

Summary of Research & Developments, June 2012 - May 2013

Presented to the International Low Vision Support Group

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INTRODUCTION

This is a summary of reports about significant research and development in the field of macular degeneration and related diseases presented since June 2012 and May 2013. I will briefly describe the conclusions of 77 studies that have been presented in the areas of therapy, prevention, technology, nutrition and daily living. Reports on the new retinal prosthesis and prevalence of AMD will also be summarized.

For those who wish more detail, references to the original resources are provided. Those sources labeled "ARVO Presentation" refer to reports and posters presented at the May 2013 meeting of the Association for Research in Vision and Ophthalmology and posted on the Web at <http://www.arvo.org/webs/am2013/abstract/section/retina.pdf>

SURGICAL THERAPY FOR DRY AMD

After targeting the macula with a nano-second pulse laser called 2RT, results suggested a potentially clinically significant reduction in the odds of progression to advanced AMD at 12 months and at 24 months. Researchers concluded that the 2RT laser has the potential to slow the progression of early AMD. A large randomised controlled trial is currently underway.

Source: ARVO Presentation 4146: Novel Laser treatment for Early Age-related Macular Degeneration (Kate Brassington1, et al)

PHARMACEUTICAL THERAPY FOR DRY AMD

In 2008, Acucela Inc. announced that it had begun a Phase I trial for its lead compound ACU-4429, an oral drug developed for the treatment of dry age-related macular degeneration (AMD). It modulates the visual cycle by significantly reducing the accumulation of a by-product of the visual cycle called A2E, which is believed to damage retinal cells.

Phase 1 safety trials were successful, and the results of Acucela's Phase 2a trial were announced at the ARVO meeting in May 2013. This study demonstrated that ACU-4429 does have the ability to modulate the visual cycle with minimal adverse events. The compound continues to show promise as a treatment for geographic atrophy from dry AMD, and a long-term Phase 2b study is now underway.

Source: A Phase 2 Double-masked, Placebo-controlled, Dose Ranging Study of Emixustat Hydrochloride (ACU-4429) in Subjects with GA Associated with Dry AMD (Pravin U. Dugel1, et al)

A flavonoid called quercetin has been found to protect against oxidative cellular injury and inhibit progression of AMD to the advanced wet form. It may, therefore, be of therapeutic value as an AMD treatment.

Source: ARVO Presentation 4123: Quercetin Protects Hydrogen Peroxide Damaged Human Retinal Pigment Epithelial (hRPE) Cells and Inhibits Vascular Endothelial Growth Factor (VEGF) Production (Andrew Kumar1, et al)

An antibiotic called minocycline has been seen in cell culture to also protect retinal cells from oxidative damage. This finding suggests that minocycline, too, may play a therapeutic role in the treatment of AMD.

Source: ARVO Presentation 4108: Minocycline protects retinal pigment epithelial cells from hypoxia (Joanna DaCosta)

A protein called Interleukin-17A (IL17A) is a driving force in chronic inflammation and its overexpression has been linked to AMD. One study found that an injection into the eye of a receptor named sIL17R could neutralize that damaging protein. Based upon results of the study, the researchers believe this should be considered as another potential treatment for AMD.

Source: ARVO Presentation 1713: Interleukin-17 neutralization ameliorates retinal degeneration in Cx3cr1-/-/Ccl2-/-/Crb1rd8 mice (Daniel Ardeljan1, et al)

We know that lipid (fatty) deposits in the retina are important factors in development of AMD. Scientists have discovered that a peptide called D-4F, primarily developed to treat atherosclerosis, also reduces lipids in the retina after injection into the eye (Rudolf et al., IOVS 2010, 51: Abstract 2984). Now, this past year, we have learned that D-4F taken orally may be almost as effective as injections, and definitely safer and more pleasant.

Source: ARVO Presentation 1714: Oral administration of Apolipoprotein A-I mimetic peptide D-4F reduces lipid accumulation in murine Bruch's membrane (BrM) (Martin Rudolf, et al)

The low vision community has shown an interest in the use of acupuncture as a means of slowing the progression of retinal diseases. No large scale clinical trials have been accomplished to measure safety and efficacy of acupuncture for this purpose, but a small study this past year did show interesting results.

Researchers applied electroacupuncture to the forehead and below the eyes, and acupuncture to the bodies of twelve retinitis pigmentosa (RP) patients over a period of two weeks. They found significant and lasting improvement in acuity, contrast, dark adaptation, and visual field, concluding that electro- and standard acupuncture entails minimal risk and may have measurable benefits for patients with RP. Further research may find that it might also be useful as a treatment for similar retinal diseases like macular degeneration. For now, it is still an alternative treatment which should be considered carefully by patients and their physicians.

