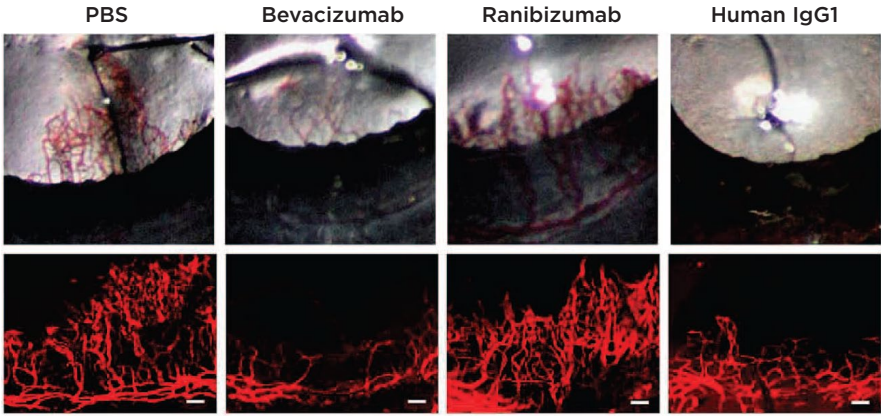
Novel Role for Antibodies in Angiogenesis



REPRESENTATIVE PHOTOS OF MOUSE EYES *(upper row) and corneal flat mounts (lower row) showing reduced growth of blood vessels (CD31+, red) in eyes treated with bevacizumab or human IgG1, but not in eyes treated with ranibizumab. PBS (phosphate-buffered saline) was used for comparison. (Scale bars, 100 µm.)*

ANTIBODIES ARE WELL KNOWN as key components of the immune system that protect against infection. Their ability to specifically recognize particular proteins has been harnessed therapeutically in the form of monoclonal antibodies (mAbs) and intravenous immune globulin (IVIg) to treat numerous ocular and nonocular diseases. However, 2 recent publications indicate that antibodies have a previously unknown function that has major implications for therapeutic use.

Target-independent effects of mAbs. The pioneering studies, led by principal investigator Jayakrishna Ambati, MD, of the University of Kentucky, show that numerous FDA-approved therapeutic antibodies have an important off-target effect: They nonspecifically inhibit blood vessel growth *independent* of their intended target. Dr. Ambati believes that this newfound function could be utilized as a novel treatment strategy to combat a wide range of diseases involving aberrant angiogenesis.

Through a series of animal and cell culture studies, the researchers found that a subtype of immune globulins, known as IgG1, suppresses angiogenesis by binding to Fc-gamma receptor I (FcγRI) sites on cell membranes.[1,2] Their data indicate that the antiangiogenic mechanism of IgG1 antibodies involves the inhibition of proangiogenic macrophage recruitment.

Is IgG1 the key? Many therapeutic mAbs consist of IgG1, which is also the most common class of antibodies in IVIg. To bolster the clinical relevance of their findings, the researchers examined biopsied tissue from organ transplant patients before and after IVIg therapy and found significant reductions in blood vessels after IVIg treatment. This finding suggests that IgG1 antibodies might have a clinically important impact on blood vessel development in humans.

"IVIg may be ripe for rapid repurposing as a systemic angio-inhibitory agent and in the near future as an intraocular inexpensive therapy for multiple neovascular blinding diseases, such as AMD [age-related macular degeneration], proliferative diabetic retinopathy or retinopathy of prematurity," Dr. Ambati and colleagues wrote.[2]

Testing ocular therapies. IVIg's current commercial formulation would require revision before it could be studied in human eyes, Dr. Ambati said. "The pH and osmolarity would have to be adjusted for intraocular use."

However, clinical testing of the underlying concept is possible with an IgG1-based mAb that ophthalmologists commonly use: the anti-VEGF drug bevacizumab (Avastin). Because bevacizumab is a whole antibody, it has the necessary structural characteristics to bind to FcγRI, whereas ranibizumab (Lucentis), which is an antibody fragment lacking the Fc region, does not, Dr. Ambati explained.

Higher dosage may be needed. "The question is why this second, additional antiangiogenic effect from Fc-receptor binding wasn't seen in the famous CATT study, which compared Avastin versus Lucentis for age-related macular degeneration," Dr. Ambati said. "We believe that the reason might be that the dose of Avastin used was insufficient to capture the second effect. Based on our calculations, if you used

Sasha Bogdanovich, MD, PhD, and Jayakrishna Ambati, MD

8 times the Avastin that we use now intravitreously, you would see this additional mechanism at work and, potentially, have an even better effect on the neovascularization."

To test this idea, Dr. Ambati and colleagues are planning clinical trials of higher-dose bevacizumab in patients with AMD and with corneal neovascularization. His group's studies in mice indicated that the current intravitreal dose of bevacizumab given to AMD patients, 1.25 mg (volume: 50 µL), would have to be increased to 10 mg to see an antiangiogenic effect from FcγRI binding, Dr. Ambati said.

