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Aflibercept Shows Promise as a Game-Changer for Patients With Age-Related Macular Degeneration

INSIDE THIS ISSUE

A review of preclinical studies, medical literature, and clinical trials of the US Food and Drug Administration (FDA)–approved anti–vascular endothelial growth factor (VEGF) drug aflibercept (eg, Eylea, VEGF Trap-Eye) confirms that the drug promises to deliver excellent visual outcomes for patients with exudative age-related macular degeneration (AMD). "Trial results indicate that patients undergo fewer injections of aflibercept than they would with ranibizumab," says Michael W. Stewart, MD, with the Department of Ophthalmology at Mayo Clinic in Florida and a coauthor of the review article. "With a wholesale cost of $1,850 per dose, the cost per patient for aflibercept treatment also promises to be lower than ranibizumab."

Early Anti-VEGF Agents

Anti-VEGF drugs introduced since 2005 have revolutionized the treatment of exudative AMD by stabilizing and, in many cases, reversing vision loss. Surgeons were enthusiastic about ophthalmologic applications for the 3 FDA-approved anti-VEGF drugs, bevacizumab, pegaptanib, and ranibizumab.

Bevacizumab, a full-length antibody against VEGF, has been used extensively since 2005 for exudative AMD, diabetic retinopathy, retinal vein occlusions, retinopathy of prematurity, and other chorioretinal vascular disorders. Pegaptanib and ranibizumab were developed specifically for intraocular use. After intraocular injection, these drugs reach the systemic circulation in concentrations sufficient to decrease baseline VEGF levels (Figure). Clinical results for all 3 drugs, however, have been mixed and regulatory hurdles, particularly those regarding off-label use of bevacizumab, have been challenging.

