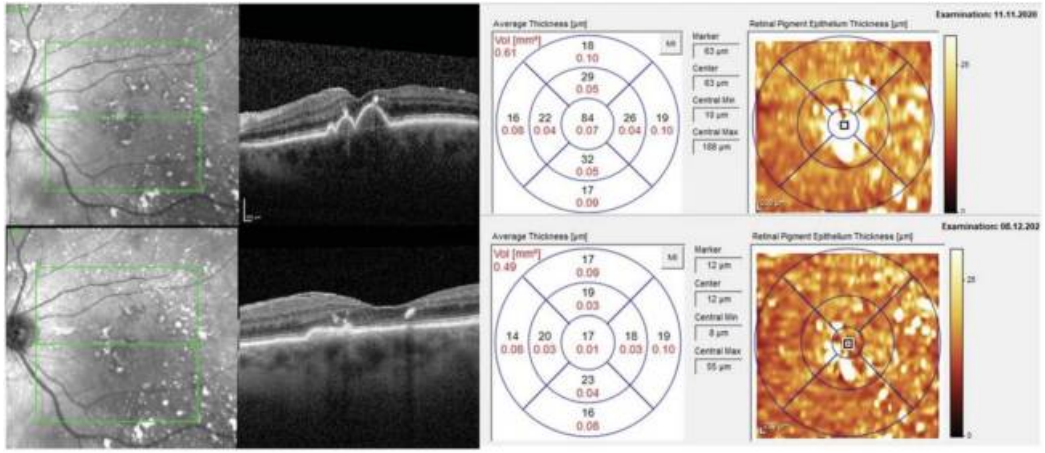


Table 1. Valeda PBM Specifications	
Light Source	LED
590 nm	4 mW/cm²
660 nm	65 mW/cm²
850 nm	0.6 mW/cm²
Treatment exposure	Total of 250 seconds/ eye