Source: ARVO Presentation 4017: Visual Function Improvements following Electroacupuncture for Retinitis Pigmentosa (Ava K. Bittner1, et al)

A drug called antifactor D has been in trials since 2011, and results are expected in September of this year. It is injected into the eye to block an enzyme called complement factor D. Factor D is thought to be associated with dry AMD by genetic association.

Source: Genentech, Inc.

ANTI-VEGF THERAPY FOR WET (NEOVASCULAR) AMD

As usual, we have seen a great deal of effort to find more effective therapies for the wet form of macular degeneration in all of its forms, to include age-related MD, myopic degeneration, and diabetic retinopathy. Here, in no particular order, is a quick run down of most of the studies this past year.

Activation of the Stat3 gene is associated with new blood vessel growth (called neovascularization) and inflammation in the retina. An eye drop of an inhibitor of Stat3, called CLT-005, given to rabbit and rodent animal models, has been shown to reduce neovascularization and also prevent dramatic loss of contrast sensitivity in animals with dry AMD. Future studies may support topical CLT-005 as a stand alone therapy or in conjunction with other treatments.

Source: ARVO Presentation 1716: Eyedrop application of CLT-005, a Stat3 inhibitor, is efficacious in animal models of Wet and Dry Age-related Macular Degeneration (Rafal Farjo1, et al)

A follow up study of Lucentis has shown that the vascular endothelial growth factor, or VEGF, that causes neovascularization was suppressed for 2 months after the initial Lucentis injection in some eyes with AMD. This means that some patients may be able to go as long as two month between injections, rather than the one month originally recommended. (1)

Another study confirmed these results by evaluating the efficacy of bimonthly Lucentis injections. After six months, these researcher also concluded that bimonthly injection may be effective and could be an option. (2)

Sources:

1. ARVO Presentation 3169: Aqueous Vascular Endothelial Growth Factor and Ranibizumab Concentrations after Monthly and Bimonthly Intravitreal Injections of Ranibizumab for Age-Related Macular Degeneration (Xiying Wang¹, et al)
2. ARVO Presentation 3804: The efficacy of bimonthly injection of ranibizumab for age-related macular degeneration for six months (Tomoko Sawada, et al)

One pertinent study was designed to assess the efficacy of retreating proactively or reactively with the anti-VEGF drugs Lucentis or Eylea. In other words, is it better to continue injections on a regular schedule or wait until neovascularization occurs? In the study, a subset of patients lost vision after switching from proactive to reactive treatment with either drug. Since vision lost from nevascularization does not usually return, proactive treatment appeared to result in better visual outcomes than reactive.

Source: ARVO Presentation 3171: Subanalysis of Visual Acuity Outcomes in the Second Year of VIEW Studies (Michaela Goldstein, et al)

We reported here in 2010 that the Oraya IRay radiation therapy system entered trials to demonstrate the safety and effectiveness of radiation therapy for the treatment of wet AMD. The system delivers a robotically controlled dose of low-energy X-ray radiation to the retina. closing leaking vessels and further stopping inflammation. In this study, the procedure was used in conjunction with anti-VEGF injections. Results showed that patients undergoing radiotherapy may experience about a 50% reduction in the need for anti-VEGF injections, and that their visual acuity may also benefit. Eyes with active leaking and without significant scarring (25-50% of the study population) achieved the greatest benefits from the treatment.

Source: www.orayainc.com/clinicaltrials.asp

Phase I trials were completed this past year evaluating another kind of radiation therapy for wet AMD using a novel episcleral brachytherapy device called SMD-1. This easily delivered brachytherapy approach was shown to be safe and tolerable, and it may prove to be an effective therapy alongside anti-VEGF drug injections. Larger phase I/II trials are planned.

Source: ARVO Presentation 3787: Novel Minimally-Invasive Episcleral Brachytherapy for the Treatment of Neovascular Age-Related Macular Degeneration (nAMD): Results of a Twelve Month Prospective Phase I Safety and Tolerability Evaluation (Kamaljit S. Balaggan, et al)

A report in late 2012 suggests that the current practice of injecting anti-VEGF drugs as a treatment for wet AMD may cause vision loss in the long run.

The researchers have shown that vascular endothelial growth factor (VEGF) is important to the health of the cone photoreceptor cells in the macula, and that removing the protein in mice retinas has led to atrophy of those cells.

Anti-VEGF drugs are effective in stopping neovascularization. We have now learned, however, that the drugs might actually be starving healthy cone cells by cutting off their nutrition supply. The researchers stress that this has not been an issue in humans during the seven years the drugs have been on the market, but that long-term safety studies have not yet been completed. In view of their findings, they recommend consideration of methods other than general blocking of VEGF. This is a long term adverse effect that merits further investigation.

