Update on Anti-VEGF Therapy in Diabetic Macular Edema, Neovascular AMD, and Retinal Vein Occlusion

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The Evolving Landscape for Treatment of Diabetic Macular Edema

CONTINUING MEDICAL EDUCATION: 2 CREDITS AVAILABLE
Guest Editor: Thomas A. Albini, MD

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Selected Reports from the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology

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RATIONALE AND PURPOSE
With the aging of the baby-boomer generation and the increase in prevalence of medical conditions related to obesity and advanced age, ophthalmologists are noticing a huge increase in the number of patients presenting with retinal diseases—as well as in the amount of research devoted to their understanding and clinical management. The articles in this issue of The Ophthalmology Report, based on research presented at the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), held May 6–10 in Fort Lauderdale, Florida, focus on new developments in the treatment of neovascular age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), and diabetic macular edema (DME), primarily through the use of novel agents that inhibit vascular endothelial growth factor (VEGF).

The authors discuss important clinical trials, some of which are still ongoing, that evaluated the efficacy and safety of intravitreal therapy with various VEGF inhibitors (ranibizumab, bevacizumab, and aflibercept) in different doses, dosing schedules (monthly versus needed), and lengths of time. Among other topics covered in this report are the use of anti-VEGF therapy to reduce visual impairment and prevent legal blindness, steroid treatment of neovascular AMD using a dexamethasone intravitreal implant, focal/grid macular laser therapy of DME, differences in retinal morphology among patients with neovascular AMD, and the prediction of patient response to ranibizumab.

The articles in this issue, written from the academic perspective of physicians-in-training at leading medical centers, summarize the import of these new findings and place them into clinical context. This activity has been developed and approved by a planning committee of nationally recognized thought leaders to meet a perceived educational need to provide ophthalmologists and other physicians with diagnostic and therapeutic strategies to help them perform their medical roles.

LEARNING OBJECTIVES
After studying this issue of The Ophthalmology Report, participants in this educational activity should be able to:

• Justify the use of VEGF inhibitors and other therapies in patients with DME.
• Review the efficacy and safety of VEGF inhibitor therapy of neovascular AMD at different doses and when given monthly versus as needed.
• Summarize the data from the CATT and IVAN trials comparing bevacizumab with ranibizumab in patients with neovascular AMD.
• Describe the results of clinical trials of VEGF inhibition in treating branch and central RVO.

TARGET AUDIENCE
Ophthalmologists and other physicians significantly involved in the diagnosis and management of retinal disease should find participating in this educational activity valuable.

ACCREDITATION AND CREDIT DESIGNATION
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Cincinnati and Direct One Communications, Inc. The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians.

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To receive credit, participants must read the CME information on these two pages, including the learning objectives and disclosure statements, as well as the full content of this monograph, and then complete the post test and evaluation form online at www.TheOphthalmologyReport.com. Upon successful completion of the post test (80% correct) and evaluation form, a CME certificate of participation will be awarded automatically. The certificate may be printed directly from the Web site or e-mailed and printed later.

There are no fees for participating in or receiving credit for this activity.

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Although bevacizumab has not been approved by the FDA for the treatment of any ophthalmic indication, in this issue of The Ophthalmology Report, Drs. Chang, Daniels, and Witmer describe studies that compared bevacizumab with ranibizumab in treating patients with neovascular AMD, and Dr. Shah refers to clinical trials of bevacizumab therapy in patients with DME. Dr. Shah also describes the investigational use of aflibercept in the treatment of DME.

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Introduction

Selected Reports from the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO)

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Age-related macular degeneration (AMD), retinal vein occlusion (RVO), and diabetic macular edema (DME) are all-too-prevalent diseases of the retina that share a common pathology—the leakage of fluid from damaged blood vessels into the macula—and are major causes of blurred vision, severe vision loss, and blindness.

The theme of the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), held in Fort Lauderdale, Florida, May 6–10, 2012, was “Translational Research: Seeing the Possibilities.” Over 12,500 attendees from around the world participated in workshops, lectures, and panel discussions that promoted collaboration between basic and clinical sciences. Many speakers explored ways that basic research translates to the effective diagnosis and treatment of patients presenting with ophthalmic pathology and to prevention of these diseases.

This edition of The Ophthalmology Report focuses on AMD, RVO, and DME and elaborates on the current state of the art in their treatment, showing just how far we have come in translating basic research into clinical practice.