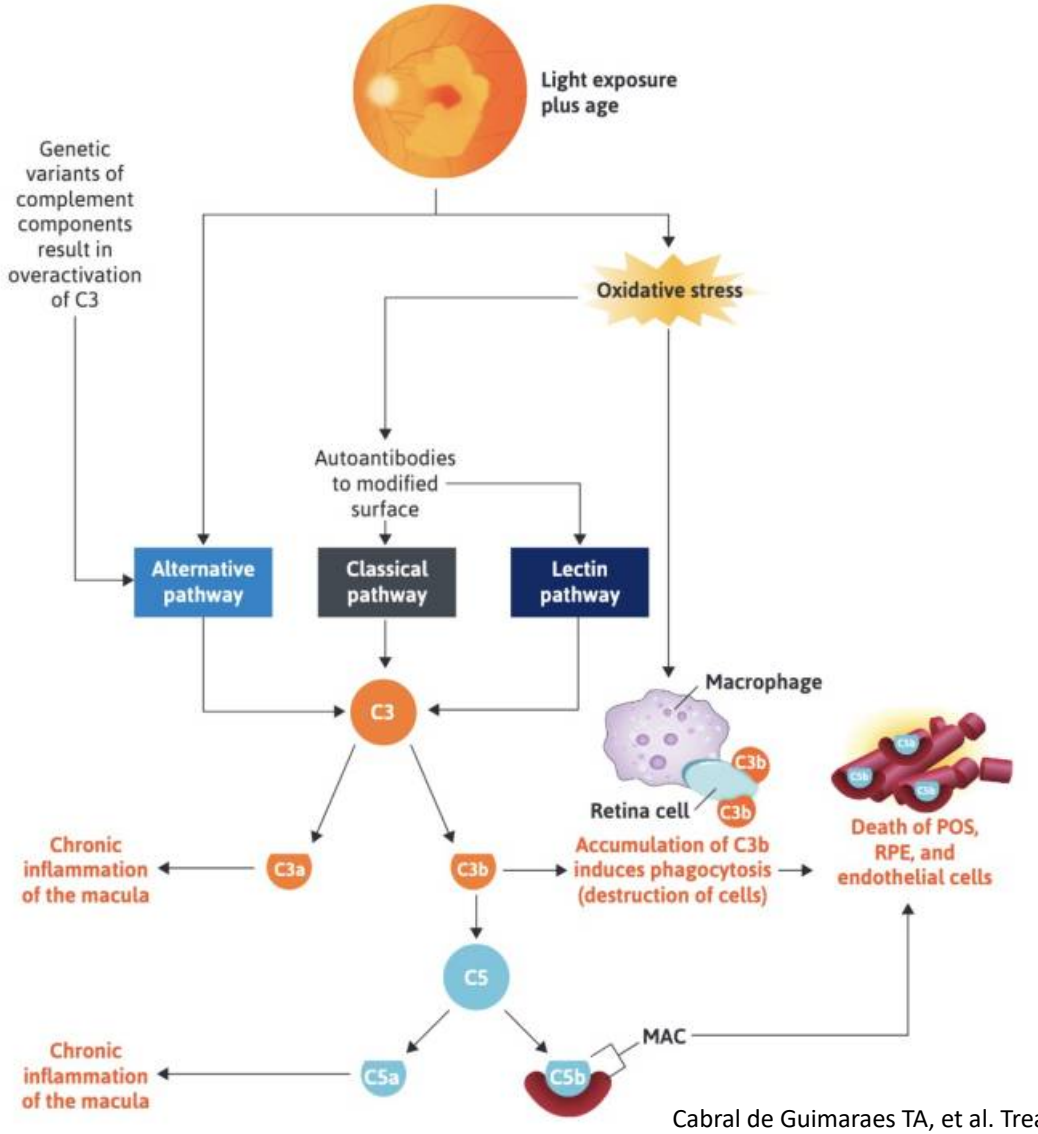


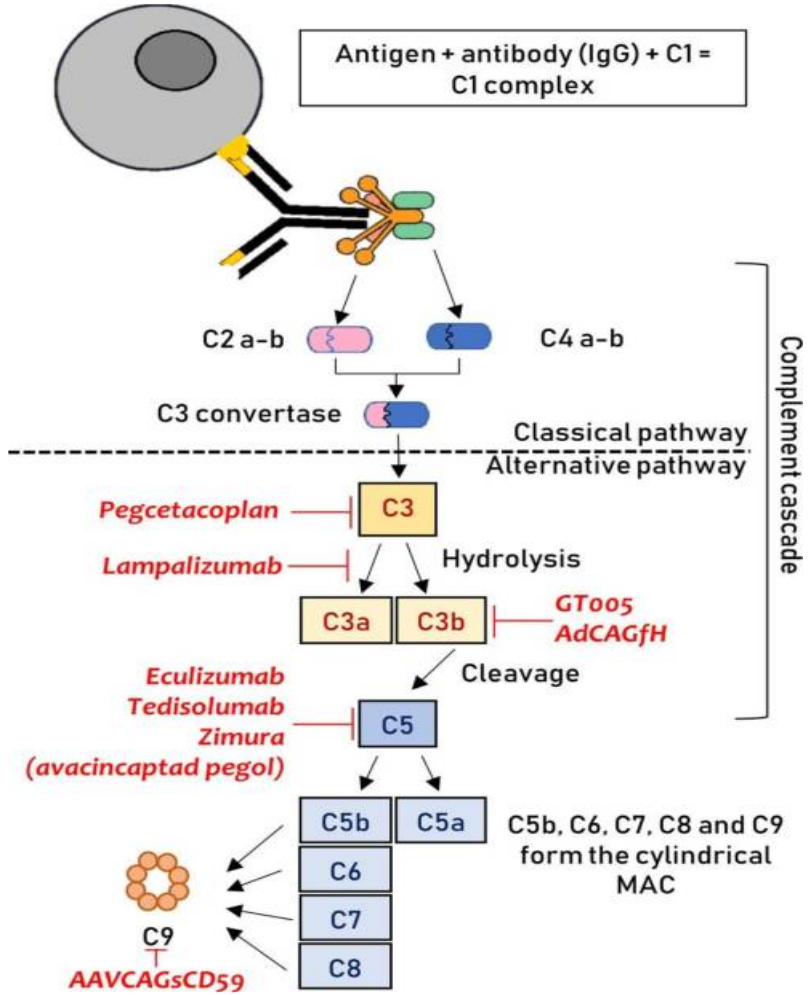


Boyer D, et al. LIGHTSITE III: 13-Month Efficacy and Safety Evaluation of Multiwavelength Photobiomodulation in Nonexuda (Dry) Age-Related Macular Degeneration Using the Lumithera Valeda Light Delivery System. Retina. 2024.

Treatments for AMD GA

The central role of Complement System in GA





Cabral de Guimaraes TA, et al. Treatments for dry age-related macular degeneration: therapeutic avenues, clinical trials and future directions. Br J Ophthalmol. 2022.