Source: Journal of Clinical Investigation., November 2012 (Martin Friedlander, MD PhD, et al. The Scripps Research Institute, La Jolla, California)

The past several years have seen a confusing mixture of study results about the safety of aspirin use by people with AMD. The most recent input comes from Emily Chew, M.D. of the National Eye Institute. She reported in 2012 that, in spite of recent reports, evidence from observational studies and randomized, controlled clinical trials suggest there is no major harmful effect of aspirin use by AMD patients. She said that results from recent studies have shown no increased hemorrhage risk and no harmful association of aspirin with progression of AMD. Furthermore, she supports that aspirin may actually offer significant protection from the development of the disease.

A recent study supported Dr. Chew's position by finding that aspirin may help to block unwanted blood vessel growth, and that it may not worsen neovascularization in people with wet AMD. (1)

10. Another new study, however, has concluded that long-term aspirin use may be found to actually enhance new blood vessel growth by increasing vascular density. (2) Past concern about aspirin has focused on the blood thinning issue, but this recent finding suggests that there may yet be more to consider.

Still, most physicians are recommending that, in light of aspirin's benefit to the cardiovascular system, the best course of action for AMD patients is to consult with their physicians and take aspirin when it is clinically indicated.

Sources:

1. ARVO Presentation 1715: Effect of Aspirin on human ARPE-19 cells and in Mouse Model of Choroidal Neovascularization (Sunali Goyal, et al)

2. Long-term Use of Aspirin and Age-Related Macular Degeneration. Barbara E. K. Klein, MD, *et al.* (JAMA. 2012;308(23):2469-2478. doi:10.1001/jama.2012.65406)

In the ongoing debate about which is the better drug for treating wet AMD, Lucentis or off-label Avastin, The National Institutes of Health has reported that, at the end of a 2-year comparison study, both drugs improve vision when administered monthly or on an as needed basis. Patients receiving Lucentis, however, fully maintained first-year vision gains with an average 5.7 injections in the second year. In contrast, patients treated with Avastin experienced a greater decline in vision despite receiving significantly more

injections over the two year period. In addition, secondary anatomical outcomes were significantly better with Lucentis.

Source: NIH News online at www.nih.gov/news/health/apr2012/nei-30a.htm

Scientists at Queen's University in Kingston Ontario have found that patients who have gotten eye injections with Avastin have been 12 times more likely to develop pain and serious inflammation in the eye than those who have received Lucentis. Their study, After studying medical records of more than 1500 patients, they concluded that significant concern still exists regarding the safety of [Avastin], and that "patients receiving [Avastin] should be counselled regarding a possible increased risk for serious adverse events."

Source: Rate of serious adverse effects in a series of bevacizumab and ranibizumab injections. Sanjay Sharma, MD, MSc, et al. Canadian Journal of Ophthalmology, June 2012)

A recall notice pertaining to off-label Avastin for wet AMD was posted on March 20, 2013 by the FDA. It applied to people being treated in Georgia, Louisiana, South Carolina, and Indiana. It resulted from contamination at a compounding pharmacy that serves clinics in those areas, where five cases of eye infection were reported. This follows previous contamination issues with Avastin in 2011 that led to stricter controls over the use of compounding pharmacies. It seems that contamination of the drug at the pharmacy level is still a problem calling for closer monitoring.

Source: www.fda.gov/Safety/MedWatch/SafetyInformation/.../ucm344664.htm

In August 2012, the FDA recommended Lucentis for treatment of diabetic macular edema (DME). DME is an eye condition in people with diabetes characterized by retinal swelling and blurred vision. It is a major cause of vision loss and blindness estimated to affect more than 560,000 people in the United States. The current standard of care for DME in the U.S. is laser surgery, which primarily serves to slow the progression of vision loss and help stabilize vision. Lucentis was first approved by the FDA for treatment of wet age-related macular degeneration in 2006 and for macular edema following retinal vein occlusion in 2010.

Source: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm315130.htm

We know that our bodies can sometimes become resistant to long term use of certain drugs. We also know that not all systems react positively to the same drugs. For these reasons, doctors may consider switching from one product to another, and it is useful for them to share reports about how patients will respond.

In one study this past few months, Eylea, the newest drug treatment for wet MD, was been found to be effective in 20 patients who were unresponsive to Lucentis and Avastin.

Source: "The Effect of Eylea (Aflibercept) in Exudative AMD Patients Recalcitrant to Ranibizumab and Bevacizumab". Vincent S Hau MD, et al. (Published online at <http://meeting2012.asrs.org/Annual-Meeting/Details/1080@Session=15&dayId=3%23dayContent3>)

Another study compared increases in intraocular pressure (IOP) from injections of ucentis and Eylea, and found that Eylea patients had a lower incidence of increased IOP than Lucentis patients.

