Jules Stein Eye Institute
U C L A

Clinical Update

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New Approaches to Macular Disease

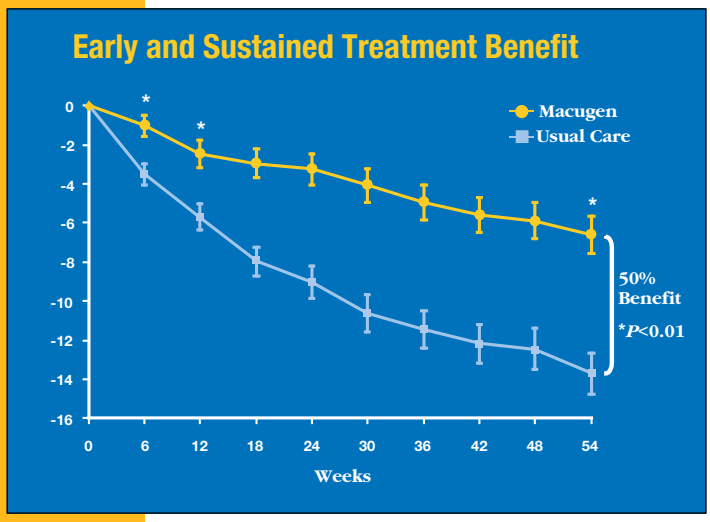

Figure 1. V.I.S.I.O.N. trial results: Macugen-treated patients did better than usual care controls in terms of mean change in vision, with a 50% treatment benefit at 54 weeks. The treatment benefit was seen as early as six weeks and was sustained throughout the first year of treatment.

For the past decade, the Retina Division of UCLA's Jules Stein Eye Institute has focused on uncovering the biologic and pathologic underpinnings of age-related macular degeneration (AMD) and diabetic eye disease, the major causes of new blindness in the developed world. The Division's approach has been successful, with major recent strides now being reported in angiogenesis, apoptosis, and gene therapy studies, as advanced scientific concepts move from the bench to the bedside.

"Our handpicked team of vitreoretinal surgeons continues to explore the translation of basic science paradigms into actual treatment interventions for patients losing vision from these all too common blinding conditions," says Steven D. Schwartz, MD, Associate Professor of Ophthalmology and Chief of the Retina Division. "We now have greatly improved treatments for these conditions, particularly for AMD, which destroys the central vision and limits everyday functioning and quality of life for millions of American seniors."

In recent years, notes Dr. Schwartz, the Division has identified urgent medical needs involving the retina and has sought to bridge basic science and clinical expertise through the work of surgeon-scientists.

Christine R. Gonzales, MD, Assistant Professor of Ophthalmology, "has made enormous contributions to the fight against AMD," reports Dr. Schwartz, with her leadership on clinical trials for Macugen® (pegaptanib sodium injection), a drug that turns off the biologic switch for the new blood vessel growth and leakage characteristic of "wet," or neovascular, AMD. Dr. Gonzales heads the team at UCLA, the leading academic center in patient enrollment in phase III trials that included 117 sites around the world – trials that have led to Food and Drug Administration (FDA) approval of the drug for patients with wet AMD. Dr. Schwartz, notes, "UCLA has played an important role in this drug from concept to completion, and we now have the first treatment that not only stabilizes vision for an expanded group of patients but may also help some patients regain vision."

The clinical trial – the largest ever held for wet macular degeneration patients – has produced strong data in support of the drug, leading the FDA to render an unusually broad verdict based on one-year results, approving the drug for the treatment of all wet macular degeneration. "It's misleading to compare data from this trial with previous results for other strategies," explains Dr. Schwartz. "The Macugen trial included all forms of wet macular degeneration – all subtypes, all lesion sizes – and, while it was effective across the board, the inclusion of

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NEW APPROACHES TO MACULAR DISEASE

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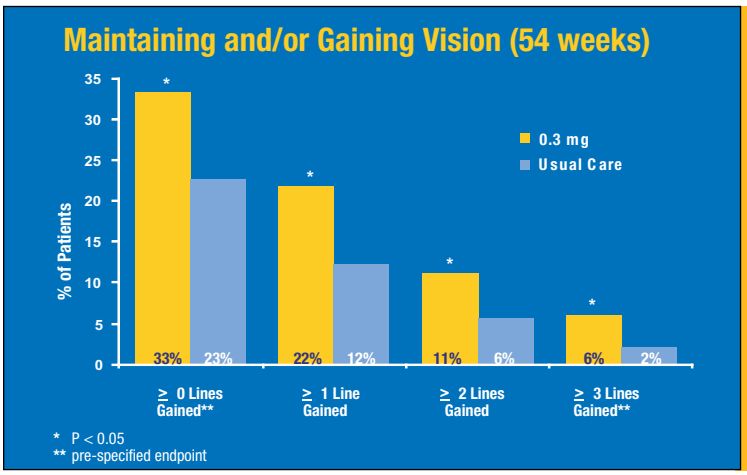

Figure 2. A substantial number of patients in the V.I.S.I.O.N. trial gained ≥1 and ≥2 lines of vision after 54 weeks of Macugen therapy (22% and 11%, respectively).

patients who were closer to end stage makes the overall result somewhat less powerful than if we had included only the patients who were not doing as poorly."