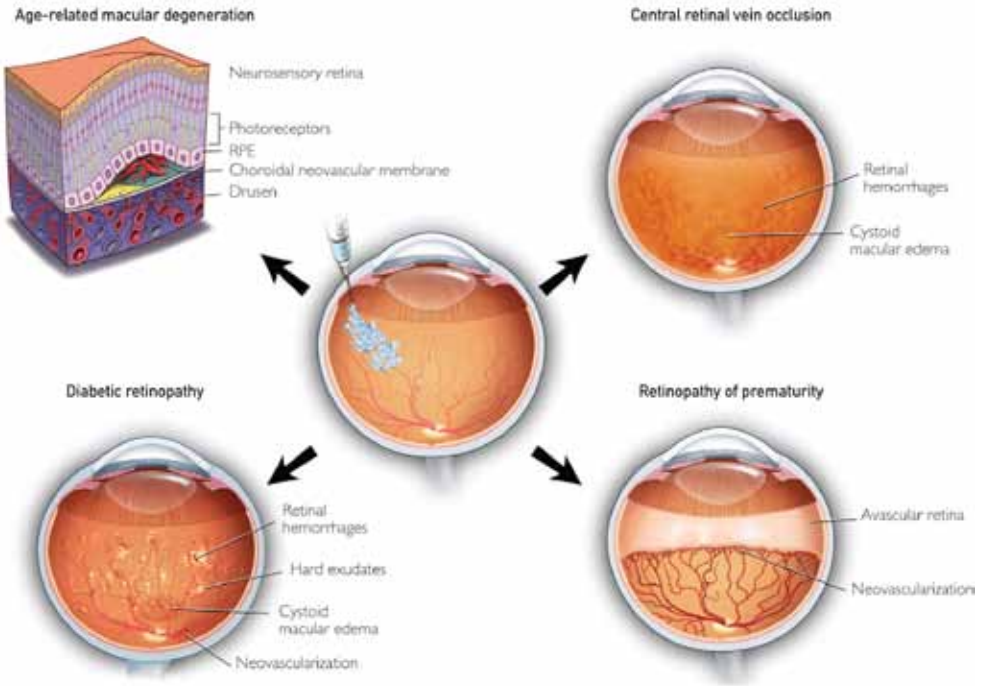

Figure. *The most common indications for intraocular anti–vascular endothelial growth factor (VEGF) injections include exudative age-related macular degeneration, background and proliferative diabetic retinopathy, branch and central retinal vein occlusions, and retinopathy of prematurity. Intraocular anti-VEGF drugs generally work through 2 mechanisms: 1) decreasing vascular permeability, thereby allowing absorption of edema, and 2) decreasing neovascularization, thereby preventing hemorrhages and tissue distortion caused by fibrous proliferation. RPE indicates retinal pigment epithelium. From Stewart MW. "The Expanding Role of Vascular Endothelial Growth Factor Inhibitors in Ophthalmology." Mayo Clin Proc. 2012;87(1):77-88. Used with permission.*

Michael W. Stewart, MD

Aflibercept

Unlike the earlier drugs that were created with antibody technology and bind only to isoforms of VEGF-A, aflibercept is a fusion protein with binding domains from native VEGF receptors that binds VEGF-A, VEGF-B, and placental growth factors 1 and 2 with high affinity.

Preclinical ophthalmologic studies demonstrated that aflibercept suppressed choroidal neovascularization in several animal models. The phase 3 Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration 1 and 2 trials showed that monthly and bimonthly aflibercept treatments were noninferior to monthly ranibizumab at preventing vision loss (<15-letter loss), with comparable vision gains and safety. Year 2 treatment involved monthly pro re nata injections with required injections every 3 months and maintained vision gains from the first year, with an average of 4.2 injections of aflibercept and 4.7 injections of ranibizumab.

The FDA approved aflibercept for the treatment of subfoveal choroidal neovascularization due to AMD in November 2011. "Trial results showed excellent short-term suppression of choroidal neovascularization in patients with exudative AMD and suggest that aflibercept provides more durable outcomes for patients than other anti-VEGF drugs," says Dr Stewart. "Aflibercept seems to offer the effectiveness of the other anti-VEGF agents with less frequent injections and monitoring—a great benefit for patients."

Dr Stewart has received research support from and is on the advisory board of Regeneron Pharmaceuticals, Inc.

Points to Remember

- Aflibercept is a fusion protein with binding domains from native VEGF receptors that binds VEGF-A, VEGF-B, and placental growth factors 1 and 2 with high affinity.
- Aflibercept suppresses choroidal neovascularization in several animal models and was approved by the FDA in November 2011 for the treatment of subfoveal choroidal neovascularization due to AMD.
- Trials showed that monthly and bimonthly aflibercept treatments were noninferior to monthly ranibizumab at preventing vision loss, with comparable vision gains and safety.

For More Information

"Aflibercept for Age-Related Macular Degeneration: A Game-Changer or Quiet Addition?" Browning DJ, Kaiser PK, Rosenfield PJ, Stewart MW. *Amer J Ophthalmol*. 2012:154(2):222-6 www.ajo.com/article/S0002-9394(12)00330-3/abstract

"Aflibercept (VEGF Trap-Eye): The Newest Anti-VEGF Drug." Stewart MW. *Br J Ophthalmol*. Published online first March 23, 2012, bjo.bmj.com/content/early/2012/03/22/bjophthalmol-2011-300654.full?sid=97aa6ac1-eaa9-4bdd-aeb2-672618355c42

"Aflibercept." Stewart MW, Grippon S, Kirkpatrick P. *Nat Rev Drug Discov*. 2012;11(4):269-70. www.nature.com/nrd/journal/v11/n4/full/nrd3700.html

Dendrimers Deliver Drug Therapy to Target Retinal Degeneration

An intracellular, sustained-release drug delivery system offers a new way to treat chronic, progressive retinal degeneration. In a study conducted by researchers at Mayo Clinic in Rochester, Minnesota, Kresge Eye Institute, and The Wilmer Eye Institute at Johns Hopkins, corticosteroids attached to dendrimers were delivered to the retina to target only inflammation-causing microglial cells, leaving the rest of the eye unaffected and preserving vision.

