Seeing Clearly:
A Therapeutic Review of Age-Related Macular Degeneration

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Disclosure

- Chelsea Khaw does not have any actual or potential conflicts of interest to disclose
- Off-label use of medication will be discussed in this presentation

Presentation Overview

- Introduction
  - Pathophysiology
  - Epidemiology
  - Clinical Presentation
  - Diagnosis
  - Risk Factors
- Prevention
- Treatment
- Pharmacist's Role

Learning Objectives for *Pharmacists*

- Identify 3 risk factors and describe the underlying pathophysiology of AMD
- Differentiate between the 2 types of AMD based on their clinical characteristics
- Summarize and evaluate the Age-Related Macular Degeneration Preferred Practice Pattern guidelines for the treatment of AMD
- Apply evidence-based medicine and individualized patient-centered care to assist in the formulation of a treatment plan for a patient based on the type of AMD
- Identify 2 ways that pharmacists can improve patient outcomes in AMD

Learning Objectives for *Pharmacy Technicians*

- Learn about the risk factors and pathophysiology of AMD
- Recognize the over-the-counter treatment options that can be recommended in patients with AMD
- Recall 2 key counseling points for OTC ocular supplements
- List the 4 intravitreal treatment options for patients with neovascular AMD

Guideline

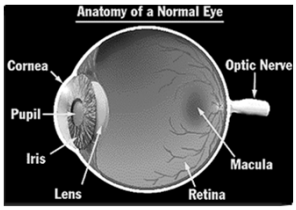
- AMD Preferred Practice Pattern from the American Academy of Ophthalmology (AMD PPP)
- SIGN grade
  - Highest quality to lowest quality: I++, I+, I-, II++, II+, II-, III
- GRADE evaluation for care recommendations
  - Good, Moderate, Insufficient
- GRADE assessment of the strength of recommendation
  - Strong, Discretionary

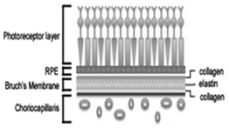
Age-Related Macular Degeneration

INTRODUCTION

What is AMD?

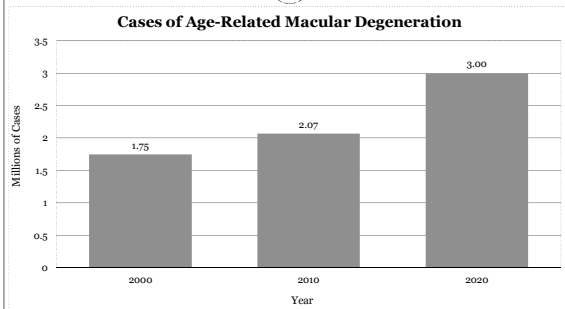
- Progressive disorder of the macula, the central portion of the retina
- Results in loss of central vision





Age-related Macular Degeneration Preferred Practice Pattern. AAO, 2008

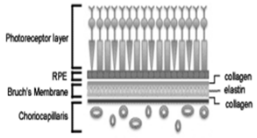
Epidemiology



Friedman, Det al Arch Ophthalmol 2004;122:564-57
Age Related Macular Degeneration. NIH: National Eye Institute

Pathophysiology

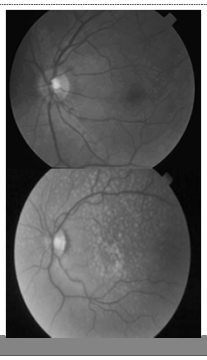
- Drusen are focal deposits composed of lipids, inflammatory components, and extracellular matrix
- They are located in Bruch's Membrane and are a clinical hallmark of AMD



Zarbin M et al *Arch Opthalmol* 2004;122(4):598-614
Age-related Macular Degeneration Preferred Practice Pattern. AAO, 2008

Drusen

- Funduscopic examination: appear as pale, yellow lesions
- Hard drusen
  - Small, well-defined margins
  - Normal in healthy aging
- Soft drusen
  - Large, with undefined edges
  - Usually pathologic



Zarbin M et al *Arch Opthalmol* 2004;122(4):598-614
Age-related Macular Degeneration Preferred Practice Pattern. AAO, 2008

Age-Related Eye Disease Study (AREDS)

- Sponsored by the National Eye Institute of the federal government's National Institutes of Health
- Prospective, multicenter, randomized controlled trials (RCT)
- Assessed disease progression, risk factors, and the effects of antioxidant vitamins and minerals
- Conducted between 1996 and 2006
  - AREDS- Released in 2001
  - AREDS2- Released in 2013

Age-Related Eye Disease study Research Groupet al Arch Ophthalmol 2001;119:1417-36
Age-Related Eye Disease study Research Group. JAMA. 2013;309(19):2005-15