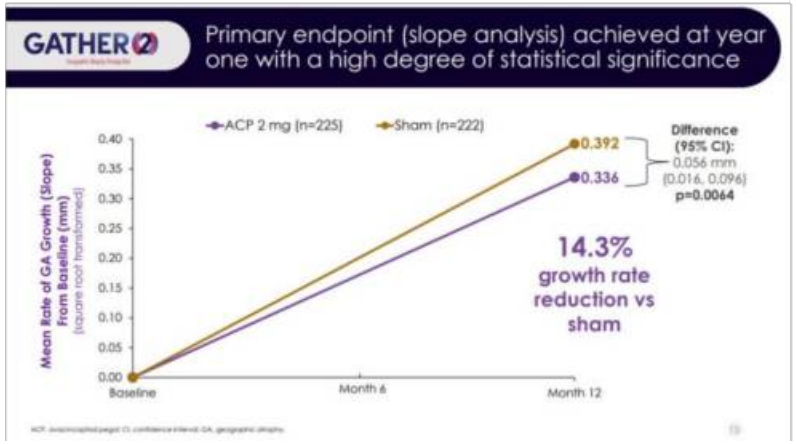
Complement inhibitors results

Lampalizumab → Antigen-binding fragment of a humanised monoclonal antibody that inhibits complement factor D.
No significant effect on GA growth rate
(CHROMA and SPECTRI)

Eculizumab
Tedisolumab → IgG antibodies involved in the inhibition of complement component C5.
No significant effect on GA growth rate

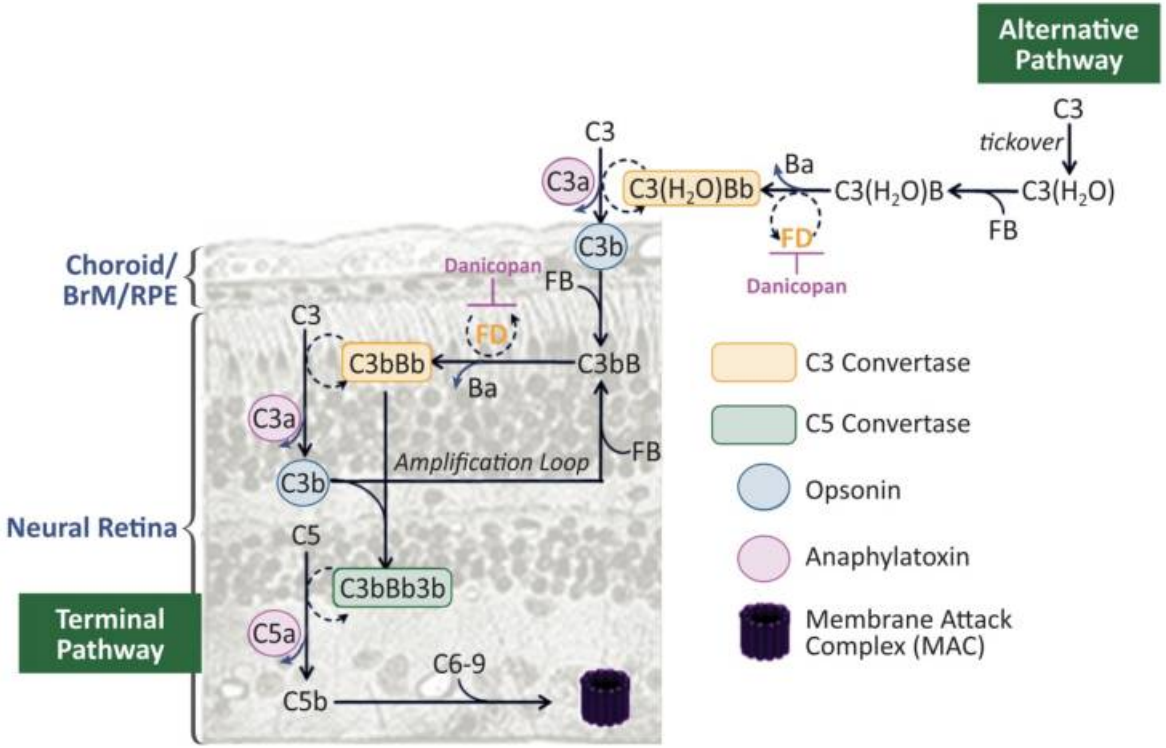
Pegcetacoplan → Pegylated bicyclic peptide inhibitor of complement C3
First and only FDA-approved treatment for GA

Zimura → PEGylated RNA aptamer designed to inhibit complement component C5.
Reduction of GA growth rate has been demonstrated (GATHER1/GATHER2)



Other approaches: Complement inhibitors

Danicopan → Factor D inhibitor that blocks cleavage of complement factor B into Ba and Bb in the alternative pathway of the complement cascade. A phase II clinical study is currently ongoing.