Jonathan S. Chang, MD, from the Bascom Palmer Eye Institute at the University of Miami, shares insights from a panel discussion on the use of vascular endothelial growth factor (VEGF) inhibitors to treat retinal disease. Dr. Chang summarizes the results of recent clinical trials comparing dosing schedules for administering anti-VEGF therapies; choices of agents for treating particular conditions; the use of corticosteroids and laser therapy in patients affected by RVO and DME, and the safety of intravitreal injection of VEGF inhibitors in patients with RVO, DME, and neovascular AMD.

The much-awaited findings of two multicenter, randomized clinical trials that compared the safety and efficacy of the VEGF inhibitors ranibizumab and bevacizumab in patients with exudative AMD are discussed by Matthew T. Witter, MD, from Weill Cornell Medical College in New York. He reviews 2-year findings from the Comparison of AMD Treatments Trial (CATT) and 1-year findings from the Inhibition of VEGF in Age-Related Choroidal Neovascularization (IVAN) trial, which were revealed for the first time at the 2012 ARVO meeting. Findings from these trials certainly add much to our understanding of the safety, efficacy, and cost-efficiency of these alternative treatments.

As diabetes becomes more and more prevalent in the United States and throughout the world, so too is DME as a result of diabetic retinopathy. Rajiv Shah, MD, from the Wills Eye Institute in Philadelphia, summarizes the results of past and current clinical trials that sought to predict the success of bevacizumab therapy administered to one or both eyes of DME patients, to test various doses of ranibizumab injected on different schedules, and to compare the use of ranibizumab or laser therapy alone or with combination therapy. In addition, Dr. Shah discusses clinical studies evaluating the potential of dexamethasone intravitreal implants and aflibercept in patients with DME.

Information from this year’s ARVO meeting surely will impact greatly how we treat retinal disease. We await the results from ongoing trials to add to our understanding of the etiology, diagnosis, and treatment of retinal disease.
Update on Anti-VEGF Therapy in Diabetic Macular Edema, Neovascular AMD, and Retinal Vein Occlusion

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Abstract The approval of vascular endothelial growth factor (VEGF) inhibitors has revolutionized the treatment of age-related macular degeneration, retinal vein occlusions, and diabetic macular edema. At a panel discussion held during the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), experts in retinal disease discussed recently reported findings on the use of VEGF inhibitors to treat pathologies of the retina. In addition, speakers compared these novel agents with conventional therapies and summarized differences in efficacy observed using different treatment schedules.

Use of anti-vascular endothelial growth factor (anti-VEGF) agents has become a mainstay in treating several common retinal diseases. Initially used to manage neovascular age-related macular degeneration (AMD),1-3 the value of this drug class recently was affirmed for treating both branch retinal vein occlusion (BRVO)4 and central retinal vein occlusion (CRVO).1 Further clinical data support their use in managing diabetic macular edema (DME).5

Ranibizumab has been approved by the US Food and Drug Administration (FDA) to treat patients with neovascular AMD; for macular edema following retinal vein occlusion (RVO); and, very recently (August 2012), for DME. Aflibercept (VEGF Trap-Eye) also is approved by the FDA for treating neovascular AMD. In addition, bevacizumab is widely used as an off-label therapy for these conditions. These agents have revolutionized the way that retina specialists address these chronic ophthalmic diseases.

Several recent studies offered additional insight into the use of anti-VEGF agents. The READ 3,7 RISE,8 and RIDE8 trials involved the use of ranibizumab in patients with DME, and the DA VINCI trial9 demonstrated the effect of aflibercept therapy in this population. In treating AMD, the 2-year results of the CATT trial,10 which compared use of bevacizumab with ranibizumab therapy, were reported. Investigators involved in the VIEW 1 and VIEW 2 studies11 reported on the use of aflibercept in patients with neovascular AMD. The management of RVO changed after analysis of the CRUISE4 and BRAVO5 study results, and further information has been gathered in the HORIZON study.12 However, questions about the management of patients diagnosed with retinal disease remain.