AMD Classification

AREDS Category	Clinical Features	Drusen Size (Diameter in μm)
1- No AMD	• No or few small drusen	<63
2- Early AMD (Dry)	• Presence of few small to intermediate-sized drusen • Hyper/hypopigmentation of the retinal pigment epithelium (RPE)	63-124
3- Intermediate AMD (Dry)	• Numerous intermediate-sized drusen • One large drusen • Geographic atrophy not involving the macula	Large drusen >125

Age-Related Eye Disease study Research Group et al Arch Ophthalmol 2001;119:1417-36
Age-related Macular Degeneration Preferred Practice Pattern. AAO, 2008

AMD Classification

AREDS Category	Clinical Features
4- Advanced Non-Neovascular AMD (Dry)	• Presence of drusen • Geographic atrophy extending to the center of the macula

4- Advanced Neovascular AMD (Wet)	• Presence of drusen
	• Neovascularization +/- sequelae
	  • Lipid deposits
	  • Hemorrhage
	  • Retinal pigment abnormalities
	  • Fibrotic scar
	  • Hard retinal exudates

Age-Related Eye Disease study Research Group et al Arch Ophthalmol 2001;119:1417-36
Age-related Macular Degeneration Preferred Practice Pattern. AAO, 2008

AMD Classification

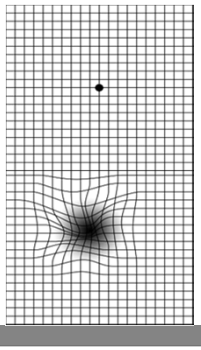
<u>Dry AMD</u>
- Non-neovascular AMD
- Atrophic AMD
- Dry AMD can progress to wet AMD

<u>Wet AMD</u>
- Neovascular AMD
- Exudative AMD
- Three Types
  - Extrafoveal
  - Juxtafoveal
  - Subfoveal
- Most advanced form

Age-related Macular Degeneration Preferred Practice Pattern. AAO, 2008

Clinical Presentation

- Dry AMD
  - Symptoms appear in one or both eyes
  - Gradual loss of vision
  - Difficulty reading
  - Blurry center of vision
- Wet AMD
  - Symptoms usually appear in one eye
  - Acute visual distortion
  - Loss of central vision
- Metamorphopsia
  - Distortion of straight lines
  - Evaluated with Amsler Grid
- Scotoma
  - Dark spot in center of visual field



Jager RDet al N Engl J Med. 2008;358(24):2606-17

Diagnosis

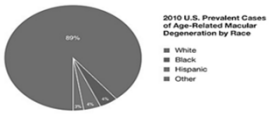
- Diagnosis based on findings of comprehensive dilated eye exam
- Diagnostic tests
  - Fluorescein Angiography
  - Fundus Photography
  - Optical Coherence Tomography

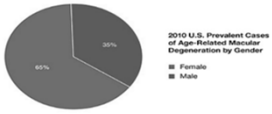
Age-related Macular Degeneration Preferred Practice Pattern. AAO, 2008

Risk Factors for AMD

Non-Modifiable

- Increasing Age (>50 y/o)
- Ethnicity
- Gender
- Genetics





Friedman, D et al Arch Ophthalmol 2004;122:564-57
Age Related Macular Degeneration . NIH: National Eye Institute

Modifiable Risk Factors For AMD

- Diet
- Low Levels of Antioxidants
- BMI
- Physical activity
- Smoking
- Hypertension
- Cardiovascular Disease
- Alcohol Use
- Sunlight Exposure
- Vitamin B and D Status
- Aspirin Use?

Khan et al Br J Ophthalmol 2006;90:75-80.
Age-related Macular Degeneration Preferred Practice Pattern. AAO, 2008
AREDS Report Number 9. Arch Ophthalmol 2001;119:1439-52

Aspirin and AMD

- Regular aspirin use (2x/week x 3 months) is associated with small increase in risk of late AMD
  - [HR] 1.63, 95% CI 1.01-2.63
- Possible bias in studies due to confounders and data collection methods
- AMD PPP
  - "Patients who have been instructed to use aspirin by a physician should continue to use it as prescribed."
  - Level of evidence: *II++; Good; Strong*

de Jong PT et al 2012, Ophthalmolog.; 119:112
Klein B et al 2012, JAMA; 308:2469
Age-related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Liew G et al. 2013 JAMA Intern Med; 173:258

Age-Related Macular Degeneration

PREVENTION

Diet

- Association between omega-3 fatty acids (OM3FA) and a reduced risk of AMD
  - Patients with the highest intake of OM3FAs were 30% less likely to progress to advanced AMD after 12 years
  - OR=0.68 (95% CI: 0.49, 0.94; $P \leq 0.02$)
- Increased risk of AMD progression seen in those with increased intake of saturated fats and a higher BMI

