

THE LATEST IN TREATMENTS AND RESEARCH

Script to accompany slides

Presenter: Dan Roberts

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1. Headlines in the News

2. Laser Rejuvenates the Retina

According to a study announced at the Euretina Congress in May 2008, a laser treatment that "cleans up" Bruch's membrane may slow down the progression to AMD.

3. Graphic: Layers of the retina

Bruch's membrane is the tissue that separates the photoreceptor cells (our sight cells) from the nourishing blood vessel layer of the retina. It is through Bruch's membrane that the nourishment passes. As we age, however, the membrane can become clogged with debris, inhibiting the process and leading to cell malnutrition.

Research at St. Thomas's Hospital in London has resulted in development of a therapeutic approach to the problem. The Retinal Rejuvenation Therapy (2RT, Ellex) uses a special green nanosecond pulse laser for "reconditioning" Bruch's membrane and photo-regeneration. Improvement in visual function has been noted in humans during preliminary studies. Now, under the guidance of John Marshall, Ph.D., researchers are setting up a trial to treat the yet-unaffected second eyes of patients who have already lost vision in one eye due to neovascular problems.

The ultimate goal, said Dr. Marshall, is to treat patients in their 40s to keep their eyes young and prevent age-related degenerations of the retina. The treatment is noninvasive and seems to have no adverse effects on the photoreceptors or other parts of the eye.

4. Good Visual Outcome Following Cataract Surgery

A new study (Nature, Aug 2008) has found good visual outcome following cataract surgery in patients aged 90 and older. The study compared visual outcome of patients with macular degeneration, glaucoma and various other ocular conditions.

Overall visual acuity improvement was 68%, whereas unchanged and worsening rates were 16% each. Results showed that AMD patients showed less

improvement than patients with glaucoma or with no visual problems.

The researchers concluded that approximately 70% of very elderly patients can achieve visual acuity improvement following cataract surgery, which rises to 82% in those without accompanying problems. Although patients with AMD show less improvement, 62.5% can still enjoy improvement in visual acuity.

5. Cataract Surgery Appears Safe

More recent studies, however, are disputing that finding, starting with a report in 2005 that patients who had cataract surgery did not have a higher risk of progressing to more advanced forms of macular degeneration when compared to those who did not have cataract surgery.

This was supported by research published in the February 2009 issue of the Journal of Ophthalmology. Led by Emily Chew, MD (also involved in the 2005 study), the team reported that, after reviewing 11 years of patient follow-up data from the large Age-Related Eye Disease Study (AREDS), "The frequency of neovascular age-related macular degeneration, geographic atrophy, and central geographic atrophy did not differ between patients who had cataract surgery and those who did not. . . [This] may provide some reassurance to patients with age-related macular degeneration who are considering cataract surgery."

A large comprehensive cohort study reported by J.J. Wang to the 2009 ARVO meeting also confirmed previous studies in finding no significant increased incidence of AMD in eyes having undergone cataract surgery. Dr. Wang stressed, however, that here may be an increase in combination with other AMD risk factors. For information about cataract surgery and AMD, see www.mdsupport.org/library/catsurg.html

6. New Drug May Reduce Number of Injections for Wet AMD

Regeneron Pharmaceuticals, Inc. and Bayer HealthCare AG Have announced that patients with wet AMD receiving VEGF Trap-Eye in a Phase 2 extension study on an "as needed" dosing schedule continued to show highly significant improvements in retinal thickness and vision gain at 52 weeks. During weeks 12 to 52, patients from all dose groups combined received, on average, only two additional injections. This supports Regeneron's expectation that, with VEGF-Trap-Eye treatment, patients' visual acuity will improve over time without the need for monthly intravitreal injections.

More info: www.mdsupport.org/library/anti-angio.html

7. Zinthionein in Trials for Treatment of Dry AMD

Zinc has been shown to be an effective antioxidant, which is beneficial to the retina. In July 2008, researchers at Pipex Pharmaceuticals announced success with a complex that evidently results in a more potent antioxidant than zinc alone. This "zinc-monocysteine" molecule was developed by combining L-cysteine and zinc in a ratio of 1:1.