During the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), held in Fort Lauderdale, Florida, a special interest group discussion panel explored several issues involving the use of VEGF inhibitors. Speakers addressed questions about monthly versus as-needed dosing, the choice of an anti-VEGF agent for treating each condition, corticosteroid and laser therapy in patients affected by RVO and DME, and the safety of intravitreal injections of VEGF inhibitors. Participants in this panel discussion included Quan Dong Nguyen, MD, MSc, of the Division of Diseases of the Retina and Uveitis at the Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland; David M. Brown, MD, FACS, of Retina Consultants of Houston, Houston, Texas; Peter A. Campochiaro, MD, of the Division of Ophthalmology and Neuroscience at the Wilmer Eye Institute; Diana Van Do, MD, Associate Professor of Ophthalmology at the Wilmer Eye Institute; and Jeffrey S. Heier, MD, Co-Director of the Tufts/Ophthalmic Consultants of Boston Vitreoretinal Fellowship at Massachusetts General Hospital, Boston, Massachusetts.

DIABETIC MACULAR EDEMA

VEGF is believed to be involved in the development of macular edema and diabetic retinopathy. In the Diabetic Retinopathy Clinical Research Network

Dr. Chang is a Surgical Retina Fellow at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida.
Ranibizumab Dosage

The RISE4 and RIDE4 trials were two parallel studies comparing the use of 0.3 or 0.5 mg of ranibizumab given monthly with sham therapy for DME. In the RIDE trial, patients using 0.3- and 0.5-mg ranibizumab doses gained 8.6 and 9.7 letters of visual acuity, respectively. Similar results were reported in the RISE trial, with patients given the 0.3-mg dose gaining 10.0 letters and those given the 0.5-mg dose gaining 9.3 letters. Patients receiving ranibizumab at either dose level demonstrated improvement in visual acuity and retinal thickness after 2 years. In addition, the level of diabetic retinopathy increased intraocular pressure. Corticosteroid therapy continues to develop new options for treatment in the coming years.

Drug Therapy vs Laser Treatment

The BOLT study15 recently compared the use of bevacizumab with focal laser therapy. Patients with DME were randomized to groups receiving either bevacizumab or macular laser therapy and were followed for 2 years. Patients in the bevacizumab group gained a mean of 8.6 letters, whereas the macular laser therapy group lost a mean of 0.5 letters. Central foveal thickness also was reduced in the bevacizumab group as compared with the laser treatment group.

Results from the DA VINCI trial9 demonstrated improvement in the eyes of patients with DME who used aflibercept as compared with patients who underwent focal laser therapy. Many ophthalmologists prefer to administer treatment at regular intervals instead of as needed in patients affected with a chronic process like DME. Persistent edema appears to be more common among patients with DME than in those with neovascular AMD, even in eyes treated regularly; further, the clinician’s threshold for residual edema may be greater, because the two diseases have different natural histories.

Because patients with DME tend to be young, they may receive a considerable number of injections over their lifetime; in addition, frequent office visits can interrupt their daily lives. To that end, the current VIVID-DME (ClinicalTrials.gov NCT01331681) and VISTA DME (ClinicalTrials.gov NCT01363440) trials are examining use of a loading dose of aflibercept every month for 6 months followed by dosing every 6 months. Data on these phase III trials should be available in the coming years.

Corticosteroid Therapy

Corticosteroid therapy continues to be an option for patients with DME, although it tends to be used now in individuals who do not respond to anti-VEGF treatment. Increased intraocular pressure and cataracts continue to be the main adverse effects related to the use of corticosteroids.

Recently, the FAME trial16 examined the use of a flucinolone acetonide implant in patients with DME. The results demonstrated efficacy with both a 0.2 and 0.5 µg/d implant. At 2 years, 28.7% of patients receiving 0.2 µg/d and 28.6% of patients receiving 0.5 µg/d of flucinolone acetonide demonstrated a greater than 15-letter improvement in visual acuity, as compared with 16.2% of the sham treatment group (P = 0.002 for each). In all, 62% of patients receiving 0.2 µg/d of the drug did not require treatment for increased intraocular pressure.

The FDA has not approved the use of flucinolone acetonide implants for treating DME because of insufficient safety data; however, marketing of the implant for this indication is approved in Europe. In selected patients, corticosteroid treatment remains an option.

