

News in Review

A LOOK AT TODAY'S IDEAS AND TRENDS

B Vitamins Getting Good Press for AMD Tx

Researchers inserted plenty of caveats in a recent paper that reported a possible protective effect against age-related macular degeneration from a triple combination of B vitamins. But the ca-

veats could not avert a flood of press reports that, magnified by the Internet, might prompt aging Baby Boomers to ask their ophthalmologists whether they should be taking the combination of folic acid, B₆ and B₁₂.

At this point, the study supports further investigation of a new hypothesis, but it does not justify recommending the supplements to patients, said Emily Y. Chew, MD, deputy director of the division of

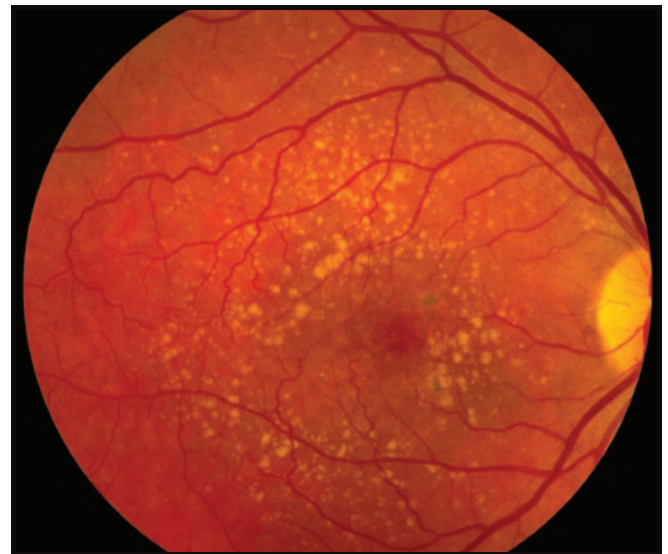
EyeNet thanks Susan B. Bressler, MD, and Christopher Rapuano, MD, for their help with this issue's News in Review.

epidemiology and clinical applications at the NEI.

"This study is a small subset of a much larger study. I'm surprised that it's getting so much attention from the media," said Dr. Chew, who was a coauthor on the paper.¹

"It was a randomized controlled clinical trial, and AMD was not the primary outcome. This was a secondary outcome—the kind of analysis that turns up interesting hints, and so you develop hypotheses to be tested in future studies."

Part of the Women's Antioxidant Cardiovascular Study, the double-blind



B VITAMINS AND AMD. Among women aged 40 and older, fewer early-stage cases of AMD were found in those taking B vitamins than those who did not take the supplements, but the difference between the groups was not significant.

clinical trial included 5,442 women health professionals, age 40 and older, who had cardiovascular disease or at least three coronary risk factors. They were randomized to take a placebo or a daily supplement of 2.5 mg of folic acid, 50 mg of vitamin B₆ and 1 mg of vitamin B₁₂ and followed for an average of 7.3 years.

The researchers initially assessed whether lowering

blood levels of homocysteine and remedying vascular endothelial dysfunction with these B vitamins would protect the treated group from cardiovascular events. They reported negative results last year.² But because endothelial dysfunction and elevated homocysteine levels also are associated with AMD, they conducted the AMD analysis.

This included only the

5,205 women who, at the study's outset, claimed not to have AMD. If, on an annual questionnaire, a woman reported an AMD diagnosis, the researchers examined her medical records. They found:

- 55 cases of diagnosed AMD in the vitamin group vs. 82 in the placebo group (relative risk, 0.66; $p = 0.02$).
- 26 and 44 cases in the treatment group and the placebo group, respectively, of visually significant AMD with BCVA of $\leq 20/30$ (relative risk, 0.59; $p = 0.03$).

- Most were early-stage cases, characterized by drusen and changes in the retinal pigment epithelium.
- The difference between the two groups began to emerge about two years after the vitamin supplementation began, and it increased over time.

If the association holds up in further clinical research, the vitamin B supplements would "appear to represent the first identified means, other than avoidance of cigarette smoking, of reducing risks of AMD in persons at usual risk," the

authors write.