"The previous treatment for subfoveal lesions was photodynamic therapy, and this was shown to be beneficial for a small subset of patients with wet macular degeneration," notes Dr. Gonzales. "Macugen treatment is going to benefit a much broader patient group." The wet form accounts for approximately 10 percent of AMD cases, and all but those patients who already have significant scarring under the macula or do not have active leakage at the time of evaluation stand to benefit. "The pivotal trial included patients with very large lesions, as opposed to some of the other clinical trials," Dr. Gonzales adds. "Macugen may also prove to be beneficial for patients with lesions that are not in the subfoveal location such as juxtafoveal or extrafoveal lesions."

Macugen acts like an antibody, binding selectively to the "bad" form of VEGF (vascular endothelial growth factor), VEGF 165 – the VEGF isoform known from preclinical studies to be responsible for pathologic neovascularization. "VEGF 165 is responsible for stimulating abnormal blood vessel growth under the retina in the wet form of macular degeneration," Dr. Gonzales explains. "Those abnormal blood vessels then leak fluid, bleed, and cause scar tissue, all of which results in progressive damage to the retina. By blocking VEGF, the growth factor responsible for pathologic angiogenesis in AMD, we can slow the growth and stop the leakage from abnormal blood vessels. The selective action of the drug, along with the fact that it is a locally delivered treatment, with little absorption into the systemic circulation, have contributed to Macugen's excellent safety profile."

In the pivotal phase III trials, significantly fewer wet macular degeneration patients lost moderate levels of vision when treated with Macugen than did patients in the usual care group, and more patients in the Macugen group maintained or gained vision. "In addition to inhibition of angiogenesis, Macugen decreases vascular permeability, thereby leading to resorption of subretinal fluid and retinal edema," Dr. Gonzales explains. "The retina and the retinal pigment epithelial cells probably experience some degree of rescue with this type of treatment. For patients who are treated early, before they have significant scar tissue, we may see more impressive vision gain." For that reason, Dr. Schwartz notes, the earlier patients with exudative macular degeneration are detected and treated with the drug, the better. "It used to be that you had to let patients get to a certain point before the risks of the treatment were worth the benefits, but Macugen changes that equation," he explains.

Other investigations are building on therapeutic approaches already in use, in an effort to minimize the risks of treatment. Tara A. Young, MD, Clinical Instructor of Ophthalmology, explains, "Patients losing vision can't wait for all the answers to come in, so we use treatments that seem to help – such as argon laser for leaking vessels in diabetic retinopathy – yet we may not know exactly how they work. Identifying the mechanisms of action would allow us to make therapies more efficient, with fewer side effects." Dr. Young has studied

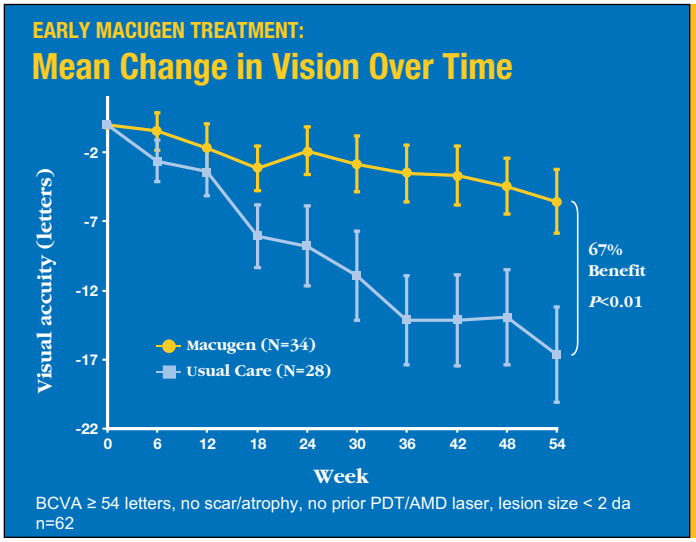

Figure 3. A subgroup analysis of patients from the V.I.S.I.O.N. trial with early lesions demonstrated an even greater treatment benefit, 67%, than the benefit seen in the overall study group. Early lesions were defined as best-corrected visual acuity ≥54 letters, no scar or atrophy, no prior PDT or AMD laser, and lesion size <2 disc areas.