NEOVASCULAR AMD

AMD is the leading cause of blindness in the United States and in other developed countries. During the past few months, data from several large trials have impacted treatment options. Use of ranibizumab for neovascular (exudative) AMD was first reported in the MARINA2 and ANCHOR3 studies. Frequency of ranibizumab dosing has been examined in the PIER,19 PrONTO,18 SUSTAIN,20 EXCITE,21 and HORIZON22 trials. As anti-VEGF treatment alternatives have expanded, ophthalmologists now have three options: ranibizumab, off-label bevacizumab, and aflibercept.

The VIEW Trials

Results from the VIEW 1 and VIEW 2 trials, which compared the use of aflibercept with ranibizumab therapy for exudative AMD, were reported recently. These parallel, noninferiority trials randomized 1,217 patients from North America to one of four treatment groups: 0.5 mg of ranibizumab monthly, 0.5 mg of aflibercept monthly, 2 mg of aflibercept monthly, or three monthly 2-mg aflibercept injections given as a loading dose followed by 2 mg of aflibercept every 2 months.

In 94%–96% of patients, moderate vision loss was prevented. The three aflibercept groups had results that were noninferior to those observed in the ranibizumab group. Patients receiving 2.0 mg of aflibercept monthly experienced a 10.9-letter gain as compared with an 8.1-letter gain observed in patients given monthly ranibizumab; this difference was statistically significant.

The VIEW 2 trial enrolled 1,240 patients in Europe, Asia, and Latin America and had outcomes similar to those of the VIEW 1 trial. Both studies had adverse event rates that were similar to each other and to those of prior studies of anti-VEGF
therapy. Aflibercept may be an option in patients who do not respond well to ranibizumab or bevacizumab.

The CATT Trial

Two-year results of the CATT trial, a study funded by the National Eye Institute, recently were presented at the 2012 ARVO meeting. A total of 1,185 patients with neovascular AMD were randomly assigned to one of four treatment groups: 0.5 mg of ranibizumab monthly, 1.25 mg of bevacizumab monthly, 0.5 mg of ranibizumab as needed, and 1.25 mg of bevacizumab as needed. The as-needed groups were seen every 4 weeks and received injections when new fluid was present on optical coherence tomography (OCT), new or persistent hemorrhage occurred, or decreased visual acuity or new leakage was seen on fluorescein angiography. After 1 year, the monthly groups were divided into monthly and as-needed treatment cohorts for 1 year.

After 2 years of therapy, the monthly ranibizumab group demonstrated a gain of 8.8 letters, the monthly bevacizumab group gained 7.8 letters, the ranibizumab as-needed group gained 6.7 letters, and the bevacizumab as-needed group gained 5 letters. Patients receiving monthly injections gained 2.4 letters more than did those given ranibizumab or bevacizumab as needed (P = 0.046). Mean retinal thickness on OCT was 29 μm less in the monthly treatment groups than in patients receiving ranibizumab or bevacizumab as needed; this difference also was statistically significant. No evidence of fluid was found on OCT in 45.5% of the monthly ranibizumab group, 30.2% of the monthly bevacizumab group, 22.3% of the as-needed ranibizumab group, and 13.9% of the as-needed bevacizumab group. Over 2 years, the mean number of injections in the monthly ranibizumab and bevacizumab groups was 22.4 and 23.4, respectively. The as-needed ranibizumab and bevacizumab groups received a mean of 12.6 and 14.1 injections, respectively.

Based on the results of the CATT trial, there is a 2.4-letter difference between monthly dosing and as-needed dosing in patients with neovascular AMD. The results also affirmed the effectiveness of off-label bevacizumab in treating neovascular AMD. It is not known whether differences in results between groups given monthly or as-needed dosing would increase further after 2 years; however, given that many patients with neovascular AMD are treated for longer than 2 years, clinicians are greatly interested in the long-term effects of therapy.

Geographic atrophy increased in the monthly dosing groups when compared with the as-needed dosing groups. It is not clear whether this finding is related to improved visualization of geographic atrophy due to a decreased amount of fluid or to a process associated with chronic anti-VEGF therapy. However, geographic atrophy is a factor to consider in future trials of VEGF inhibitors, and other imaging may be useful in this regard. The study also did not address the efficacy of the commonly used “treat-and-extend” protocol for administering ranibizumab or bevacizumab.

Elsewhere in this issue of The Ophthalmology Report, Matthew T. Witmer, MD, takes a closer look at the 2-year data emerging from the CATT study and the first-year results of a parallel comparative study, IVAN, being conducted in the United Kingdom.