Targeted Drug Delivery

Since the discovery of dendrimers, many studies have examined the role of their unique nanoscale architecture on the delivery of therapeutics and imaging agents. For this study, researchers used hydroxyl-terminated polyamidoamine (PAMAM) dendrimer–drug conjugate nanodevices to explore targeted drug therapy for the attenuation of neuroinflammation in the retina. The type of PAMAM dendrimers used in this study are noncytotoxic and are cleared intact through the urine.

Results showed that on intravitreal administration, PAMAM dendrimers selectively localized within activated outer retinal microglia in 2 rat models of retinal degeneration, but not in the retina of healthy control subjects. This pathology-dependent biodistribution was exploited for drug delivery by covalently conjugating fluocinolone acetonide (FA) to the dendrimer. The conjugates released the drug in

a sustained manner over 90 days.

"Once intracellular enzymes release the steroid medication from the nanoparticle, inflammation is shut down, leaving remaining steroid medications on the particle. When the anti-inflammatory steroid effects wear off, the enzyme systems wake up and cleave off more anti-inflammatory medication from the dendrimer. It's like a sustained-release device inside the cell," says Raymond Iezzi Jr, MD, with the Department of Ophthalmology at Mayo Clinic in Minnesota and lead author of the study.

The conjugates provided significant neuroprotection, preserving photoreceptor health and outer nuclear layer thickness and attenuating neuroinflammation, over an entire month.

The researchers chose FA because it has been previously shown to slow photoreceptor cell loss and dampen retinal neuroinflammation. "The use of FA may also enable eventual comparisons between dendrimer-based delivery and commercial, nonerodible intravitreal implants for the same drug," says Dr Iezzi.

For More Information

"Dendrimer-Based Targeted Intravitreal Therapy for Sustained Attenuation of Neuroinflammation in Retinal Degeneration." Iezzi R, Guru BR, Glybina IV, et al. *Biomaterials*. 2012;33(3):979-88. www.sciencedirect.com/science/article/pii/S0142961211012130. View video at www.youtube.com/watch?v=iFCZXOsI2YQ

Points to Remember

- Neuroinflammation has a key role in the pathogenesis of various neurodegenerative diseases, including retinitis pigmentosa and age-related macular degeneration.
- Polyamidoamine dendrimers (flexible, microscopic particles of repetitively branched molecules) have an intrinsic ability to selectively localize in activated microglia and can deliver drugs inside these cells for a sustained period for the treatment of retinal neuroinflammation.

Raymond Iezzi Jr, MD

Cancer Immunotherapy Eradicates Tumors From Within

A research team at Mayo Clinic in Rochester, Minnesota, has used the immune systems of mice to eradicate cancerous tumors in a genetic combination of human DNA from melanoma cells delivered directly into tumors through the highly immunogenic vector vesicular stomatitis virus (VSV). In early studies, 60% of tumor-burdened mice were cured in less than 3 months and with minimal adverse effects.

In this cancer immunotherapy-based technology, successful tumor eradication is associated with the ability of mouse lymphoid cells to mount a tumor-specific CD4+ interleukin-17 recall response in vitro. The research team used this characteristic response to screen the VSV–complementary DNA (cDNA) library and identified 3 different VSV-cDNA virus clones that, when used in combination but not alone, were as effective in inducing tumor rejection as the complete parental virus library in mice with melanoma.

Future Applications

The research team will use this technology to define repertoires of tumor-associated antigens that work in combination to induce antitumor immune responses for other cancers. The identification of arrays of tumor-associated antigens that cooperate in vivo to cure established tumors may also permit the cloning of antigens that can play a role in the development of cancer vaccines.

Jose S. Pulido, MD, an ocular oncologist at Mayo Clinic in Minnesota, is a coauthor of the study.