Source: IOP in Patients With Neovascular AMD Receiving Intravitreal Aflibercept or Ranibizumab Injection. K Bailey Freund, et al. (Published online at www.abstractsonline.com/Plan/ViewAbstract.aspx?mID=2866&sKey=aa3d0ab1-c373-4ac8-9953-1825cc2a538b&cKey=bf3fcd14-a17c-4206-b585-f7f967bbaf59&mKey=%7BF0FCE029-9BF8-4E7C-B48E-9FF7711D4A0E%7D)

Further research assessed the effect of switching from Avastin and/or Lucentis to Eylea in AMD patients. One group found that, on average, 41% had improved visual acuity, and 57% had a decrease in swelling of the retina. (1)

Another group found that, in the first twelve months after switching from Lucentis to Eylea, a patient on Eylea would likely experience more injections than on Lucentis, but there should be a large reduction in monitoring visits. (2)

A third group found that Eylea injections are a prudent alternative to Lucentis and Avastin where a patient has become unresponsive. This retrospective case study suggested that beginning Eylea rescue therapy can resolve blood vessel growth in 25% of eyes previously nonresponsive to the other drugs. The data also showed that 70% of eyes undergoing rescue therapy had maintained or gained acuity following the three rescue injections. Neovascularization, however, is unlikely to stop if it does not do so during the initial three rescue injections. (3)

Sources:

1. ARVO Presentation 3827: The effects of aflibercept following bevacizumab or ranibizumab on visual acuity and central macular thickness in patients with age-related macular degeneration (Ambar Faridi, et al)
2. ARVO Presentation 3813: Impact of using the aflibercept dosing regimen for wet macular degeneration on numbers of injections and monitoring visits over three years (Niro Narendran, et al)
3. ARVO Presentation 3806: Eylea Rescue Therapy in Eyes with Proven Non-Response to Other anti-VEGF Molecules (Benjamin Guidry, et al)

Some researchers are finding that antibiotics may not be necessary after drug injections into the eyeball. One retinal surgeon reported that, after administering 15,029 injections using an antiseptic, but no topical antibiotic, only one case of infection occurred. The antiseptic Betadine was used in conjunction with all of the treatments.

Source: Eliminating Antibiotic Prophylaxis for Intravitreal Injections: A Consecutive Series of 15,029 Injections by a Single Surgeon. Abdhish R Bhavsar MD (Published online at

<http://www.abstractsonline.com/Plan/ViewAbstract.aspx?mID=2866&sKey=ce12315b-3ddb->

A vitrectomy is a surgical operation that involves removal and replacement of the vitreous gel from the inside of the eyeball. Patients with wet AMD who have undergone vitrectomies have been noted to have a reduced response to anti-VEGF injections. Researchers looked into this and found that such patients do benefit from the treatments, but that the drugs seem to have a shorter half-life in the eye. The researchers concluded that these eyes may require more frequent injections, or more powerful drugs may be needed.

Source: ARVO Presentation 4135: Approach to Previously Vitrectomized Patients with Neovascular Age-Related Macular Degeneration with Reduced Response to Anti-vascular Endothelial Growth Factor Treatment (Mohammad Zubair Y. Arain, et al)

The media has recently reported a new finding about cholesterol and AMD. We have know for years that cholesterol buildup in the retina can lead to inflammation (i.e. wet AMD), and researchers have been working to find ways to treat it. Statin drugs have been considered, but with little success, and now we hear that restoring the function of our macrophage cells may someday be the way to go.

Macrophages are key immune cells that remove cholesterol and fats from tissues. As they begin to malfunction from age, however, excessive cholesterol builds up. These lipid deposits gradually become more numerous in the retina, destroying the macula and leading to loss of central vision.

Researchers speculate that drugs now being used to prevent atherosclerosis might be effective also in preventing wet macular degeneration. They have identified a protein that macrophages use to do their work, and they discovered how they might be able to improve the level of that protein in the aging macrophages. From this they think the drug might also prevent new blood vessel growth and leakage in AMD patients, since inflammation is a direct result of cholesterol buildup.

This is promising research, but macrophage restoration as a treatment for wet AMD is still a few years away.

Source: Apte RS et al. Impaired cholesterol efflux in senescent macrophages promotes age-related macular degeneration. Cell Metabolism, vol. 17(4), published online April 2, 2013

ANTI-VEGF THERAPY FOR MYOPIC MD

Myopic macular degeneration is the leading cause of vision impairment from neovascularization in people under 50 years old. Also called pathologic myopia, studies are being conducted to find treatments for the condition other than coagulation of the leaking vessels with a cool laser. This procedure, called photodynamic therapy (PDT), was a standard treatment for wet AMD before the advent of anti-VEGF drug injections in 2006. At least two studies compared PDT with Lucentis during the past year, both finding that visual function was significantly improved in the subjects receiving Lucentis.