Under the commercial name Zinthionein, it was then administered as a 25 mg oral capsule twice a day to 80 test subjects for a period of six months. According to the phase 2 study results (David Newsome, primary investigator), these patients demonstrated a highly statistically significant improvement in visual acuity, contrast sensitivity and photorecovery time. Continued success in the trials could lead to a new and effective therapy for dry AMD.

More info: www.adeonapharma.com

8. New Dry AMD Gene Found

As reported in the Aug. 28 online edition of the New England Journal of Medicine, researchers have found a genetic link associated with dry AMD. That's the good news. The bad news is that siRNA drug therapy may increase the risk for dry AMD in patients who have that genetic variant.

The research team found that the protein TLR3 helps fend off certain viral infections. However, it also increases the risk for dry AMD in subjects taking an experimental anti-VEGF drug called "small interference ribonucleic acid" (siRNA), which activates TLR3. In fending off viral infections, TLR3 also attacks infected retinal cells, resulting in "a 60 percent spike in retinal cell death among mice and humans genetically susceptible to developing dry AMD."

Patients currently involved in the siRNA study (labeled Cand5) sponsored by Acuity Pharmaceuticals should contact their doctors for more information. More information: www.mdsupport.org/library/sirna.html

9. "Low Luminance Deficit" May Predict More Severe Vision Loss

It appears that, of people with advanced dry AMD (geographic atrophy) who have a corrected visual acuity of 20/50 or better, those who test more poorly in dim light may progress sooner to more severe vision loss.

A research team under the direction of MD Support advisor Janet Sunness,

M.D. (Hoover Services for Low Vision and Blindness, Greater Baltimore Medical Center), found that visual dysfunction under low light can predict subsequent visual acuity loss in late-stage AMD patients.

Of subjects with a visual acuity of 20/50 or more, those who had the worst "low luminance deficit" at the beginning of the study showed a significantly greater loss of visual acuity at two years. 40% of this group showed a loss of three or more lines on the acuity test chart. Identification of this risk factor may provide an important means of predicting the rate of vision loss in patients with advanced dry AMD.

10. Brain Reorganizes to Adjust for Loss of Vision

A new study from Georgia Tech shows that when patients with macular degeneration focus on using another part of their retina to compensate for their loss of central vision, their brain seems to compensate by reorganizing its neural connections. The study appears in the December edition of the journal Restorative Neurology and Neuroscience.

Eric Schumacher, assistant professor in Georgia Tech's School of Psychology, said, "Our results show that the patient's behavior may be critical to get the brain to reorganize in response to disease. It's not enough to lose input to a brain region for that region to reorganize; the change in the patient's behavior also matters."

In this case, that change of behavior comes when patients with AMD make up for this loss by focusing with other parts of their visual field.

Schumacher and his research team found that when patients visually stimulated the preferred retinal locations, they increased brain activity in the same parts of the visual cortex that are normally activated when healthy patients focused on objects in their central visual field. They concluded that the brain had reorganized itself.

While there is evidence with other tasks that suggests that the brain can reorganize itself, this is the first study to directly show that this reorganization in patients with retinal disease is related to patient behavior.

The research group is currently studying how long this reorganization takes and whether it can be fostered through low-vision training in eccentric viewing. For the complete article on this topic, see www.mdsupport.org/library/brain.html.

11. The Latest on AREDS

Emily Chew, M.D., reported to the ARVO meeting that genotypes determine the

extent of protection offered by the AREDS formula. In the ARED study, people with genotype TT showed the greatest protective effect, while those with genotype CC showed the greatest risk of progression to advanced geographic atrophy.

Dr. Chew said that patients can probably discontinue the AREDS supplements once the advanced wet stage is reached. Patients with non-central geographic atrophy (dry MD) and no choroidal neovascularization (vessel growth and leakage) should continue.