SAFETY OF ANTI-VEGF THERAPY

With the increased use of anti-VEGF therapy in ophthalmology, safety in terms of intraocular and systemic adverse effects continues to be of interest. In recent clinical trials evaluating VEGF inhibition in patients with DME, exudative AMD, or RVO, endophthalmitis occurred in about 1% of patients, about the same frequency as reported in prior studies. As previously mentioned, increased geographic atrophy has been observed in patients with neovascular AMD receiving monthly injections of ranibizumab or bevacizumab; however, this finding has not been reported in patients who were treated with VEGF inhibitors for DME or RVO. It is not clear whether this increase in geographic atrophy is directly related to anti-VEGF therapy.

Systemic adverse effects in patients with neovascular AMD previously were evaluated in the SAILOR trial. In the CATT trial, 39.9% of the bevacizumab group and 31.7% of those receiving ranibizumab developed one or more serious effects in patients with DME, exudative AMD, or RVO, endophthalmitis occurred in about 1% of patients, about the same frequency as reported in prior studies. As previously mentioned, increased geographic atrophy has been observed in patients with neovascular AMD receiving monthly injections of ranibizumab or bevacizumab; however, this finding has not been reported in patients who were treated with VEGF inhibitors for DME or RVO. It is not clear whether this increase in geographic atrophy is directly related to anti-VEGF therapy.

Systemic adverse effects in patients with neovascular AMD previously were evaluated in the SAILOR trial. In the CATT trial, 39.9% of the bevacizumab group and 31.7% of those receiving ranibizumab developed one or more serious
systemic adverse events, a statistically significant difference \( (P = 0.004).\) Serious adverse events included death (6.1% for bevacizumab vs 5.3% for ranibizumab), arterial thrombotic events (5.0% vs 4.7%), venous thrombotic events (1.7% vs 0.5%), and hypertension (0.7% vs 0.5%). The data were statistically significant for overall systemic effects, but they were difficult to evaluate in the aging population and did not affect selection of VEGF inhibitors.

**CONCLUSION**

The use of anti-VEGF therapy continues to be a mainstay of medical retina therapy. With further study and an increasing number of agents available, more information about the frequency of dosing, the selection of agents, and the long-term effects of these agents in patients with DME, AMD, and RVO is becoming available. Increased use of these agents also has led to questions about their efficacy and safety, frequency of treatment, the possible application of “treat-and-extend” therapy, and the potential role of corticosteroid implants in treating DME and RVO. A better understanding of the VEGF pathways and ways that VEGF affects normal physiology also will increase our knowledge of these diseases.

In DME, there appears to be a role for anti-VEGF agents. Regular monthly injections of these agents seem to produce greater benefit than does as-needed dosing, but the long-term management of DME patients still is not fully understood. Recent data from several large AMD trials demonstrated the efficacy of aflibercept and validated the off-label use of bevacizumab for neovascular AMD, albeit at the risk of a greater frequency of serious systemic adverse events when compared with ranibizumab. Monthly dosing also appeared to produce better outcomes in AMD than did as-needed dosing.

For RVO, anti-VEGF agents have changed treatment planning from observation to earlier intervention; further investigation is needed to determine long-term treatment strategies for these patients. Recent trials have not demonstrated any higher frequency of adverse systemic effects or additional adverse events from VEGF-inhibitor therapy. Future studies will supply greater details on the safety and efficacy of these agents and optimal dosing schedules.

**REFERENCES**

Treatment of Exudative AMD: Data from the CATT and IVAN Trials

Matthew T. Witmer, MD
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Abstract The latest results of two prospective, randomized clinical trials comparing the use of ranibizumab and bevacizumab in treating patients with exudative age-related macular degeneration (AMD) were presented at the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO). The Comparison of AMD Treatments Trial (CATT) and the Inhibition of VEGF in Age-Related Choroidal Neovascularization (IVAN) trial were designed to examine and compare the safety and effectiveness of these medications. The 2-year results from the CATT and 1-year results from the IVAN trial have clinical and financial implications for the treatment of exudative AMD.

The use of monoclonal antibodies specific for vascular endothelial growth factor (VEGF) has dramatically improved the treatment of exudative (also known as “neovascular” or “wet”) age-related macular degeneration (AMD).