Sources:

ARVO Presentation 1247: Twelve-month efficacy and safety of ranibizumab 0.5 mg(RBZ) versus verteporfin photodynamic therapy(vPDT) in the treatment of visual impairment(VI) due to choroidal neovascularization(CNV) secondary to pathologic myopia(PM) (Francesco Bandello. Ophthalmology, Univ Vita Salute-Scient Inst San Raffaele, Milan, Italy)

ARVO Presentation 1245: Impact of Ranibizumab on Patient-Reported Visual Functioning in Myopic Choroidal Neovascularization: 3- and 6-Month Results Kyoko Ohno-Matsui, et al)

ANTI-VEGF THERAPY RISK FACTORS

Anti-VEGF drug injections are now the standard treatment for wet macular degeneration. The leading drugs are Lucentis, Eylea, and off-label Avastin. There is no doubt about their benefit to thousands of AMD patients, but some risks are also being noticed in follow up studies.

One concern has been the effect of blood thinning medication on of such drugs. That concern, however, has been alleviated in at least one study concluding that there was no significant increase in retinal hemorrhaging between patients with wet AMD taking blood thinners and those who were not

Source: ARVO Presentation 6309: Association of Systemic Anticoagulation and Rate of Intraocular Hemorrhage Following Intravitreal Anti-VEGF Therapy for Age-related Macular Degeneration (Joanna Olson, et al)

Another concern is that the blood vessel layer of the retina (the choroid) may grow thinner after multiple injections of anti-VEGF drugs. This is a sign of retinal atrophy, which can result in vision loss.

One study found a decrease in the thickness of the choroid after as few as 3 injections. The subjects already had thinner choroids with an average of 12 prior injections. Over the following 8 months, however, there was no statistically significant change with further treatments.(1)

A second study found reduction over time of thickness of the macula, as well. (2) These are only two of several reports on this issue, and not all of them agree, so further study is needed.

Sources:

1. ARVO Presentation: Choroidal Thickness following Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration (Charlotte So, Zac Ravage)

2. ARVO Presentation 6265: Retinal and choroidal thickness changes over time in patients with neovascular age-related macular degeneration treated with anti-VEGF (Thais S. Mendes, et al)

A disturbing risk factor has arisen since anti-VEGF treatment began. It appears that some patients with wet MD are developing vision loss after successful regression of the

blood vessels. The changes in the retina resemble the atrophy seen in advanced dry macular degeneration (geographic atrophy). (1) (2) Researchers have reported that sight cells appear to be injured in up to 20% of patients after prolonged anti-VEGF injections. (3) They recommend that larger studies be undertaken to determine if this could be a result of the drugs or if it is just part of the natural course of the disease.

Sources:

1. ARVO Presentation 6284: Cellular Features of Retinal Pigment Epithelial Atrophy after Regression of Choroidal Neovascularization (Mina M. Chung)
2. ARVO Presentation 6295: The Role of Anti-VEGF Therapy in the Development and Progression of Geographic Atrophy in Patients with Wet Age-Related Macular Degeneration (Justin Shaw, et al)
3. ARVO Presentation 3658: Geographic atrophy risk factors in participants of the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) (Juan E. Grunwald, et al)

According to two reports during the period, scarring of the retina is another concern associated with anti-VEGF treatment, no matter which drug or dosage schedule is used. The risk factors for scarring, which can permanently impair vision, may lead to development of treatments that decrease scarring caused by the damaging vessels.

Sources:

1. ARVO Presentation 3661: Risk Factors for Scarring in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) (Ebenezer Daniel, et al)
2. ARVO Presentation 3659: Sustained Severe Visual Acuity Loss in the Comparison of AMD Treatments Trials (CATT) (Gui-Shuang Ying, et al)

COMBINATION DRUG THERAPY

Three drugs have been recently studied that hold promise as combination therapies for treatment of wet MD.

A new drug called Fovista completed phase 2 clinical trials this past year. Used in combination with an anti-VEGF drug, it blocks pericyte cells that hinder the effectiveness of the drugs. The makers of Fovista reported a 62% higher relative visual benefit when it was used in combination with Lucentis.

Source: www.businesswire.com/news/home/20120613005333/en/Ophthotech's-Anti-PDGF-Combination-Agent-FovistaTM-Demonstrated-Superior

Another combination therapy is anti-VEGF injection along with photodynamic therapy (PDT), a low voltage laser applied to an injected drug (verteporfin) that coagulates existing blood vessels. Some patients were found to require no further treatment after this combination treatment, which inspired researchers to test it further. Five reports were found concluding that combining anti-VEGF injections with PDT treatment did result

in longer-term closure and control of neovascularization. If proven successful in further research, this procedure could reduce the number of injections required for treatment of wet AMD. (1) (2) (3) (4) Similar good results were reported after this combination was applied to patients affected by a kind of sub-group of wet AMD called polypoidal choroidal vasculopathy (PCV) (5)

Sources:

1. ARVO Presentation 4509: Long-Term and Lasting Outcomes of Combination Treatment for Age-Related Macular Degeneration with Photodynamic Therapy and Intravitreal Injection of Anti-Vascular Endothelial Growth Factor (Colleen M. McLellan, et al)
2. ARVO Presentation 3790: AURORE STUDY: a french multicenter retrospective study in wet AMD patients treated with Verteporfin PDT plus Ranibizumab in routine clinical practice (Franck Rumen1, et al)
3. ARVO Presentation 3791: INTRAVITREAL ANTI-VEGF FOLLOWED BY PHOTODYNAMIC THERAPY VERSUS ANTI-VEGF MONOTHERAPY FOR RETINAL ANGIOMATOUS PROLIFERATION (Pietro Monaco1, et al)
4. ARVO Presentation 3792: Long-term Results of Combination Therapy with Half-time Reduced Fluence Photodynamic Therapy and Intravitreal Ranibizumab for Retinal Angiomatous Proliferation (Hirotaka Yokouchi, et al)
5. ARVO Presentation 3789: Photodynamic therapy, anti-vascular endothelial growth factor therapy, and combination therapy for polypoidal choroidal vasculopathy (Hae Min Kang, et al)

Finally, treatment with a non-steroidal anti-inflammatory eye drop called Ketorolac has also been found to increase the effectiveness of Lucentis in treatment of wet AMD.

Source: ARVO Presentation 4175: Prospective randomized controlled trial of combination ranibizumab and ketorolac for wet age-related macular degeneration (Andrea Russo, et al)

ANTI-VEGF DRUG RESISTANCE (tachyphylaxis)

Since the advent of anti-VEGF drug treatment in 2006, thousands of people have been able to retain their eyesight. One recent study showed that with strict monthly follow-up and prompt retreatment with Lucentis as needed, good vision can be achieved and maintained for a period as long as four years, with the need for retreatment seeming to decrease significantly after the first 12 months. (1)

2. This kind of response has been a lifesaver for many, but doctors are finding that more than 10% of patients do not respond completely to the treatment. Resistance to the drugs is suspected to account for many of these. In other words, some people may be developing an immunity to the very drug that is intended to help them. Researchers, for example, evaluated the characteristics of eyes with visual acuity loss at a two-year follow-up in patients with wet AMD who were initially treated with Lucentis. The number of patients losing visual acuity increased, especially after 12 months. (2)

3. Realizing that drug resistance might become a serious roadblock to effective treatment for wet MD, researchers are trying to develop ways to identify at-risk patients and to devise alternative methods for helping them. (3)

Sources:

1. ARVO Presentation 3826: Four year results of visual outcome in Neovascular Age Related Macular Degeneration (AMD) treated with Ranibizumab (Anchal Kailey, et al)
2. ARVO Presentation 3795: Visual acuity loss at a two-year follow-up in patients with exudative age-related macular degeneration treated with ranibizumab and as needed retreatment basis (Takeya Kohno, et al)
3. ARVO Presentation 3170: Detection of anti-ranibizumab antibodies among exudative AMD patients (Nicolas Leveziel, et al)

Regeneron, the company that developed the newest anti-VEGF drug, Eylea, has received the most attention as a potential solution. Five studies found that patients who have developed resistance over time to Lucentis and off-label Avastin, are responding well when switched to Eylea. Those studies are listed here:

ARVO Presentation 6270: Aflibercept (Eylea) Effect on Macula Thickness and Visual Acuity in Exudative AMD Patients Recalcitrant to Ranibizumab and Bevacizumab (Vincent Hau, et al)

ARVO Presentation 4176: Aflibercept Rescue of Bevacizumab- or Ranibizumab-Resistant Choroidal Neovascularization in Age-Related Macular Degeneration (Cheryl A. Arcinue, et al)

ARVO Presentation 3833: Short-term Effectiveness of Intravitreal Aflibercept for Persistent Exudative Age-Related Macular Degeneration (Andrew A. Chang¹, et al)

ARVO Presentation 3834: Visual And Anatomical Outcomes Following Intravitreal Aflibercept In Eyes With Recalcitrant Neovascular Age Related Macular Degeneration (Dilraj S. Grewal, et al)

ARVO Presentation 3828: Comparison of the Relative Efficacy of Aflibercept in the Treatment of Neovascular Age Related Macular Degeneration in Patients Previously Treated with Alternative Vascular Endothelial Growth Factor Inhibitors (Khushboo K. Agrawal, et al)

On the other hand, a large comprehensive study found that development of antibodies in patients undergoing Lucentis treatment for up to two years had no significant impact on their response to the drug.

Source: ARVO Presentation 3793: Analysis of 24 month data from the HARBOR study indicates that anti-therapeutic antibodies status had no significant impact on the treatment response to ranibizumab (Gary Sternberg, et al)

And another study concluded that there was no visual benefit seen by changing to Eylea in patients who were unresponsive to Lucentis and/or off-label Avastin

Source: ARVO Presentation 3801: Comparison of outcomes after switching treatment from intravitreal bevacizumab or ranibizumab to aflibercept in neovascular age-related macular degeneration (Frank X. Venzara¹, et al)

As a side note, a single study found that switching stabilized patients to Eylea may lead to

a temporary loss of visual acuity in some, with most of them recovering and improving after further treatment. This event, the researchers concluded, may or may not be different for those patients who have become resistant to the first drug.