But as the only ophthalmologist among the investigators, Dr. Chew emphasizes the self-reported, limited nature of the study's ophthalmic data—a sharp contrast to the tight standardization of the centrally graded fundus photographs that supported recommendations from the Age-Related Eye Disease Study. "We're not even sure that it's only the macular degeneration that is causing the vision loss in these subjects," she said.

On the other hand, the

study has sparked scientific questions worth pursuing, Dr. Chew said. "The saving grace is that it is a randomized trial, so there's a reason to follow the hypothesis. The real question is, we didn't find any effect from these supplements in the cardiovascular system, so why would it be different for eyes? And the bigger question is: Does it really work?"

—Linda Roach

1 Christen, W. G. et al. *Arch Intern Med* 2009;169(4):335–341.

2 Albert, C. M. et al. *JAMA* 2008;299(17):2027–2036.

Clinical Trials News

Landmark Study Still Seeking Patients

The Comparison of AMD Treatments Trials (CATT) continues to recruit patients at 43 sites in the United States. "Almost any newly diagnosed wet AMD patient is eligible," said study chairman Daniel F. Martin, MD.

CATT, regarded by many as a landmark study, is comparing the relative efficacy and safety of Lucentis (ranibizumab) and Avastin (bevacizumab). Lucentis was approved by the FDA in June 2006 for treatment of neovascular AMD. Avastin was approved in 2004 for the treatment of colorectal cancer and is widely used off-label to treat AMD.

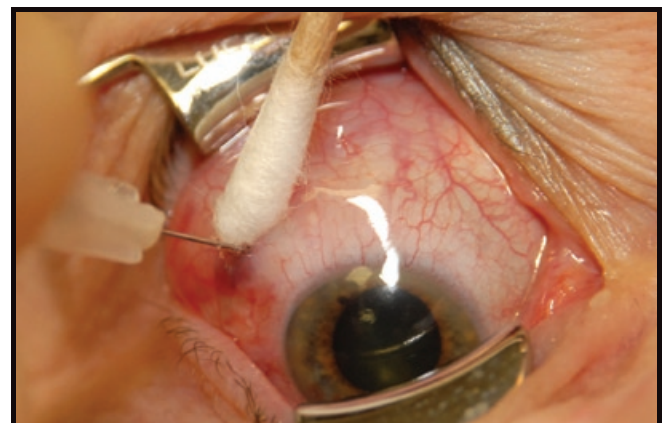
While many people regard CATT only as a head-to-head comparison of Avastin and Lucentis, Dr.

Martin said it's more than that. "Equally important is not just how Lucentis compares to Avastin, but what is the optimal dosing frequency? The CATT will help to determine the optimal way to treat patients."

To that end, patients are randomized into four groups:

- Injection of Lucentis once every four weeks for one year, with random assignment in the second year to every four weeks or variable dosing schedule depending on response.
- Injection of Avastin following the same protocol.
- Injection of Lucentis on a variable schedule.
- Injection of Avastin on a variable schedule.

Few clinicians administer Lucentis on a fixed schedule



REFER YOUR PATIENTS. The Comparison of AMD Treatments Trials not only will pit Avastin and Lucentis against each other, but it also should help determine optimal dosing for patients. Recruitment is going slowly, however.

as established in clinical trials (most notably MARINA and ANCHOR), said Dr. Martin, who is chairman of the Cole Eye Institute, Cleveland Clinic. "Almost everyone administers Lucentis on an as-needed basis. Yet the long-term visual outcomes from this treatment strategy have never been established."

Ideally, data from the CATT will be used to identify which subgroup of patients is likely to respond to a particular dosing sched-

ule. "There is tremendous heterogeneity in the clinical response to anti-VEGF therapy," Dr. Martin explained. "What you would like to know when you first see a patient is how frequently you will need to dose the patient to achieve the best visual result," he said. "Right now, it is one size fits all."

—Miriam Karmel

Information on the CATT and the nearest clinic for your eligible patient is available at www.nei.nih.gov/CATT/.

