

News in Review

A LOOK AT TODAY'S IDEAS AND TRENDS

Possible Toxicity With Anti-VEGF Treatment

Recent experimental findings suggest that overuse of anti-VEGF drugs to treat wet AMD might interfere with normal retinal maintenance and lead to the development or worsening of dry

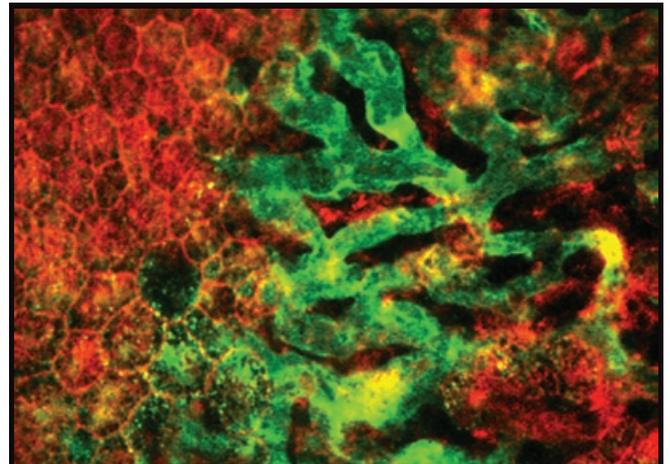
AMD in treated eyes.¹

The research in mice showed that, when soluble forms of VEGF were not available to diffuse from the retinal pigment epithelium into the choriocapillaris, a degenerative process developed that resembled human geographic atrophy. The choriocapillaris atrophied; there were abnormalities in the RPE and Bruch's membrane; and areas of RPE loss and choroidal remodeling appeared. At later stages,

photoreceptor death was apparent.

"The data suggest an important role for soluble VEGF in the normal function of the retina and in the maintenance of the choriocapillaris by the RPE. Because of this, therapies aimed at blocking VEGF need to be approached with caution," said principal investigator Patricia D'Amore, PhD, MBA. Dr. D'Amore is a senior scientist at Schepens Eye Research Institute and professor of ophthalmology and pathology at Harvard.

Her group used mice that were genetically engineered to produce only an insoluble



MOUSE MODEL. Aged VEGF188/188 mice, which only produce the membrane-bound form (not the soluble form) of VEGF, display large regions of RPE loss (red) and atrophic choriocapillaris (green), a phenotype similar to dry AMD.

form of VEGF. Unlike soluble isoforms secreted by normal RPE, insoluble VEGF cannot efficiently diffuse through Bruch's membrane to the choriocapillaris. The resulting lack of VEGF signaling in the choriocapillaris led to degenerative changes characteristic of geographic atrophy and dry AMD, the researchers concluded.

Both ranibizumab (Lucentis) and bevacizumab (Avastin) have relatively short half-lives, so they

might not reduce endogenous VEGF below levels required for retinal maintenance, Dr. D'Amore said.

Still, she hopes the study's results will prompt clinicians to become more cautious in using VEGF-blocking drugs. "More is not necessarily better," she said. She suggests using the lowest effective doses and delivering them only as needed.

Her biggest worry is the potential impact of chronic anti-VEGF therapy in younger patients with dia-

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betic retinopathy or diabetic macular edema. “They are much younger than AMD patients, and they would be treated for much longer,” she said.

“Even with wet AMD, I have a concern about possible retinal and/or choroidal damage in people who are getting relatively continuous treatment over three or more years,” Dr. D’Amore said. “Many of these patients also have findings of dry AMD and/or geographic atrophy, and there is no good way for clinicians to determine whether worsening of the dry AMD is due to the anti-VEGF treatment or is simply the natural

course of the pathology.”

Another leader in ocular VEGF research, Jayakrishna Ambati, MD, agreed that the mouse data suggest that clinicians should not be cavalier about using anti-VEGF drugs. “However, I don’t think any immediate change in clinical management of AMD is warranted,” said Dr. Ambati, professor and deputy chairman of ophthalmology at the University of Kentucky.

Although VEGF-blockade toxicity now has been detected in the retinal ganglion cells, photoreceptors and choriocapillaris of rodents, it is not yet clear whether this also happens in

humans, Dr. Ambati said.