Systemic considerations. The discovery that an entire subclass of antibodies suppresses both angiogenesis and macrophage infiltration, which is involved in metastasis of some tumors,[3] is also relevant to cancer treatment, Dr. Ambati said. For instance, it might explain why oncologists have reported antimetastatic effects from treating patients with immune globulin,[4,5] he said. It also suggests the need for caution in prescribing mAbs or high-dose IVIg for patients with preexisting blood vessel disease, he said. —*Linda Roach*

1 Bogdanovich S et al. *Signal Transduction and Targeted Therapy.* Published online Jan. 28, 2016. www.nature.com/articles/sigtrans20151.

2 Yasuma R et al. *Signal Transduction and Targeted Therapy.* Published online Jan. 28, 2016. www.nature.com/articles/sigtrans20152.

3 Leek RD et al. *Cancer Res.* 1996;56(20):4625-4629.

4 Merimsky O et al. *Int J Oncol.* 2002;20(4):839-843.

5 Shoenfeld Y et al. *Isr Med Assoc J.* 2001;3(9):698-699.

Relevant financial disclosures: Dr. Ambati is named as an inventor on patent applications filed by the University of Kentucky relating to the technology used in this work.

CATARACT SURGERY

Risk Factors for Postop Macular Edema

WITH THE BENEFIT OF SUBSTANTIAL numbers of cases, uniform data collection, and rigorous isolation of risk factors, a retrospective database study of electronic medical records (EMRs) has deepened ophthalmology's understanding of the incidence of macular edema after cataract surgery.[1]

Data collection. Researchers in the United Kingdom mined a database of nearly 82,000 eyes that had undergone phacoemulsification at 8 National Health Service (NHS) sites over 4 years —making this the largest clinical study ever published on pseudophakic macular edema (PME).

The researchers capitalized on the NHS' standardized ophthalmology-specific EMR, which routinely collects very detailed data about patients. "This includes information on the status of diabetics, operative complications, and copathologies," said lead author, Colin J. Chu, PhD, clinical lecturer in ophthalmology at the University of Bristol.

Analysis by risk strata. The large population and copious data allowed the researchers to sequentially isolate individual risk factors and to stratify patients into 3 groups. Patients who had received prophylactic nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded from the analysis.

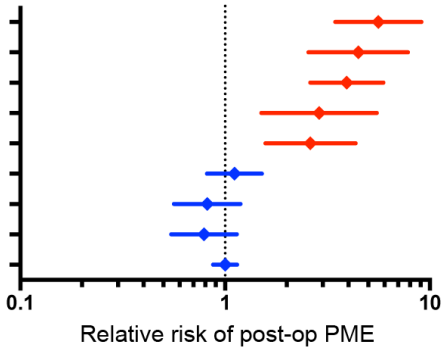
Group 1 included 35,563 eyes of patients with no identified risk factors or diabetes at the time of surgery. PME was diagnosed in 415 eyes, yielding an incidence of 1.17%.

Group 2 patients had at least 1 risk factor but no diagnosis of diabetes at the time of surgery. PME was diagnosed in 178 of 11,429 eyes, for an incidence of 1.56%.

Group 3 included patients with diabetes at the time of surgery. PME was diagnosed in 181 of 4,485 eyes, an incidence of 4.04%. The number of patients allowed the researchers to analyze outcomes based on the presence or absence of diabetic retinopathy at time of surgery.

Relative risks of PME. As expected, said Dr. Chu, the presence of ocular comorbidities including epiretinal membrane, retinal vein occlusion, and uveitis was linked to a higher relative

	No PME (eyes)	PME (eyes)	Incidence (%)	Relative risk (and 95% CI)
Epiretinal membrane	229	16	6.53	5.596 (3.452 to 9.074)
Retinal vein occlusion	218	12	5.22	4.471 (2.556 to 7.820)
Previous RD repair	479	23	4.58	3.926 (2.604 to 5.919)
Uveitis	259	9	3.36	2.878 (1.503 to 5.509)
PC-tear/vitreous loss	477	15	3.05	2.610 (1.573 to 4.339)
Prostaglandin analogues	3,350	44	1.30	1.111 (0.816 to 1.513)
High Myopia	3,009	29	0.95	0.818 (0.562 to 1.190)
Dry ARMD	3,230	30	0.92	0.789 (0.545 to 1.140)
Reference cohort	35,148	415	1.17	1.000 (0.874 to 1.145)



RELATIVE RISK FOR EYES FROM PATIENTS WITHOUT DIABETES *with a single copathologic feature or risk factor. The mean relative risk compared with the reference cohort is plotted with 95% CIs. Because only a single risk factor was permitted, each diagnosis was mutually exclusive, so eyes were analyzed only once. Red indicates factors that were found to be statistically significant (p < .05). ARMD, age-related macular degeneration; PC, posterior capsule; RD, retinal detachment.*

Chu CJ et al. *Ophthalmology.* 2016;123(2):316-323.

risk of PME, as were intraoperative complications such as posterior capsular rupture and vitreous loss (see graph, page 24). Surprisingly, men were found to have a higher risk than women, a result that had not been seen in earlier studies.