Finally, Dr. Chew on the new AREDS2 study. This is a followup to the original "Age-Related Eye Disease Study" completed in 1998. That study resulted in most doctors recommending the AREDS formula to patients in the intermediate stage of AMD, in order to slow progression to the advanced stage. The formula contains vitamin C, 500 mg; vitamin E, 400 IU; beta carotene, 15 mg; and zinc, 80 mg. The new formula now being tested is slightly altered, with less zinc, no beta-carotene, and the addition of lutein, zeaxanthin and omega-3 fatty acids DHA and EPA. The purpose is to see if the new formula will be even more effective. The AREDS2 cohort has been fully recruited, and first results are expected in 5 years. For more about this research, see www.mdsupport.org/library/study.html

12. PDT Still a Viable Treatment in Some Cases

Several years ago, photodynamic therapy (PDT) was the most effective treatment for wet AMD, but it has been mostly replaced by the new antiangiogenic drugs. This treatment involved injection of the light-activated drug Verteporfin (Visudyne) into a vein, followed by targeting the leaking blood vessel with a low power laser. This destroyed the vessel and stopped the leakage, but it also caused some residual damage to surrounding cells after repeated procedures. Still, PDT is used in some cases where the vessel's location is not close to the center of the macula and quick action is necessary.

Now, a new less damaging and more effective approach called "Targeted" Photodynamic Therapy (TPT) is being studied. According to Dr. R.A. Adelman in a report to the ARVO meeting, a protein called Factor VII is conjugated with Verteporfin. Intravitreal injection of the compound in a rat model with choroidal neovascularization showed efficacy at 1/10th the usual dose of Verteporfin and 3x better visual function after lasering. This proved to be more effective and safer for surrounding cells than standard PDT at a significantly lower dose. For more information about PDT with Visudyne, see www.mdsupport.org/library/photther.html

13. The Latest on Lucentis

Lucentis, developed by Genentech Pharmaceuticals, is one of two FDA approved

drugs used in treatment of wet AMD. The other is Macugen, which has been shown to be less effective. Avastin is also being used off-label with reported success, but it has yet to be shown to be safe and efficacious in large studies.

Three followup studies of Lucentis, called HORIZON, EXCITE and SUSTAIN, were reported on at the ARVO meeting by Drs. M. Singer, C. Simader and F.G. Holz.

The HORIZON study, which ended in Sep 2008, followed Genentech's Marina, Anchor and Focus trials, all of which were followup studies of Lucentis. The results showed that the rate of ocular and nonocular adverse events was low, repeated injections were well tolerated after 4 years, and delay in initial treatment resulted in a higher loss of vision.

The EXCITE study compared quarterly treatment with monthly treatment using Lucentis. Best corrected visual acuity and retinal morphology were found to be better with a monthly regimen of injections.

The SUSTAIN study analyzed safety of monthly dosages of 0.3 and 0.5 mg. Lucentis was found to be safe and effective, no matter what the amount of dosage or the interval of time between treatments.

Since monthly treatment on an as-needed basis at 0.5 mg has been found to be most effective, more refined testing (eg. higher resolution OCT) will be needed in order to better judge if and when patients need to be retreated.

14. Bilateral Injections Appear Safe

Dr. KariAnne Galler reported to the ARVO meeting that there is no particular increase in risk for patients with bilateral macular degeneration treated with bilateral injections of anti-VEGF drugs. Also, there is a strong patient preference for the ease and convenience of having bilateral rather than unilateral injections.

15. Obama Lifts Limits on Stem Cell Research

President Obama has lifted the Bush administration's limits on human embryonic stem cell research. Mr. Obama announced the decision on March 9, saying he hoped Congress would follow with bipartisan legislation that would ease the existing restrictions even more.

The president acknowledged that studying stem cells extracted from human embryos is deeply divisive, but he said the majority of Americans "have come to a consensus that we should pursue this research; that the potential it offers is great, and with proper guidelines and strict oversight the perils can be avoided."