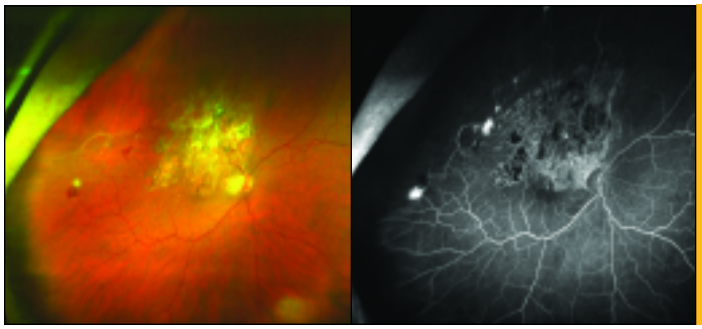

Figure 4. Wide-field color photography and angiography acquired with a prototype Optos(tm) imaging system showing profound peripheral ischemia and neovascularization associated with a branch retinal vein occlusion

how apoptosis – triggering selected cells to commit suicide – is activated by photodynamic therapy with the drug Visudyne® (verteporfin) in certain forms of wet AMD. "In the laboratory, we are looking at specific molecular pathways and cascades of drug action, to better understand how this therapy causes unwanted photoreceptor cell death," Dr. Young says. "Controlling apoptosis may help us refine AMD treatment and allow us to spare healthy cells so therapy may be less destructive than our current Visudyne treatments."

Dr. Young's angiogenesis research, which she began as a clinical fellow at Harvard, shows that the collateral damage caused by photodynamic therapy with Visudyne, through apoptosis of the retina's photoreceptor cells, can be seen only on a microscopic scale. "These are preliminary findings, but not something we had expected," she says. "Perhaps in the future when we are designing new drugs we can target the factors that trigger this process and prevent collateral damage to healthy tissue from occurring."

Since arriving at UCLA, Dr. Young has been applying molecular and immunologic basic science principles to ocular oncology. "Uveal melanoma in the past has only focused on treating the local tumor and whether it is small, medium or large; there has been little attention to molecular factors predictive of metastasis," says Dr. Schwartz. "Dr. Young is applying cutting-edge molecular biology and immunobiology in her clinical evaluation and treatment of patients with ocular cancer."

Gene therapy is also being studied as a treatment for macular disorders. "Gene therapy clinical trials have arrived and for the first time, human ocular disease interventions on the genetic level are being investigated in patients," reports Assistant Professor Anurag Gupta, MD. UCLA's JSEI is working with Johns Hopkins University and select sites around the country. "The idea is simple," explains Dr. Gupta. "We neuter the virus by taking the ability to replicate and a few other features out of the viral DNA and replace it with the message for a therapeutic protein, in this case, PEDF [pigment epithelial derived factor]. We inject the altered, non-reproducing virus into the eye. It infects the target tissues and instead of making new virus and propagating an infection, it tricks the host cells into making the desired therapeutic protein right where the eye needs it most."

Dr. Gupta reports the phase I trials proved the approach safe at various doses; phase II trials are planned. "Some patients are hesitant about injections into the eye," he notes. "More often than not, their anticipation of discomfort is much worse than the actual experience. In fact, most people say that getting blood drawn hurts more." Dr. Gupta and colleagues are also studying a drug that may prevent the onset of wet macular degeneration in the unaffected eye of patients suffering severe visual loss in one eye. This drug, anecortave acetate, has not proven effective for the treatment of active wet AMD, but may hold promise as a prophylactic agent. As Dr. Gupta notes, "We won't have the answer for at least five years, but if it's positive, it's worth waiting for."

Dr. Gupta has also helped to pioneer a new imaging technology that provides wider-field view of the retina without sacrificing resolution. Wide-field, fluorescein angiography takes a picture that is approximately 200 degrees, a potential boon for advanced diagnostics. JSEI retina surgeons are also continuing their pioneering work in minimally invasive vitreoretinal approaches and are taking advantage of newly available diagnostic tools. "We now have a powerful imaging technology called OCT, or ocular coherence tomography," reports Dr. Gonzales. "OCT measures the thickness of the retina and subretinal fluid. The next phase of clinical trials with Macugen are underway, in which we are examining whether OCT is a better monitor of therapeutic effectiveness than fluorescein angiography in patients with macular degeneration."

By applying fundamental scientific knowledge to blinding eye diseases – with a focus on new discoveries, improving safety and efficacy of treatments, and disease prevention – the Retina Division and its team in the Clinical Research Center are translating decades of basic science work into clinically relevant treatment interventions for countless patients.

RECENT PUBLICATION

Gragoudas ES, Adamis AP, Cunningham ET, Feinsod M, Guyer DR, for the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for Neovascular Age-Related Macular Degeneration. N Engl J Med 2004;351:2805-16.

JSEI Continuing Education Programs & Grand Rounds Schedule 2005-2006

May 20-21, 2005
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36th Jules Stein Lecture
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Edwin M. Stone, MD, PhD
Professor of Ophthalmology, University of Iowa

Bradley R. Straatsma Lecture
"Stemming Vision Loss with Stem Cells"
Martin Friedlander, MD, PhD
Associate Professor of Cell Biology, University of California, San Diego

Thomas H. Pettit Lecture
"Multidisciplinary Treatment of Thyroid Orbitopathy"
Donald O. Kikkawa, MD
Professor of Ophthalmology, University of California, San Diego.

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