AREDS report number 19 et al 2005, Ophthalmology;112:533-9
AREDS report 30 et al 2009 ,Am J Clin Nutr ;90:1601-7
Age- Related Macular Degeneration Preferred Practice Pattern. AAO, 2008

Exercise

Women's Health Initiative Observational Study

- A 54% lower odds for developing early AMD in those women in the highest quintile for physical activity
- A 71% lower odds for developing AMD was associated with a combination of 3 healthy behaviors (diet, physical activity, non-smoker) (p<0.001)
- Increasing physical activity and adapting healthy lifestyles may reduce the risk for early AMD by 3 fold

AREDS report number 19 et al 2005, Ophthalmology;112:533-9
AREDS report 30 et al 2009 ,Am J Clin Nutr ;90:1601-7
Age- Related Macular Degeneration Preferred Practice Pattern. AAO, 2008

Smoking

- Associated with increased risk of progression from early to advanced AMD
- Dose-response relationship
  - Strong association between pack-years of smoking and AMD (p=0.002)
  - Smoking cessation reduced odds of AMD
  - Odds of AMD after smoking cessation for 20 years is equivalent to a non-smoker
- Smokers have poorer responses to therapy
- AMD PPP
  - Smoking cessation is strongly recommended when advising patients
  - Level of evidence: *I++; Good; Strong*

Beaver Dam Eye Study et al 1998 Am J Epidemiol; 147:103
AREDS report no 19 et al 2005, Ophthalmology ;112:533-9
Khan JC et al 2006, Br J Ophthalmol;90:75-80

Antioxidant and Vitamin Supplements

- The role of antioxidant and vitamin supplements is unclear in the prevention of AMD
- Several studies and meta-analyses have not found benefit of supplementation for prevention of AMD
  - Vitamins A, C, E, zinc, lutein, zeaxanthin
  - Risk ratio of AMD prevention in those who took supplements was 0.98 (95% confidence interval 0.89 to 1.08)
    - Not at decreased or increased risk of AMD development

Evans JR et al 2012, Cochrane Database Syst Rev;CD000253

Patient Case

AD is a 45 y/o Caucasian female with a family history of AMD. She has a PMH of hypertension, hx stroke, and is a 0.5 PPD smoker. Her current medications include lisinopril 10 mg daily and aspirin 81 mg daily. Her current diet consists of mostly processed and fast foods.

BP	150/88 mmHg
Weight	160 lbs
Height	66 in
BMI	27.4

She stops by the pharmacy today to pick up her prescription and she tells you that she went to the optometrist last week, who told her she may be at risk for developing AMD.

Patient Case

Which of the following groupings are risk factors AD has for AMD development?

1. Aspirin use, smoking, gender, age
2. Gender, race, family history, smoking
3. Stroke history, smoking, BMI, age, family history
4. Cardiovascular disease and aspirin use, hypertension, age

Patient Case

Which of the following is the best prevention measure over which you can counsel AD?

1. Start taking antioxidant supplements and a multivitamin
2. Begin exercising every day and increase the amount of OM3FAs in diet
3. Discontinue aspirin 81 mg daily
4. Smoking cessation

Age-Related Macular Degeneration

TREATMENT

Lifestyle Modifications

- **Smoking cessation**
- Dietary changes
- Controlling blood pressure
- Weight management/lowering BMI
- Recommended for all AREDS categories

Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Age-Related Eye Disease Study Research group et al 2001

Antioxidant Vitamin and Mineral Supplements

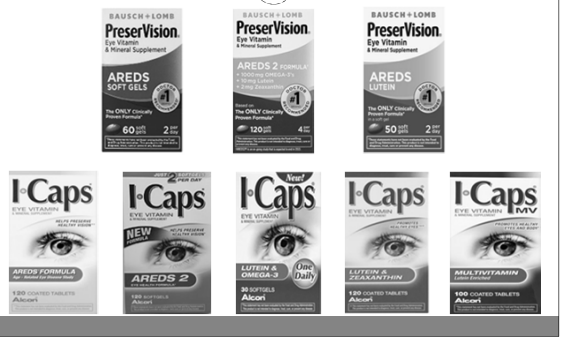
- Recommended for AREDS Categories 3 and 4
  (Level of evidence: I++; Good; Strong)
- AMD PPP: "There is no evidence to support the use of antioxidant vitamin and mineral supplements for patients who have less than intermediate AMD"
  (Level of evidence: *II++; Good; Discretionary)*

National Eye Institute Recommended Formula	
Nutrient	Amount Per Day
Vitamin C	500 mg
Vitamin E	400 IU
Zinc	80 mg
Copper	2 mg
Lutein/Zeaxanthin*	10 mg/2 mg
Beta-carotene**	15 mg