16. First Human Embryonic Stem Cell Study Approved By FDA

Geron, a biotech company, has announced that the federal government will allow the world's first test in people of a therapy derived from human embryonic stem cells. Until now, federal financing for research on embryonic stem cells has been restricted, because creation of the cells entails the destruction of human embryos. The intended reversal of this policy by the newly-elected administration may or may not have influenced this recent decision.

Geron will enroll paralyzed patients who can be treated within 2 weeks of their injury. The subjects will then be evaluated for at least one year, after which the company hopes to increase the dose and expand the number of participants.

This release of government funding is expected to set a precedent for more stem cell research in the low vision field. For more information about the research to this point, see *The First Seven Years: An Overview of Stem Cell Transplantation Research for Treatment of Retinal Disease* in the MD Support Library.

17. Stem Cell Therapy Presents Challenges

A special interest group discussed the challenges of bringing stem cell therapy to the patients. The topics were addressed by P.J. Coffey (Institute of Ophthalmology, University College, London), H. Klassen (Univ. of California, Irvine), and M. Friedlander (Scripps Research Institute).

18. The topics of discussion were:

- Ways of getting the cells to the site of action, either by surgical insertion or injection into the vitreous fluid.
- The safety of the procedure
- The length of time it will take for the procedure to have an effect
- The question of whether the body will reject the implants
- Sources of stem cells

To summarize:

Dr. Coffey stated that the goal of The London Project at Moorfields Hospital is to reconstruct the macula by repopulating the retinal pigment epithelium (RPE) to

nourish the photoreceptors. This has been accomplished successfully by macular translocation and RPE transplantation. The problem, however, is that these procedures take several hours and at least two separate visits to the clinic. The solution, said Dr. Coffey, is to implant (by injection) a permanent artificial membrane of human embryonic cells. This has been shown to stop pig photoreceptors from dying, and there has been no immunological response (i.e. rejection) so far.

Dr. Klassen discussed culture and transplantation of retinal progenitor cells (RPC), which he says is a key developmental stage in the pathway to replicating rod photoreceptors, even for Müller and ciliary cells. RPCs have been obtained from animals and encouraged (by adding a growth factor) to differentiate into photoreceptors. They have been well-tolerated in the treated retinas. He added that human RPCs have been successfully used in China to repair the optic nerve.

Dr. Friedlander discussed adult stem cell based therapies. Sources for such cells are the cornea, bone marrow, peripheral blood, spinal cord blood, skin, hair and dormant stem cells. He introduced a new strategy involving rebuilding retinal vessels instead of inhibiting neovascularization. He described how this "vasculotrophic rescue" can be done with bone marrow derived stem cells.

For more background information about stem cells that will help your understanding of these discussions, see www.mdsupport.org/library/7years.html

19. FDA Panel Recommends Approval of IMT

On March 27, 2009, the FDA's ophthalmic device panel recommended approval of Vision Care Ophthalmic Technology's implantable miniature telescope (IMT) for patients with advanced stage AMD. After 5 years of trials and a prior unsuccessful submission to the panel, the IMT has now met all requirements for safety and efficacy.

The FDA usually follows the recommendations of an advisory panel, but is not required to do so. The panel recommended approval of the device with conditions including post-approval surveillance and labeling suggestions. The panel decision was reached by a vote of 8 to 0.

Allen W. Hill, CEO of VisionCare, said "We are pleased with the panel's recommendation for approval and will work closely with FDA to address the approval conditions. We look forward to providing the ophthalmic community a new treatment option to improve vision and quality of life for patients with untreatable, end-stage age-related macular degeneration."

I spoke to the panel shortly before the vote. I told them that, until now, nothing has offered long-term vision restoration for people in the advanced stage of the disease. That stage has traditionally been one of transition to nonvisual skills such as cane

use and Braille. With the IMT, it may be possible for some of us to put that off indefinitely, and that gives us one more cannon to fire.