Other approaches: Gene therapy (ongoing trials)

JNJ-1887 (Hemera Biosciences (Waltham, Massachusetts, U.S)

- Intravitreal administration
- Aim to augment the expression of a soluble form of CD59, preventing the formation of the MAC, which represents the final step in complement-mediated cell lysis
- Stage: Phase IIb PARASOL clinical trial (NCT05811351)

GT005 (Gyroscope/Novartis)

- Surgical administration
- Aim to improve the expression of Complement factor I (CFI), inhibiting complement-mediated cellular apoptosis
- Stage: phase 2 HORIZON trial (recently discontinued by Novartis)

Other approaches: Gene therapy (new proposals)

4D Molecular Therapeutics (4DMT) (Emeryville, California, U.S)

- Intravitreal AAV-based gene therapy
- Aim to improve the expression of Complement factor H (sCFH, stabilizing complement-mediated cellular apoptosis
- Stage: N/A

Adverum Biotechnologies (AAV-CFI) (Redwood City, California, U.S)

- Intravitreal administration
- Aim to improve the expression of Complement factor I (CFI), inhibiting complement-mediated cellular apoptosis
- Stage: N/A

Kriya Therapeutics (KRIYA-82) (Palo Alto, California, U.S.)

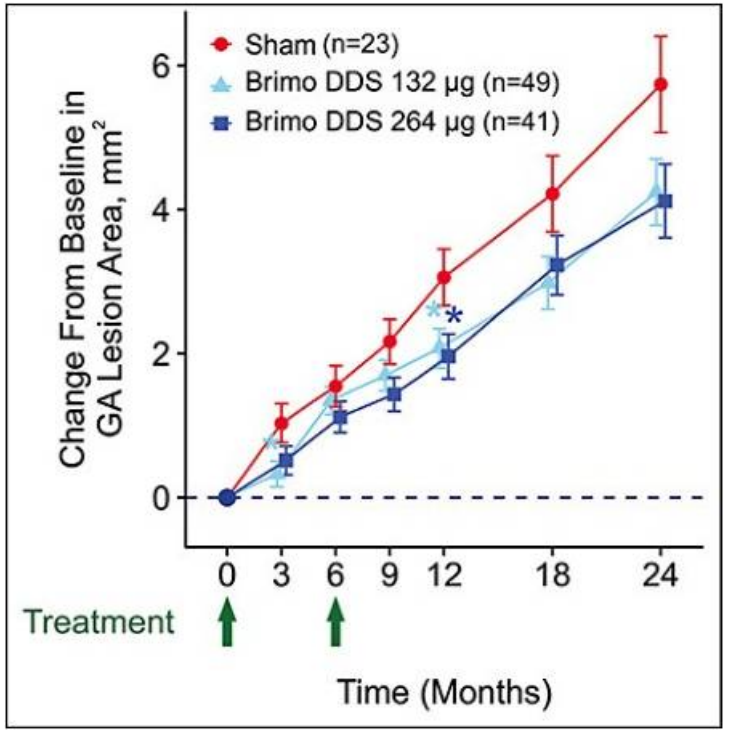
- Surgical administration
- Aim to improve the expression of fusion protein inhibiting complement C3 and C5
- Stage: N/A

Other approaches: Neuroprotective agents

CNTF → Ciliary Neurotrophic Factor delivered by encapsulated cells implanted intravitreally.
No significant effect on GA growth rate

Brimonidine tartrate

Alpha2-adrenergic receptor agonist that has been established as an intraocular pressure-lowering agent. The BEACON study showed that **primary efficacy endpoint at 24 months was not met, but there was a numeric trend for reduction in GA** progression at 24 months compared with sham treatment



WR Freeman. Brimonidine Drug Delivery System for Geographic Atrophy. An implant with potential to slow lesion growth.