Retina Report

Laser Burns May Damage Much More Than Retina

One of the more intriguing traits shared by the brain and the eye is immune privilege, which provides immune protection from the accompanying inflammation seen in other body systems. One group of researchers has found that retinal laser burn in one eye not only disrupts the protective immune privilege in that eye but causes the fellow eye to lose immune privilege as well.¹

In their study, principal investigator Joan Stein-

Streilein, PhD, and her research group at the Schepens Eye Research Institute in Boston, made four laser spots at the 9 o'clock position of the retina in the right eyes of mice. The eyes were then injected with the antigen ovalbumin.

As early as one day and as late as 56 days after the retinal laser burn, the scientists observed damage of the retinal pigment epithelium and nuclear layer.

The researchers also made another observation: as early as six hours and as

late as 56 days after retinal laser burn, the ability to induce anterior chamber-associated immune deviation in the eye that received the retinal laser burn was impaired. They found that the induction of an inflammatory response in the back of the eyes altered the immune privilege in the anterior segment of the eye.

“What really proved fascinating, however, was that retinal laser burn interfered with anterior chamber-associated immune deviation in both the retinal laser burn eye and the contralateral eye,” said neuroscientist and coauthor Kenyatta Lucas, PhD. “Obviously there is some type of communication going on between the eyes.”

The researchers also observed that inoculation

of antigen into the anterior chamber of the burned eye led to immunization and a delayed hypersensitivity response. However, this immunization response did not carry over into the contralateral eye.

“We now are focusing our research on what appears to be different mechanisms that allow disruption of the immune privilege in both eyes yet do not allow for the immunization effect in both eyes,” Dr. Lucas said.

From a clinical perspective, the researchers conclude the expanded use of lasers in medicine and industry may increase the risk of immune inflammation in the eye. —Lori Baker Schena

1 Qiao, H. et al. *Am J Pathol* 2009;174:414-422.

Oncology Update

Moles May Be Markers for Uveal Melanoma

Evidence suggesting a relationship between the development of uveal melanoma and atypical or common cutaneous nevi, cutaneous freckles or iris nevi is mounting, according to a team of researchers led by Ezekiel Weis, MD, MPH, assistant professor ophthalmology at the University of Alberta in Canada. Some combination—not yet fully understood—of environmental insult and genetic predisposition is thought to trigger melanoma onset.

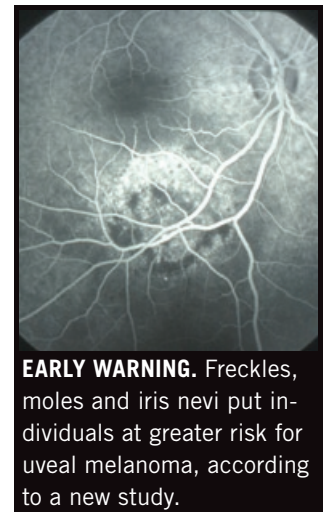
“The presumed environmental insult is ultraviolet light, though we have not been able to confirm this,” said Dr. Weis.

Although treatment options for uveal melanoma have improved significantly during the last five decades, the 10- to 15-year mortality rate remains constant at 50 percent. “Because improved treatment has not led to a decrease in mortality rate, we wanted to determine causation of uveal melanoma and therefore improve prevention,” said Dr. Weis.

In an effort to ascertain the potentially modifiable causal factors, he and his colleagues conducted a series of epidemiological meta-analyses. The result of the group’s third and final analysis showed that the odds of developing uveal melanoma are:

- 2.82 times greater for persons with atypical moles,
- 1.74 times greater for persons with common moles,
- 1.22 times greater for persons with freckles, and
- 1.53 times greater for persons with iris nevi.

Patients with premalignant melanocytic lesions of the uvea should be watched more closely if they have freckles and moles, fair skin, light eyes and/or sunburn easily. “I tell patients that although we have not yet fully proven the hypothesis as-



EARLY WARNING. Freckles, moles and iris nevi put individuals at greater risk for uveal melanoma, according to a new study.

sociating UV light and uveal melanoma, protecting your eyes from the sun is not harmful, is helpful for other eye conditions and is easy to do,” Dr. Weis said.

—Leslie Burling-Phillips

1 *Ophthalmology* 2009;116(3): 536-543.e2.