*from AREDS 2 Trial
**from AREDS Trial

Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial et al 2013 JAMA: 309(19):2005-15

Antioxidant Vitamin and Mineral Supplements



AREDS Trial

Trial Design:	11-center, double-masked, randomized, clinical trial
Population:	3640 enrolled study participants, aged 55–80 years, high risk for progression to a more advanced stage of AMD
Study Arms:	1. Antioxidants (500 mg vitamin C, 400 IU vitamin E, and 15 mg beta carotene) 2. 80 mg zinc oxide and 2 mg copper 3. Antioxidants plus zinc/copper or 4. Placebo
Outcome:	Progression to or treatment for advanced AMD and at least moderate visual acuity loss from baseline (≥15 letters) Assessed as loss of letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart
Follow-up:	6.3 years

Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Age-Related Eye Disease Study Research Group et al 2001 Arch Ophthalmol;119:1417-36

AREDS Results

	Antioxidants Alone	Zinc Alone	Antioxidants + Zinc
RRR of developing advanced AMD at 5 years	17%	21%	25%
RRR of vision loss	10%	11%	19%
OR of developing advanced AMD vs placebo	0.80 [99%CI, 0.59-1.09]	0.75 [99% CI, 0.55-1.03]	0.72 [99% CI, 0.52-0.98]
No statistically significant adverse medication events were associated with any of the formulations.			

RRR= Relative Risk Reduction
OR = Odds Ratio

Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Age-Related Eye Disease Study Research Group et all 2001 Arch Ophthalmol;119:1417-36

AREDS 2 Trial

Trial Design:	Multicenter, randomized, double-masked, placebo-controlled phase 3 study with a 2 × 2 factorial design
Population:	4203 enrolled study participants, aged 50–85 years, high risk for progression to a more advanced stage of AMD
Study Arms:	1. Lutein + zeaxanthin 10 mg/2 mg 2. Omega-3 Fatty Acid: eicosapentaenoic acid (EHA) + docosahexaenoic acid (DHA) [650 mg/350 mg] 3. Combo of the above 4. Placebo Secondary randomization to 1 of 4 variations of varying zinc and beta-carotene formulas
Outcome:	Progression to or treatment for advanced AMD and at least moderate visual acuity loss from baseline (≥15 letters)
Follow-up:	Median= 5 years

Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Age-Related Eye Disease Study Research Group et all 2001 Arch Ophthalmol;119:1417-36

AREDS 2 Trial Results

Progression to Advanced AMD After 5 years

	Probability of Progression to Advanced AMD (%)	Reduction in Progression to Advanced AMD (HR)
Placebo	31 (n=406)	
Lutein + Zeaxanthin	29 (n=399)	0.90 [98.7% CI, 0.76-1.07] P=.12
DHA + EPA	31 (n= 387)	0.97 [98.7% CI, 0.82-1.16] P = .70
Lutein + Zeaxanthin and DHA +EPA	30 (n=387)	0.89 [98.7% CI, 0.75-1.06] P = .10
More lung cancer in beta-carotene vs non beta-carotene group in former smokers: 2.0% vs 0.9%, P=0.04		

Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial et al 2013 JAMA: 309(19):2005-15

AREDS2 Trial Summary

- Addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD
- However, because of potential increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation
- AMD PPP
  - A lower zinc dose (25 mg) in the AREDS2 formulation could be considered
    - Level of evidence: *I++; Good; Discretionary*

Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial et al 2013 JAMA: 309(19):2005-15

Adverse Effects

- Beta-carotene
  - Increased risk of lung cancer development in former smokers
  - Increased yellowing of the skin
- Zinc
  - Increased risk of hospitalization due to genitourinary causes
  - Copper-deficiency anemia

Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Age-Related Eye Disease Study Research Group et al 2001 Arch Ophthalmol;119:1417-36

Patient Case

20 years later…

AD is a 65 y/o female with a PMH of hypertension, hyperlipidemia, hx stroke, and recently diagnosed AMD AREDS category 2. Current medications include atorvastatin 40 mg daily, aspirin 81 mg daily, and lisinopril 10 mg daily. She is a 0.5 PPD smoker.

Vitals	Reading
BP	158/88 mmHg
Weight	86 kg
Height	175 cm

Which of the following is the best treatment recommendation?