For More Information

"Using Virally Expressed Melanoma cDNA Libraries to Identify Tumor-Associated Antigens That Cure Melanoma". Pulido J, Kottke T, Thompson J, et al. *Nat Biotechnol*. 2012;30(4):337-43. www.sciencedirect.com /science/article/pii/S0142961211012130

Points to Remember

- Cancer immunotherapy strategy uses a genetically engineered version of VSV to deliver a broad spectrum of genes derived from melanoma cancer cells directly into tumors.
- Researchers will use this technology to identify combinations of antigens that work to induce antitumor responses for other cancers.
- The identification of arrays of antigens that cooperate to eradicate established tumors will also inform strategies for the development of clinical vaccines.
- A cDNA library is a combination of cloned cDNA fragments inserted into a collection of host cells that together constitute some portion of the set of all RNA molecules produced in 1 cell or a population of cells of the organism.

Jose S. Pulido, MD

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Mayo Medical School Receives RPB Grant

Research to Prevent Blindness (RPB) has awarded a $110,000 grant to the Department of Ophthalmology at Mayo Medical School to support its research into the causes, treatment, and prevention of blinding diseases. “We are honored to receive this grant from RPB,” says Jay C. Erie, MD, department chair. “The funding supports and reinforces our commitment to research that contributes to a greater understanding of blinding diseases.”

Sanjay V. Patel, MD, Named Department of Ophthalmology Chair

Sanjay V. Patel, MD, has been appointed chair of the Department of Ophthalmology at Mayo Clinic in Rochester, Minnesota. Dr Patel, who holds the academic rank of professor, has been a member of the Mayo Clinic consulting staff since 2004 and is board certified by the American Board of Ophthalmology. He has been chair of the Ophthalmology Research Committee since 2009.

A graduate of The University of Nottingham Medical School, Dr Patel also completed residencies in ophthalmology and internal medicine at Mayo Graduate School of Medicine. Dr Patel’s research interests include corneal transparency, corneal and corneal endothelial cell transplantation, and Fuchs endothelial dystrophy. He has authored and coauthored more than 70 publications related to these topics.

Cheryl L. Khanna, MD, Named Ophthalmology Residency Program Director

Cheryl L. Khanna, MD, has been appointed director of the Ophthalmology Residency Program at Mayo Clinic in Rochester, Minnesota. Dr Khanna holds the academic rank of assistant professor. She is a graduate of the Medical College of Wisconsin and the Mayo Graduate School of Medicine and is fellowship trained in glaucoma at University of Iowa Hospital and Clinics.

Dr Khanna is board certified by the American Board of Ophthalmology. Her research interests include standardization of glaucoma care, genetics of glaucoma, surgical outcomes of glaucoma treatment in Olmsted County, Minnesota, and the change in aqueous humor dynamics after cataract extraction.

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Mayo Clinic Retina Update and Case Conference
September 21-22, 2012, Rochester, Minnesota

Current Concepts in Primary Eye Care
November 8, 2012, Rochester, Minnesota

2012 Visiting Faculty/Guest Lecturer Series
If you are interested in receiving advance notice of guest speakers or would like to attend a presentation, please contact Jay C. Erie, MD, at erie.jay@mayo.edu. There is no fee and your visit will include a tour of the department if requested. The lectures may also provide credits in continuing medical education.

October 1, 2012
Stella K. Kim, MD, Associate Professor of Ophthalmology; Adjunct Associate Professor of Radiation Oncology; and Director, Clinical Research in Ophthalmology, The University of Texas MD Anderson Cancer Center, Houston, Texas. Dr Kim will present at the Department of Ophthalmology Grand Rounds from 7:15 to 8:00 AM.

October 8, 2012
Laura L. Wayman, MD, Assistant Professor and Director of Resident Education at Vanderbilt Eye Institute, Vanderbilt University School of Medicine, Nashville, Tennessee, will present 2 lectures at the Department of Ophthalmology Grand Rounds, from 7:15 to 8:00 AM and from 12:00 to 1:00 PM, addressing the improvement of residency programs, faculty burnout, and encouragement of participation.

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