Among the preselected conditions that were not found to increase PME risk are preoperative prostaglandin analogue use, high myopia, and dry age-related macular degeneration.

New data on diabetes. "Previous studies have made half-hearted attempts at examining links between diabetes and PME," said Dr. Chu, "or they've excluded patients with diabetes due to challenges in determining whether the macular edema is caused by the surgery or the disease itself."

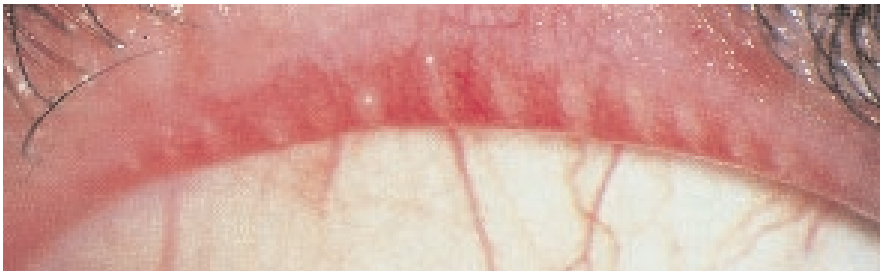
In this study, however, patients had a preoperative structured assessment of diabetic retinopathy and maculopathy to generate a precise Early Treatment Diabetic Retinopathy Study (ETDRS) grading. Sufficient data were available through the EMR, said Dr. Chu, to confidently exclude patients who had evidence of preoperative macular edema. "Once we excluded preexisting maculopathy, we saw a nearly linear increase in risk in PME with increases in the ETDRS severity of retinopathy."

Don't underestimate PME impact. Within the clinical community, said Dr. Chu, some have expressed a feeling that macular edema often "sorts itself out." But that's not what this study showed. Vision of patients in group 1, even those who received treatment for PME, including NSAID drops or intravitreal injections, did not catch up even by 24 weeks, he said.

"This suggests that prevention is likely better than treatment," said Dr. Chu. By homing in on individual risk factors, this study can aid in counseling and monitoring patients and help to guide clinical approaches, such as the use of prophylactic NSAIDs, for those in high-risk groups. —*Annie Stuart*

1 Chu CJ et al. *Ophthalmology*. 2016;123(2):316-323.

Relevant financial disclosures—Dr. Chu: None.



MEIBOMIAN GLAND DISEASE *(note keratin plugs blocking the gland orifices) is often associated with tear film irregularities and ocular surface disorders. Can the oral antibiotics used for MGD improve OSD?*

OCULAR SURFACE DISEASE

Oral Antibiotics: The Jury Is Still Out

OCULAR SURFACE DISEASE (OSD) affects some 15% of Americans 65 and older and is one of the most common reasons for a visit to the ophthalmologist. Meibomian gland disease (MGD), which causes instability of the tear film, frequently contributes to OSD.

An Academy *Ophthalmic Technology Assessment* (*OTA*) has delivered a mixed message on the use of oral antibiotics to treat OSD related to MGD. After reviewing the literature, the *OTA* committee found that while oral antibiotics appear to be beneficial in treating at least some patients with OSD, there is no level I evidence to support their widespread use.[1]

Examining the literature. The review yielded 87 articles reporting investigations to evaluate the efficacy of oral doxycycline, minocycline, or azithromycin in managing OSD. Eight studies met the inclusion criteria for use in the final analysis, and each of these demonstrated some therapeutic benefit for the outcomes assessed. But how strong is the supporting evidence? Two of the 8 studies were graded as providing level II evidence, and 6 were graded level III.

"The studies demonstrated at least some utility, and the reported benefits were often quite robust," said committee member Edward J. Wladis, MD, associate professor of ophthalmology, Albany Medical College. He added, however, that further investigations are needed to confirm existing study results and to define the benefits patients may expect to receive for antibiotic therapy.

The dearth of studies for so common a clinical scenario surprised Dr. Wladis. "Hopefully, stronger future studies will provide a clearer road map," he said.

Clinical considerations. For now, he advised doctors to reserve antibiotic use for patients whose MGD has not responded to standard treatments, such as warm compresses and topical lubrication. He also warned doctors to be mindful of side effects in patients with worrisome allergies and comorbidities, such as a history of Stevens-Johnson syndrome or difficult-to-manage anticoagulation.

"Clinicians should have open conversations with their patients regarding possible side effects of these agents and the level of confidence that they should place in them," Dr. Wladis said.

—*Miriam Karmel*

1 Wladis EJ et al. *Ophthalmology*. 2016;123(3):492-496.

Relevant financial disclosures: Dr. Wladis—None.

Quality of Evidence

Level I: Well-conducted randomized controlled trials (RCTs)
Level II: Well-conducted case-control or cohort studies and lower-quality RCTs
Level III: Case series and lower-quality case-control and cohort studies

For the financial disclosure key, see page 8. For full disclosures, including category descriptions, view this News in Review at www.eyenet.org.