1. Antioxidant vitamin and mineral supplements as recommended from the AREDS and AREDS2 reports
2. Intravitreal injections to prevent progression
3. Lifestyle management with healthy diet, blood pressure control, and physical activity
4. Discontinue aspirin due to increased risk of progression

Vascular endothelial growth factor (VEGF) inhibitors

- Ranibizumab (Lucentis)
- Bevacizumab (Avastin)
- Aflibercept (Eylea)
- Pegaptanib (Macugen)

- First line therapy for the stabilization and treatment of neovascular AMD (AREDS Category 4)

- The delay in initiation of VEGF injections (≥ 21 weeks vs 7 weeks) after first symptoms of neovascular AMD is associated with poorer vision outcomes

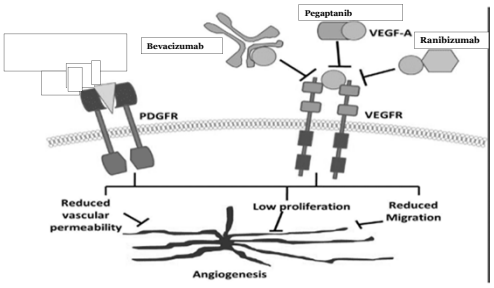
Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Lim JH et al 2012 . Am J Ophthalmol 2012; 153:678.

Role of VEGF in AMD

- Mediates neovascularization
- Induces angiogenesis
- Increases vascular permeability
- Plays a role in ocular inflammation

VEGF inhibitors for AMD and diabetic macular edema. Med Lett Drugs Ther. 2015;57(1464):41-2.

VEGF Inhibitors- Mechanism of Action



Roy et al 2014 Austin J Nanomed Nanotechnol;2(3):1027

VEGF Inhibitors - Dosing

Drug	Intravitreal Dose Can increase dosing interval as needed.	Cost/injection
Pegaptanib/Macugen	0.3 mg every 6 weeks	$870.00
Ranibizumab/Lucentis	0.5 mg every 28 days	$2,340.00
Bevacizumab/Avastin *off label	1.25 mg every 4 weeks	$910.25
Aflibercept/Eylea	2 mg every 4 weeks x 12 weeks, then 2 mg every 8 weeks	$2,220.00

Avery RL et al 2006. Ophthalmology; 113:363-72
Bashshur Z et al 2008 Am J Ophthalmol; 145:249-56
Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Micromedex. Truven Health Analytics LLC. Ann Arbor, MI.

VEGF Inhibitor Dosing Schedule

- Optimal frequency of dosing is unknown
- "Treat and Extend Method"
  - Treat initially as done in RCTs
  - Extend dosing interval 2 weeks if no neovascular activity is present
  - Reduce dosing interval 2 weeks if neovascular activity, fluid, or hemorrhage
  - Helps to decrease the number of clinic visits per year
  - AMD PPP Level of evidence: *III; insufficient; discretionary*

Arnold JJ et al 2015 Ophthalmology; 122:1212.

Pegaptanib VISION 1 and 2 Trials

VEGF Inhibition Study in Ocular Neovascularization Study

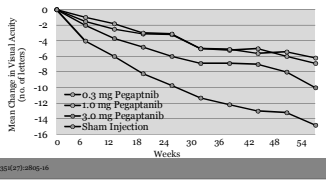
Trial Design:	Prospective, randomized, double-blind, multicenter, dose-ranging, controlled clinical trials at 117 sites
Population:	2419 total patients with established neovascular AMD, aged 50 years and older
Study Arms:	Sham injection or intravitreous injection of pegaptanib
Outcome:	VISION 1-Proportion of patients who had lost fewer than 15 letters of visual acuity at 54 weeks VISION 2-Mean change in visual acuity over time
Follow-up:	2 years

Gragoudas E et al 2004 N Engl J Med; 351(27):2805-16
Chakravarthy U et al 2006 Ophthalmology; 113(9):1508e1-25.

VISION 1 Trial

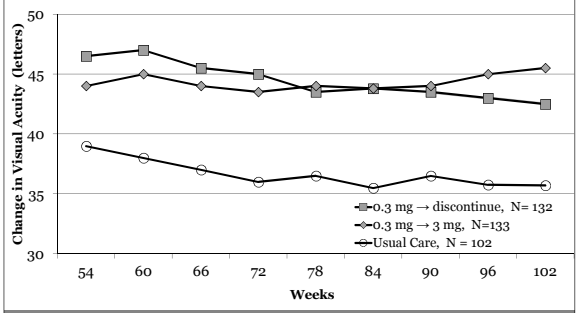
Pegaptanib shown to be effective for patients with established neovascular AMD

Treatment	Visual loss of 15 letters or less	P value	Visual gain of 15 letters or more	P value
Pegaptanib 0.3 mg	70%	<0.001	33%	0.003
Placebo	55%	<0.001	23%	0.003



Gragoudas E et al 2004 N Engl J Med;351(27):2805-16

VISION 2 Trial



Chakravarthy U et al 2006 Ophthalmology;113(9):1508.e1-25

Pegaptanib

- Less used…
  - Does not improve visual acuity in patients with new onset neovascular AMD
  - More ADRs than other agents
- AMD PPP
  - "The few patients treated with pegaptanib sodium injection should have follow-up examinations approximately 6 weeks following each injection"
    - Level of evidence*: III;Good; Strong*

Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008

Ranibizumab MARINA Trial

Trial Design:	Phase 3, multicenter, double-masked, RCT
Population:	716 participants, aged 50 years and older with previously untreated active choroidal neovascularization due to AMD
Study Arms:	Randomized 1:1:1 to receive monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) or placebo
Outcome:	• The proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months • The proportion of patients gaining more than 15 letters from baseline visual acuity at 12 months
Follow-up:	2 years

Rosenfeld PJ et al 2006 N Engl J Med; 355(14):1419-31

MARINA Trial Results

Ranibizumab injections prevented vision loss and improved mean visual acuity, with low rates of adverse events

	Visual loss of 15 letters or fewer	Visual gain of 15 letters or more	Average letter number improvement	P value
Ranibizumab 0.3 mg	94.5%	24.8%	+6.5 letters	P<0.001
Ranibizumab 0.5 mg	94.6%	33.8%	+7.2 letters	P<0.001
Placebo	62.2%	5.0%	-10.4 letters	P<0.001

Rosenfeld PJ et al2006 N Engl J Med; 355(14):1419-31

Ranibizumab ANCHOR Trial

Trial Design:	Phase 3, multicenter, double-masked, RCT
Population:	423 participants, aged 50 years and older with previously untreated active choroidal neovascularization due to AMD
Study Arms:	Randomized 1:1:1 to receive monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) plus sham photodynamic therapy (PDT) or monthly sham injections plus active PDT
Outcome:	• The proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months • The proportion of patients gaining more than 15 letters from baseline visual acuity at 12 months
Follow-up:	2 years

ANCHOR Study Group et al 2006 N Engl J Med;355:1432-44

ANCHOR Trial Results

Ranibizumab superior to PDT with low rates of adverse events

	Visual loss of 15 letters or fewer	Visual gain of 15 letters or more	Average letter number improvement	P value
Ranibizumab 0.3 mg	94.3%	35.7%	+8.5 letters	P<0.001
Ranibizumab 0.5 mg	96.4%	40.3%	+11.3 letters	P<0.001
PDT	64.3%	5.6%	-9.5 letters	P<0.001

ANCHOR Study Group et al 2006 N Engl J Med;355:1432-44

Bevacizumab

- Similar in structure to ranibizumab
  - Increased binding to VEGF
- Off-label use in the US
- Less expensive than ranibizumab
  - $910 vs. $2340

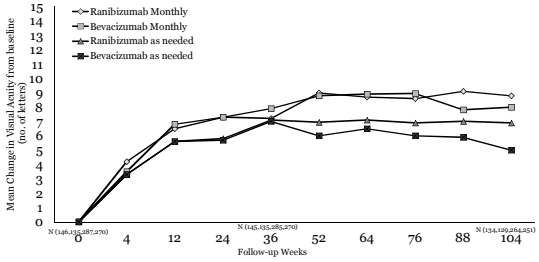
Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008

CATT Trial

Trial Design:	Multicenter, double-masked RCT
Population:	1185 participants, aged 50 years and older, with previously untreated neovascularization due to AMD
Study Arms:	1. Bevacizumab 1.25 mg every 4 weeks 2. Ranibizumab 0.5 mg every 4 weeks 3. Bevacizumab 1.25 mg as needed 4. Ranibizumab 0.5 mg as needed After one year, patients initially assigned to monthly treatment were randomly reassigned to monthly or as needed treatment, without changing the drug assignment
Outcome:	Mean change in visual acuity between baseline and 1 year
Follow-up:	2 years

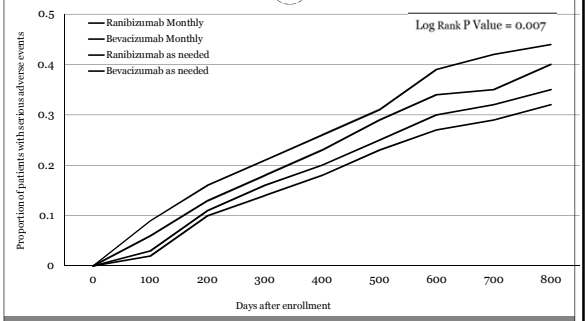
Martin et al 2011 Ophthalmology;119(7):1388-98.

CATT Trial Results



Martin et al 2012 Ophthalmology;119(7):1388-98.