“While it is tempting to speculate that an as-needed treatment regimen might prove safer for patients, it is important to note that recently published data² suggest that such a regimen is likely to result in visual outcomes not comparable with a regimen consisting of more frequent drug administrations,” Dr. Ambati said.

Nonetheless, it is essential to determine if human retinas show similar retinotoxicity from anti-VEGF drugs over time, he said.

“If this were occurring in patients with wet AMD, it would be extremely difficult to detect or distinguish

from the disease’s natural history. That said, some recent studies using sophisticated methods such as high resolution OCT have shown that the inner-outer photoreceptor segment junction is less likely to be visible with increasing numbers of anti-VEGF injections.³ It is critical that we develop highly sophisticated detection tools,” Dr. Ambati said.

—Linda Roach

1 Saint-Geniez, M. et al. *Proc Natl Acad Sci USA* 2009;106(44):18751–18756.

2 Dadgostar, H. et al. *Ophthalmology* 2009;116(9):1740–1747.

3 Sayanagi, K. et al. *Br J Ophthalmol* 2009;93(5):622–626.

Neuro-Ophthalmology Report

Rx Rituximab for Graves: When Steroids Fail

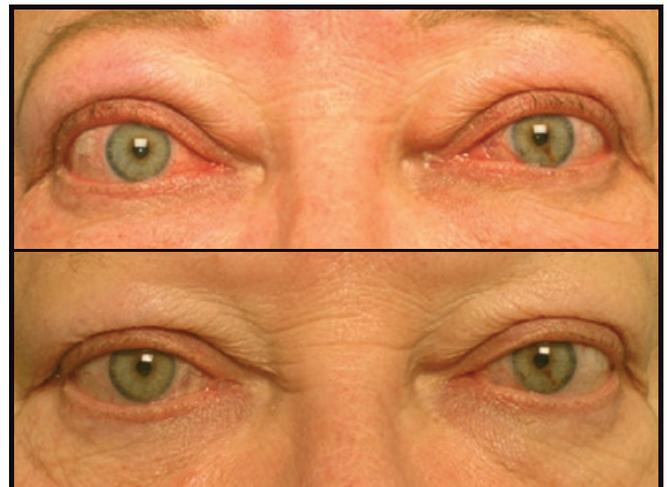
A drug widely used to treat rheumatoid arthritis was extremely effective in stopping progression of severe, corticosteroid-resistant thyroid-associated ophthalmopathy (TAO, or Graves ophthalmopathy), according to University of Michigan researchers.

Rituximab calmed inflammation and stopped disease progression in six patients otherwise headed for surgery. Four of those patients had progressed to refractory dysthyroid optic neuropathy, which was also resolved by the treatment protocol: two 1-g infusions of rituximab, two weeks

apart. Results, seen as early as four weeks following the first infusion, were sustained at least six months post-treatment.¹

Though the study was small, coauthor Raymond S. Douglas, MD, PhD, would not hesitate to prescribe rituximab for patients with intractable TAO. “It’s a very reasonable alternative,” said Dr. Douglas, associate professor of ophthalmology and visual sciences at the University of Michigan, Ann Arbor.

He cautioned, however, that rituximab be reserved for patients with severe disease and said it should be administered only by



GRAVES OPHTHALMOPATHY. Patient with orbital inflammation before rituximab treatment and 18 months after.

someone familiar with it, most likely a rheumatologist. Though rituximab has relatively few side effects—fewer than those associated with corticosteroids—it is not benign, he said.

Rituximab is a monoclonal antibody designed to deplete B cells. Though not fully understood, B cell depletion appears associated with enhanced production

of T cells, which may dampen autoimmune responses and promote disease resolution. Dr. Douglas and colleagues found an abundance of T cells within two weeks after initiating rituximab.

But rituximab did not slow the fibrosis associated with TAO. For that, Dr. Douglas envisions a cocktail therapeutic approach, not unlike the protocol for

Refractive Issues

LASIK vs. Contacts: Comparing Safety

In the past, the contact lens industry largely competed on convenience and comfort, while the LASIK industry competed on visual acuity. Now researchers have devised a model to contrast the risks of the two options—no small matter, given that this may seem to be an apples-to-oranges comparison.

Reviewing previously published data—including

rheumatoid arthritis, which couples rituximab with methotrexate.

Still, rituximab alone had a pronounced effect. Orbital inflammation and dysthyroid optic neuropathy improved in all six patients. “We were surprised that without the cocktail, we were able to get as good a result with just the one drug,” Dr. Douglas said.