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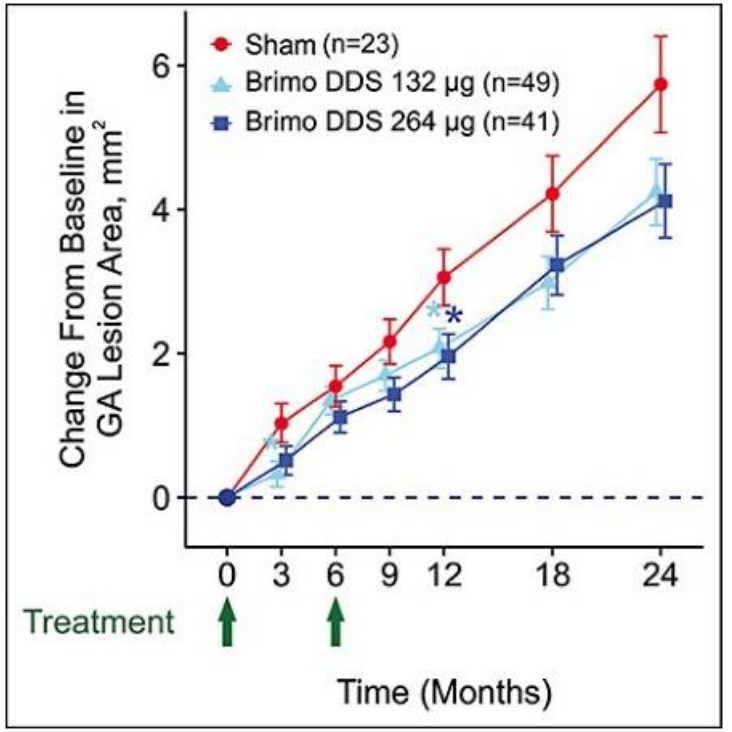
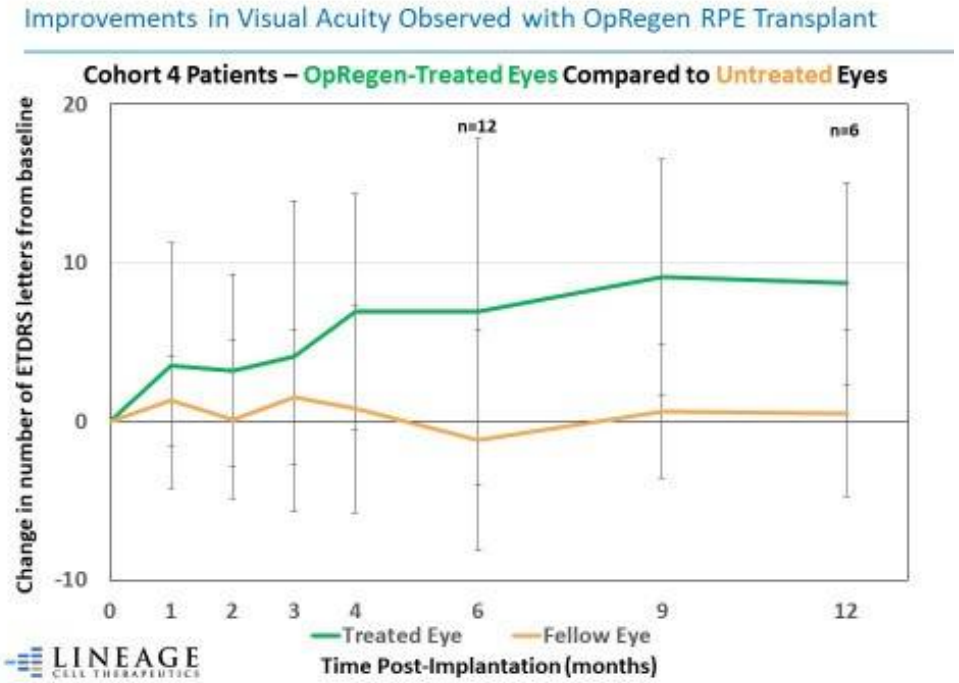


WR Freeman. Brimonidine Drug Delivery System for Geographic Atrophy. An implant with potential to slow lesion growth.