Source: ARVO Presentation 3796: Short-term vision changes after switch to aflibercept therapy for age-related macular degeneration previously treated with other antiVEGF agents (Irene A. Barbazetto, et al)

Another attempt at solving the drug resistance problem has been to switch to *either* of the other anti-VEGF drugs. The results suggested that doing so may provide short-term benefits. (1)

Researchers have even suggested that alternating drugs, specifically Lucentis and Avastin, bi-weekly might be an answer. Their study showed this regimen to show significant improvement in so-called recalcitrant patients. (2)

Sources:

1. ARVO Presentation 3823: Effect of anti-VEGF medication change on central macular thickness and visual acuity in patients with neovascular age-related macular degeneration (John P. Campbell, et al)

2. ARVO Presentation 3811: The Efficacy Of Biweekly Alternating Intravitreal Bevacizumab And Ranibizumab In Recalcitrant Choroidal Neovascularization Secondary To Age-Related Macular Degeneration (Radha Ram, et al)

ENDOPHTHALMITIS

Eye infection (endophthalmitis) from the injection protocol has also been a concern since the advent of anti-VEGF drug treatment. Recent research, however, has found that the incidence has been low, and that post-injection antibiotic drops do not appear to significantly reduce the risk of developing infection. If infection does occur, it can be easily treated with topical steroids, and in most cases, the condition will not result in vision loss. Patients should be cautioned to be vigilant about any evidence of infection for 24 hours after an injection, and to report any such evidence to their physician.

Sources:

ARVO Presentation 1118: Meta-Analysis of Infectious Endophthalmitis After Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents (John Fileta, et al)

ARVO Presentation 1114: Incidence of Endophthalmitis after Anti-VEGF Injections and use of Anti-Microbials in the Comparison of AMD Treatments Trials (CATT) (Colin A. McCannel1, et al)

ARVO Presentation 1113: The role of antibiotic prophylaxis to prevent post-injection endophthalmitis (Philip P. Storey, et al)

ARVO Presentation 1104: The Incidence of Noninfectious Intraocular Inflammation after Intravitreal Aflibercept Injection (Kunjai K. Modi, et al)

STEM CELL THERAPY

One exciting potential therapy for macular degeneration and myopic degeneration is stem cell therapy. This involves transplanting stem cell-derived retinal tissue to replace dysfunctional tissue and maintain photoreceptor function. In trials so far, the procedure has been shown to be safe, and there has even been some success in restoring vision.

In July, Advanced Cell Technology, Inc. (ACT) treated the tenth and final patient in their Phase 1/2 clinical trial at Moorfields Eye Hospital in London. The outpatient transplant surgery was performed successfully without any complications, and the patient was reported to be recovering uneventfully. The company said that improvements in visual acuity initially reported had persisted for a year, and preliminary results indicated that the research is on the right track.

In February of this year, ACT that they had gained approval from the FDA to begin safety trials to evaluate the safety and tolerability of embryonic stem cell replacement in people with severe myopia. This refers specifically to degenerative myopia (aka "myopic macular degeneration"), offering hope for people who have lost vision to this condition.

Sources:

ACT press release: <http://www.advancedcell.com/news-and-media/press-releases/advanced-cell-technology-to-host-conference-call-to-discuss-2013-first-quarter-results-and-provide-a-corporate-update-on-thursday-may-9th/index.asp>

Scientists are continuing to search for sources of stem cells that replicate the power of embryonic cells without confronting the ethical issues that have arisen. Two new sources have shown potential this past year, to include the skin of the patients themselves and human breast tissue.

Sources:

"Stem cell trial to treat eye disease" by Simeon Bennett (San Francisco Chronicle, October 9, 2012)

"New Type of Pluripotent Cell Discovered In Adult Breast Tissue" by Elizabeth Fernandez (published online March 04, 2013 at www.ucsf.edu/news/2013/03/13610/new-type-pluripotent-cell-discovered-adult-breast-tissue)

GENETICS

Researchers from the Miller School of Medicine have collaborated with an international team to locate more genes associated with AMD. So far, they have identified new locations near seven different genes. For a list of previously discovered genes associated with AMD, see Genetics Home Reference on the web site of the National Institutes of Health (NIH). More information about specific gene discoveries may also be found online in the MD Support Library.

Source: "Seven New Loci Associated with Age-Related Macular Degeneration," (published online, in Nature Genetics, March 3, 2013)

Genetics is a fascinating science that can help identify pathologies of inherited diseases like AMD. By identifying the altered genes and replacing them, we could theoretically cure every condition. But it's not as simple as it sounds, and the technology is not yet in place. And that's why the American Academy of Ophthalmology (AAO) recommends that eye physicians and surgeons avoid genetic testing at this time for complex eye disorders until treatment or surveillance strategies can be shown to be of benefit.