Next, he hopes to find a way to identify patients likely to develop severe TAO. To that end, a consortium of orbital surgeons, endocrinologists and rheumatologists has formed the International Thyroid Eye Disease Society, with the goal of conducting collaborative clinical trials. The group has already developed a disease severity grading system for future trials.

—Miriam Karmel

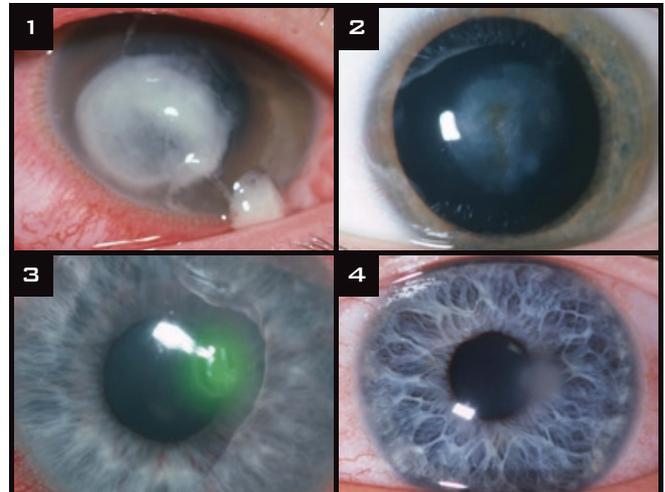
1 Khanna, D. et al. *Ophthalmology* 2010;117:133–139.

several large epidemiological studies on contact lenses as well as data from the U.S. Army’s refractive surgery program—the researchers created a model to compare the risks of reduced corrected-distance visual acuity.¹ And their results challenged the long-held assumption that contact lenses are always safer than LASIK.

“Although this finding is of interest, the study’s biggest value is its methodology, which is transferable to many other medical circumstances,” said William D. Mathers, MD, the paper’s coauthor, professor of ophthalmology at Oregon Health & Science University in Portland, and former president of the Contact Lens Association of Ophthalmologists.

“It sets out a rational way of assessing risks that accrue over a long time, which are difficult to understand, versus risks that occur as single events, which are easy to understand,” said Dr. Mathers. “And, as the variables and assumptions change, one can apply this model to reassess the conclusions.”

The researchers constructed a decision tree using Markov modeling to calculate the probability of vision loss from LASIK and contact lenses over time. To account for differences in timing and severity of vision loss, they developed an outcome variable called visual



CONTACT LENS-RELATED RISKS. *Pseudomonas* infection from an extended-wear soft contact lens (1). Healed central corneal scar from a daily-wear soft contact lens-induced infection (2). *Acanthamoeba* keratitis with a ring infiltrate from daily-wear soft contact lens use (3). Central corneal ulcer from daily-wear soft contact lens use (4).

acuity-adjusted life year. With a 30-year simulation, the researchers weighted each year of vision loss according to relative severity of vision loss.

Assumptions about severity of vision loss were based largely on the literature, with the understanding that post-LASIK vision loss usually occurs early or within five years of surgery as the result of ectasia. Vision loss from lens wear—moderate, severe or very severe—was assumed to result from infectious keratitis.

The researchers used a discount rate to make adjustments related to the duration of the vision loss. “It’s not just the severity of the vision loss that’s important,” said Dr. Mathers, “but also how long you’ve had the vision loss.” In addition, Hall T. McGee, MD, MS, first author on the study, conducted sensitivity analyses to account for the range of values for various assumptions made in the paper.

Except when assump-

tions were least favorable to LASIK, the researchers found LASIK to be safer than extended-wear lenses. And LASIK was safer than daily-wear soft lenses, but only when assumptions were chosen most favorable to LASIK. “However, rigid gas-permeable lens wear can lay claim to being a very safe approach to vision correction, safer than laser surgery under any set of assumptions,” said Dr. Mathers.

While epidemiological data about contact lens vision loss used in the study were limited, Dr. Mathers noted that LASIK-related ectasia stood out as a significant variable in the study. “This speaks to the need for continuing research to help minimize this risk and make patient care better.”

—Annie Stuart

1 McGee, H. T. and W. D. Mathers. *J Cataract Refract Surg* 2009;35;1860–1867.

Dr. Mathers reports no related financial interests.