For more information on the research, visit VisionCare's website at www.visioncareinc.net or call (408) 872-0526.

20. Seeing With Your Tongue

One of the most exciting developments reported at Vision 2008 in Montreal was new device called BrainPort, which (according to the abstract) enables perception of visual information using the tongue and camera imaging system as a paired substitute for the eye.

Visual information is collected from a head mounted image sensor and translated into electrical patterns displayed on the surface of the tongue.

The system has tested favorably on subjects with no vision, and it is now being adapted to assist individuals with macular degeneration and related diseases.

The long term goal is to develop a fully portable, unobtrusive device that will track with the user's gaze point, capture information centered in the area of vision loss, and display the information on the tongue. This device will "fill in" the area of vision loss, will be compatible with other vision-assisting devices, will not be surgically invasive, and will be easily customizable and upgradeable.

Developers are hoping to have the BrainPort commercially available within 2 years. Here is where you can read more about it:

vision.wicab.com/technology

DIET & NUTRITION

21. Statins May Hasten Onset of Wet AMD

What effect do cholesterol-lowering drugs have on the retina? A pilot study in 2006 found "that treatment with simvastatin increased blood-flow velocity in the retinal arteries and veins and decreased intraocular pressure. (Nagaoka T et al. Arch Ophthalmol 2006; 124:665-670.)

This study supports the thinking that increased blood flow is generally beneficial to the retina. Recent research, however, has shown that taking statins to lower cholesterol levels might hasten the onset of wet AMD in people who are already affected by the dry form. The abstract for this study may be read on the Web at

www.tinyurl.com/5ksj6a.

Considering the proven beneficial effects of drugs like simvastatin for people with circulatory problems and high cholesterol, it would be wise to keep this information in mind, but it would not be wise to stop taking them altogether without professional consultation. Until researchers have sorted out the facts, a patient's decision should be based upon individual circumstances and discussed with professional care providers.

More details about cholesterol research as related to AMD may be found in the MD Support Library at www.mdsupport.org/library/cholesterol.html.

22. Vitamin C May Lower Statin Levels

A UC Berkeley study, led by Gladys Block, PhD, suggests that 1,000 mg of daily supplemental vitamin C can lower concentrations of C-reactive protein (CRP), the marker associated with systemic inflammation. (Free Radical Biology and Medicine, Jan. 1, 2009). It suggests that a daily dose of supplemental vitamin C can lower CRP levels in healthy, non-smoking adults in two months.

Gladys Block and her staff found that for people with elevated CRP levels, the amount of CRP reduction achieved by taking vitamin C in this particular study is comparable to that in many statin studies.

A multinational clinical trial led by researchers at Harvard Medical School (the Jupiter Trial), found that among people who had high levels of CRP at baseline, levels of CRP were 37 percent lower in the subjects who took statins compared to those who took the placebo.

In the UC Berkeley study on vitamin C, participants who started out with CRP levels greater than 2 milligrams per liter had 34 percent lower levels of CRP with vitamin C compared with a placebo after two months.

"This is clearly a line of research worth pursuing," said Dr. Block. "It has recently been suggested by some researchers that people with elevated CRP should be put on statins as a preventive measure. For people who have elevated CRP but not elevated LDL cholesterol, our data suggest that vitamin C should be investigated as an alternative to statins, or as something to be used to delay the time when statin use becomes necessary."

The benefits to the consumer are that Vitamin C is considerably less costly, and it does not carry the risk of serious side-effects associated with statins.

Source: Ellen Troyer, MT, MA (Chief Research Officer, Biosyntrx .com)

23. Excess Weight Contributes to Mortality

by Ellen Troyer, MT MA

Biosyntrx Chief Research Officer

Excess weight is an epidemic in the United States. There is strong scientific agreement that excess weight (BMI over 25) contributes to overall mortality. It also significantly increases the risk of serious degenerative diseases, including cataracts, macular degeneration, glaucoma, and diabetic retinopathy.