Reporting to the AAO members at their annual meeting in 2012, Dr. Edwin Stone said current genetic tests for AMD are flawed and cannot reliably help predict clinical outcomes. Until such time as genetic testing becomes more reliable, he said, "combining a patient's family history of eye disease with a standard eye exam will remain the best way to determine his or her risk for AMD."

Source: Edwin Stone, MD. AAO presentation (Chicago, July 2012)

TECHNOLOGY

Hundreds of low vision devices are now on the market, with the quality of imaging and audio improving at enormous speed. The biggest news this past year, was approval in the United States of a retinal prosthesis that is allowing people with severe vision loss to see again. In September, the FDA Ophthalmic Devices Advisory Panel recommended market approval for Second Sight's Argus II Retinal Prosthesis System.

The system converts video images captured by a miniature camera, housed in the patient's glasses, into a series of small electrical pulses. These pulses are transmitted wirelessly to an array of microchips to stimulate the retina's remaining cells resulting in perceptions of patterns of light in the brain. The resulting image is a simple pixelation of light and dark, but it is providing basic sight to patients who have had no light perception at all.

The Argus II received CE Mark approval in Europe last year, and on February 14 of this year, the FDA unanimously approved it for people who have lost significant vision from retinitis pigmentosa. As the technology advances, the system may someday be useful also for people with degenerative diseases of the macula.

Source: <http://2-sight.eu/en/home-en>

DIET & NUTRITION

Curcumin is found in the popular Indian spice turmeric. Scientists have learned from a study of rodents that curcumin can suppress neovascularization. Curcumin supplementation, therefore, and by extension, tumeric, is now being considered as a potential therapy for wet AMD.

Source: ARVO Presentation 1242: Suppression of experimental choroidal neovascularization by curcumin in mice (Ping Xie, et al)

A study published July 29, 2012 in American Journal of Epidemiology has concluded that drinking more than 20 g of alcohol per day was associated with an approximate 20% increase in the odds of early AMD when compared with those who reported no alcohol intake at baseline. A typical glass of wine contains about 15 g. The positive association, drawn by researchers at the Centre for Eye Research Australia, was apparent for wine,

beer, and spirits.

This is interesting in light of previous research showing red wine to be beneficial to the retina for its antioxidant properties. It is not, however, the alcohol content that provides this benefit, so, as substantiated by these new findings, one glass per day should be the limit.

Source; aje.oxfordjournals.org/content/176/4/289.abstract

DAILY LIVING

Researchers identified why, in addition to central field loss, adults with AMD have trouble recognizing and identifying people's faces. They believe that it could largely be due to abnormal eye movement patterns and fixations associated with the condition.

The study found that AMD patients made more frequent eye movements compared to those with healthy vision. They believe it could have a lot to do with the way the brain coordinates eye movement. And that gives hope that eye movement control training and training of allocation of attention could improve face perception and eye scanning behavior in individuals with AMD.

Source: Optometry and Vision Science (January 2012)

PREVALENCE OF AMD

A new Northwestern Medicine study shows that senior citizens are reporting fewer visual impairment problems than their counterparts from a generation ago. The researchers said that “improved techniques for cataract surgery and a reduction in the prevalence of macular degeneration may be the driving forces behind this change”.

From 1984 until 2010, the decrease in visual impairment in those 65 and older was highly statistically significant, while there was little change in visual impairments in adults under the age of 65. The study showed that in 1984, 23 percent of elderly adults had difficulty reading or seeing newspaper print because of poor eyesight. By 2010, there was an age-adjusted 58 percent decrease in this kind of visual impairment, with only 9.7 percent of elderly reporting the problem.

The researchers also reported a substantial decline in eyesight problems that limited elderly Americans from taking part in daily activities, such as bathing, dressing or getting around inside or outside of the home. They credited three likely reasons for the decline:

- Improved techniques and outcomes for cataract surgery
- Less smoking, resulting in a drop in the prevalence of macular degeneration
- Treatments for diabetic eye diseases are more readily available and improved, despite the fact that the prevalence of diabetes has increased

Future studies should identify which treatment strategies help prevent vision in older adults and then make those treatments available to as many people as possible.

Source: <http://medicalxpress.com/news/2012-06-debilitating-eyesight-problems-decline-older.html#jCp>

CONCLUSION

This concludes my summary for this year. I hope it will leave you with confidence in our future and the future of those who are following us. Please pass this information along to them. And if you don't remember the details of the overwhelming amount of research being done (and who could?), just tell them things are getting better at an ever-quickenning pace, thanks to the unceasing dedication of researchers and developers around the world..

Our hope lies with them and in the doctors who make the therapies and treatments available to us. We thank them for that, and I thank you for listening.