Other approaches: Cells transplant

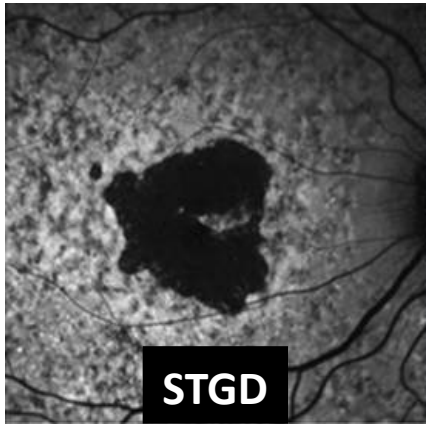
Palucorcel → Subretinally delivered human umbilical tissue-derived cells.
No significant effect on GA growth rate

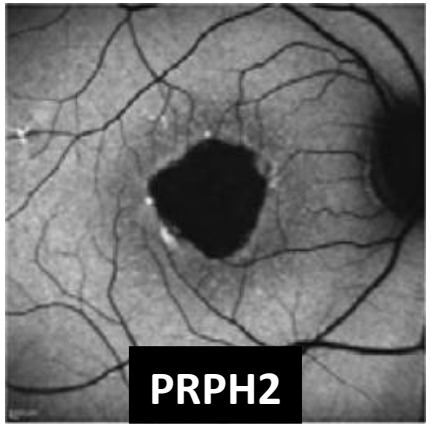
OpRegen → Single injection of human RPE cells derived from an established pluripotent cell line and transplanted subretinally.
Currently being evaluated in a phase 2 trial

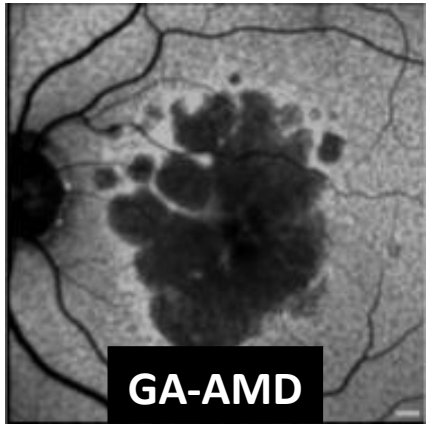


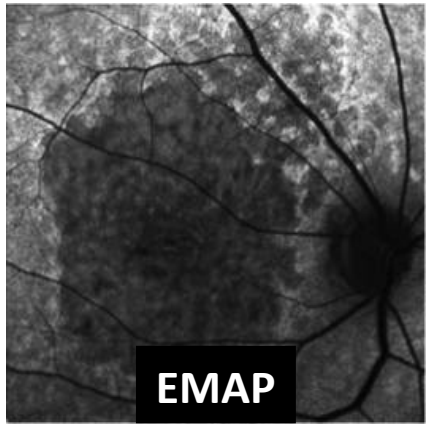
Improvements in Visual Acuity Observed with OpRegen RPE Transplant (Graphic: Business Wire)

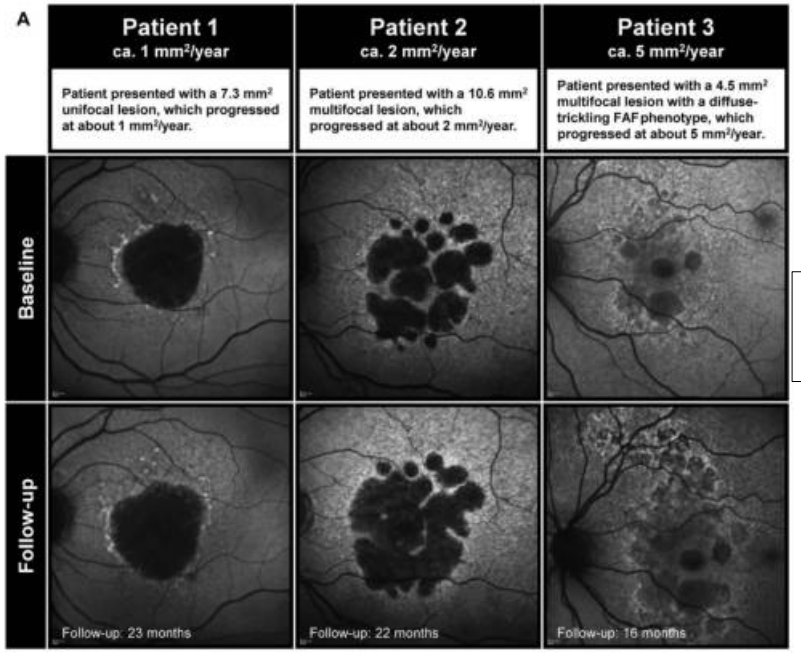
Are we sure we are targeting GA only?











Fleckenstein M, et al. The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. Ophthalmology. 2018.

Take home messages

- Dry AMD represents the most frequent phenotype
- Several intermediate AMD subtypes exist
- Many therapeutic options are already available for intermediate AMD
- Prevention is the most important therapeutic strategy
- GA AMD still represents a major therapeutic challenge

Thank you for the kind attention!

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