CATT Trial Results: Adverse Events



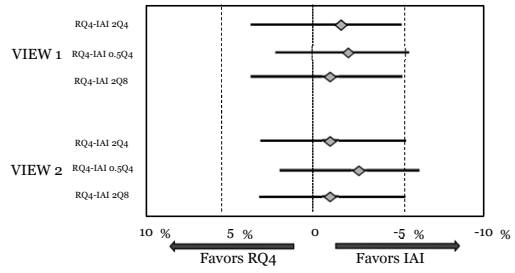
Martin et al 2012 Ophthalmology;119(7):1388-98.

Aflibercept

VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD: VIEW 1 and 2 Trials	
Trial Design:	Phase 3, multicenter, double-masked, parallel-group RCT
Population:	2419 participants
Study Arms:	1. Aflibercept 0.5 mg monthly 2. Aflibercept 2 mg monthly 3. Aflibercept 2 mg every 2 months after 3 initial monthly doses 4. Ranibizumab 0.5 mg monthly
Outcome:	Noninferiority of aflibercept to ranibizumab in the proportion of patients that maintained vision at week 52 (assessed as loss of <15 letters)
Follow-up:	1 year

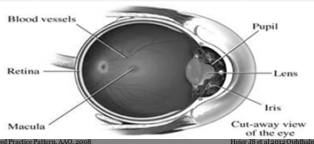
Heier JS et al 2012 Ophthalmology;119(12):2537-48

Aflibercept VIEW Trial



Therapy Complications with VEGF Inhibitors

	Pegaptanib	Ranibizumab	Bevacizumab	Aflibercept
Endophthalmitis	1.3%	<1% over 2 years	0.16%	<1.0% over 1 year
Retinal detachment	0.7%	<0.1%	0.16%	--
Vitreous hemorrhage	--	--	0.02-0.16%	--
Uveitis	--	--	0.09%	--
Traumatic lens injury	0.6%	--	--	--
Anaphylaxis/anaphylactoid reactions	Rare	--	--	--



Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
Martin et al 2011 Ophthalmology;118(7):1388-98
Chakravarthy U et al 2006 Ophthalmology;113(9):1508.e1-25
Heier JS et al 2012 Ophthalmology;119(12):2537-48
Rosenfeld PJ et al 2006 N Engl J Med; 355(14):1419-31
Gragoudas E et al 2004 N Engl J Med;351(27):2805-16

Photodynamic Therapy (PDT)

- How it works…
  - IV injection of verteporfin, a photosensitizing dye
    - Injected into arm, moves up into eye, and pools in to newly damaged blood vessels
  - Low-power laser is applied through the eye
    - Seals the leaking vessels
- Place in therapy…
  - Role has decreased with increasing use of VEGF inhibitors
  - Used alone or in combination in patients who fail to respond to anti-VEGF therapy alone – AREDS Category 4
- Adverse events…
  - Infusion site extravasation, infusion-related back pain (1-2%), photosensitivity reaction (<3%), severe decrease in central vision, that may be permanent (1-4%)

Blumenkranz M et al 2002 Ophthalmol; 120:1307
Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008

Combination Therapy

- MONT BLANC and DENALI Trials
  - Ranibizumab and PDT vs. ranibizumab alone in new-onset neovascular AMD
  - No significant benefit seen of adding PDT to anti-VEGF inhibitor treatment
- EVEREST Trial
  - Fewer anti-VEGF intravitreal injections needed with combination PDT and anti-VEGF therapy
- Combination therapy recommended in AREDS Category 4 subfoveal AMD only

EVEREST study et al 2012, Retina;32:1453-64
Age-Related Macular Degeneration Preferred Practice Pattern. AAO, 2008
MONT BLANC Study Group et al 2012 Ophthalmology;119:922-1000
DENALI Study Group et al 2012, Ophthalmology;119:1001-10

Refractory AMD Treatment Options

- Combination therapy with PDT
- Switching VEGF inhibitors
  - Aflibercept has a higher binding efficacy and a wider spectrum of action
  - Patients who were unresponsive to bevacizumab, can be responsive to ranibizumab
- Decrease the dosing interval
- Increase the dose

Shin J et al 2013 *Korean J Ophthamol*; 27(6):425-432
Yang S et al 2016 *Drug design, Development and Therapy* 10; 1857-1867
Toser K et al 2013 *Ophthalmology*; 120:2099-2014

Patient Case

- Several years later…
- AD is a 70 y/o female with a PMH of hypertension, hyperlipidemia, hx stroke, and newly diagnosed category 4, neovascular, subfoveal AMD
- She is a former 0.5 PPD smoker (quit 5 years ago)
- Current medications:
  - Atorvastatin 40 mg daily
  - Aspirin 81 mg daily
  - Lisinopril 10 mg daily
  - Multivitamin 1 tablet daily

Patient Case

AD comes into the pharmacy because her ophthalmologist told her to buy an eye supplement. Which of the following is the best recommendation for this patient?