The National Center for Health Statistics estimates that 65% of the U.S. population is overweight, with 34% of the population being clinically obese. Scientists have also identified the significantly increased risks associated with excess weight for 20 other diseases or conditions. According to the U.S. Surgeon General report, excess weight and obesity are responsible for 300,000 deaths every year in the U.S.

24. Vitamins B-6, B-12 and Folic Acid May Protect Against AMD

Ellen Troyer, MT MA

Biosyntrx Chief Research Officer

A recent study suggests that a combination of vitamin B-6, vitamin B-12 and folic acid may protect women against age-related macular degeneration.

Epidemiologists at Harvard Medical School and Women's Hospital in Boston analyzed data collected as part of a large trial originally designed to test the effects of other vitamins

on women with heart problems. All subjects were permitted to take multivitamins with B-6, B-12 and folate up to, but not exceeding, recommended daily allowances (RDAs). Those getting the B-6, B-12 and folate supplements received much larger amounts.

After 7.3 years, researchers found 82 cases of age-related macular degeneration among women taking placebos and only 55 cases in the women receiving the high-potency B vitamin supplements.

While an explanation for the apparent protection from macular degeneration remains unknown, it is known that folate, B-6 and B-12 can drive down blood concentrations of homocysteine, a methionine metabolism by-product compound suspected of damaging blood vessels.

On the surface this study seems to be very positive, but it raises some concerns about the folic acid dosage. Excessive supplemental folic acid can mask or obscure fairly common vitamin B-12 deficiencies in older people. This can result in an

increased risk of progressive, unrecognized neurological damage. Dosage of supplemental folic acid over 1 mg per day has also been associated with impaired gastrointestinal absorption of zinc in some cases.

It's good to remember that more is not always better.

25. Too Much Red Meat?

Research* has revealed that a diet high in red meat may increase one's risk of developing AMD, while consumption of chicken may lower the risk.

Researchers followed 6,734 persons aged 58-69 years, from 1990 through 2006. Final data showed that higher red meat intake was positively associated with early AMD. The odds ratio for consumption of red meat 10 or more times a week versus less than 5 times a week was 1.47. Conversely, consumption of chicken 3.5 or more times a week versus less than 1.5 times a week was inversely associated with late AMD. The team concluded that different meats may differently affect AMD risk and may be a target for lifestyle modification.

Inflammation is being identified as the main culprit in the development of AMD, and cholesterol is inflammation's "partner in crime." Fatty red meat is a major source of cholesterol, while lean red meat actually produces less than the body does by itself. High quantities of red meat, therefore, may be an important risk factor, but it appears that we can sidestep the problem by consuming less, and only the leanest cuts.

*Red Meat and Chicken Consumption and Its Association With Age-related Macular Degeneration, Elaine W.-T. Chong, et al (American Journal of Epidemiology, November 25, 2008).

26. Occurrence of AMD Declining

A new study reports a lower 5-year incidence of early AMD in patients born or examined more recently, compared to similarly aged persons born or examined in an earlier period.

The study included 2,968 participants with early AMD and 3,588 participants with late stage AMD, all of whom were examined at 5-year intervals between 1988 and 2005 as part of the Beaver Dam Eye Study.

The investigators cannot yet explain the results. Improvements in health care and lifestyle over the previous 15 years do not explain the decline, but other factors might. These include other exposures earlier in life (e.g., infectious disease outbreaks such as the flu pandemic of 1918), dietary restrictions specific to a period

(e.g., the Great Depression), or other unmeasured factors.

Personally, I would like to think that greater health consciousness and awareness of the risk factors for AMD have made a positive contribution. We can play a part in maintaining that decline by continuing to educate ourselves and others about how we may fend off this disease, at least until these promising cures we hear about reach our hospitals and clinics.

Thank you for listening to this summary. The fact that it has been lengthy is testament to the encouraging work being done in the field, and let's continue to remain positive about the positive outcomes, whether for our benefit or for the benefit of those who follow us.