1. AREDS Softgels
2. AREDS2 Softgels
3. Ocuvite Softgels
4. Centrum Silver for Women

Patient Case

Based on clinical trial results, which of the following is the best treatment option for this patient?

1. Bevacizumab 1.25 mg every 4 weeks
2. Pagaptanib 0.3 mg every 4 weeks
3. Ranibizumab 0.5 mg every 2 weeks
4. PDT therapy with IV injection of verteporfin

Patient Case

After 6 months of monthly intravitreal injections of bevacizumab, AD's ophthalmologist determines that there is progression of neovascularization. What is the best treatment option for subsequent therapy in this patient?

1. Stop VEGF inhibitor therapy
2. Add on PDT
3. Switch to aflibercept
4. Increase the dosing interval of bevacizumab intravitreal injections
5. Increase the dose of bevacizumab

Pharmacist's Role in AMD

- Assist patients who are at risk for AMD
  - Identify risk factors
  - Prevention education
- Assess patients diagnosed with AMD
  - Suggest supplements for treatment that slow the disease progression
  - Ensure that the patient is taking appropriate ocular supplements
    - Consideration of patient-specific factors to identify patients who should be treated with AREDS vs AREDS2 formula
  - Confirm correct dosing schedule of VEGF inhibitors
- Explain benefits of smoking cessation in AMD

Panesar, K. Age-Related Macular Degeneration. US Pharm. 2015;40(6):22-26

Treatment Summary and Recommendations

AREDS Category	Treatment	Follow-up
1- No AMD	• Observation with no medical therapy	• 6-24 months if asymptomatic • Prompt follow up if new symptoms
2- Early AMD (Dry)	Lifestyle modifications • Smoking Cessation • Dietary Changes • Blood pressure control • Weight management	• 6-24 months if asymptomatic • Prompt follow up if new symptoms
3- Intermediate AMD (Dry)	• Lifestyle and Dietary Modifications • Antioxidant vitamin and mineral supplements as recommended from the AREDS and AREDS2 reports (Level of evidence: I++; Good; Strong)	• 6-18 months if asymptomatic or prompt exam if new symptoms

Age-Related Macular Degeneration Preferred Practice Pattern. AAO. 2008

Treatment Summary and Recommendations

AREDS Category	Treatment	Follow-up
4- Advanced Non-Neovascular AMD (Dry)	• Lifestyle Modifications • Antioxidant vitamin and mineral supplements as recommended from the AREDS and AREDS2 reports (Level of evidence: I++; Good; Strong)	• 6-24 months if asymptomatic • Prompt follow up if new symptoms

4- Advanced Neovascular AMD (Wet)	• 1st line: Anti-VEGF Therapy
	  • Bevacizumab 1.25 mg
	  • Aflibercept 2.0 mg
	  • Ranibizumab 0.5 mg
	(Level of evidence: I++;Good; Strong)
	• Lifestyle Modifications
	• Antioxidant vitamins
	• PDT with verteporfin
	• Thermal laser photocoagulation
		• Anti-VEGF therapy: 4 weeks after initial injection (III; Good; Strong), then as determined by ophthalmologist clinical judgment (I++; Moderate; Discretionary)
		• PDT: every 3 months until stable, then as determined by ophthalmologist clinical judgement
		• Laser Photocoagulation: 2-4 weeks post treatment, then 4-6 weeks thereafter

Age-Related Macular Degeneration Preferred Practice Pattern. AAO. 2008

Trial Summaries

Drug	Visual Loss (%) of 15 letters or less	Visual Gain (%) of 15 letters or more	Cost/injection
Pegaptanib/Macugen *VISION Trial*	70	33	$870.00
Ranibizumab/Lucentis *MARINA Trial*	94.5 (0.3 mg) 94.6 (0.5 mg)	24.8 (0.3 mg) 33.8 (0.5 mg)	$2,340.00
Bevacizumab/Avastin *CATT Trial*	94 (monthly) 91 (PRN)	31 (monthly) 28 (PRN)	$910.25
Aflibercept/Eylea *VIEW Trial*	96 (0.5 mg, monthly) 95 (2.0 mg, monthly) 96 (2.0 mg monthly, then every 8 weeks)	34 (0.5 mg, monthly) 31 (2.0 mg, monthly) 25 (2.0 mg monthly, then every 8 weeks)	$2,220.00

Take Home Points

- Important risk factors include smoking, increasing age, ethnicity, gender, and genetics
- Drusen are a clinical hallmark of AMD
- AREDS supplementation is recommended for AMD AREDS categories 3 and 4
- VEGF inhibitors are first line therapy in neovascular AMD
- Pharmacists can play an important role in AMD prevention and education

Seeing Clearly: A Therapeutic Review of Age-Related Macular Degeneration

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