Bevacizumab is a 149-kD humanized monoclonal antibody that inhibits VEGF-A, a signal protein that stimulates angiogenesis and vasculogenesis in AMD. Intended for use in the management of various cancers, bevacizumab has been shown to decrease retinal thickness and improve visual acuity in patients with exudative AMD.1,2

Ranibizumab is a 48-kD monoclonal antibody fragment (also referred to as an “Fab fragment”) that inhibits VEGF and is specifically formulated for intravitreal use. After several clinical trials demonstrated that intraocular administration of ranibizumab dramatically improved the visual acuity of patients with exudative AMD with minimal side effects, this monoclonal antibody was approved by the US Food and Drug Administration for the treatment of neovascular AMD.3,4 However, with the price of ranibizumab exceeding that of bevacizumab by almost 40-fold, bevacizumab continues to be used frequently to treat exudative AMD, albeit off-label.

Questions about the efficacy and safety of these two medications in relation to one another have remained. The Comparison of AMD Treatments Trial (CATT) and the Inhibition of VEGF in Age-Related Choroidal Neovascularization (IVAN) study were designed to compare the efficacy and safety of bevacizumab and ranibizumab treatment in a head-to-head, multicenter, randomized clinical trial.

CATT TRIAL

Based on a presentation by Daniel F. Martin, MD, Chairman, Cleveland Clinic Cole Eye Institute, Cleveland, Ohio

The CATT trial is a multicenter, prospective, noninferiority, clinical trial funded by the National Eye Institute to evaluate the safety and efficacy of ranibizumab or bevacizumab in the treatment of exudative AMD.3 The trial began in February 2008 and initially enrolled 1,208 patients with neovascular AMD at 44 clinical centers within the United States.

Recruitment for the CATT trial occurred from February 2008 through December 2009. Eligibility requirements included age ≥ 50 years, presence of previously untreated choroidal neovascularization (CNV) in one eye, and visual acuity between 20/25 and 20/320 in the affected eye. CNV needed to be identified by leakage with fluorescein angiography (FA) and demonstrated fluid (intraretinal, subretinal, or sub-retinal pigment epithelial) on optical coherence tomography (OCT). The presence of CNV, fluid, or hemorrhage needed to be located underneath the fovea.

The CATT trial had four primary treatment arms: (1) 0.5 mg of ranibizumab administered monthly; (2) 0.5 mg of ranibizumab administered as needed; (3) 1.25 mg of bevacizumab given monthly; or (4) 1.25 mg of bevacizumab given as needed. In the as-needed groups, patients were evaluated monthly with OCT. FA was repeated at the physician’s discretion. The decision to treat the as-needed groups was determined by the presence of active neovascularization, defined as fluid visualized with OCT, new or persistent hemorrhage, decreased visual acuity as compared with the previous examination, or dye leakage or increase in lesion size on FA. Administration of only the first intravitreal injection was mandated in the as-needed group.

The primary outcome measure of the CATT trial was the mean change in visual acuity at 1 year. A five-letter difference in visual acuity used to determine noninferiority of the medications was decided at the beginning of the trial. The secondary outcome measures were the number of injections given to the as-needed treat-
ment groups, a three-line change in visual acuity (equivalent to 15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters), a change in subretinal and intraretinal fluid on OCT, a change in lesion size on FA, the incidence of ocular side effects (eg, endophthalmitis) and other adverse events, and cost.

One-Year Study Results

In May 2011, the authors of the CATT trial reported 1-year study results. These results included data from 43 clinical centers with 1,185 patients; one study center with 23 patients did not comply with the protocol and was not included in the data set.

Efficacy. The 1-year results revealed that, when administered monthly, bevacizumab was noninferior to ranibizumab in terms of the primary outcome (mean change in visual acuity). Patients given monthly ranibizumab gained a mean of 8.5 letters, whereas those given monthly bevacizumab gained a mean of 8.0 letters. When given the drugs as needed, patients receiving ranibizumab gained 6.8 letters and those receiving bevacizumab gained 5.9 letters. A comparison of bevacizumab or ranibizumab given monthly with bevacizumab given as needed, however, yielded inconclusive results, since the confidence interval of those two comparisons exceeded a five-letter difference. However, results with ranibizumab given as needed were equivalent to those obtained with bevacizumab given monthly.

In terms of secondary outcomes after 1 year, there was no significant difference among all study groups in terms of the number of eyes that lost or gained ≥ 15 letters of visual acuity. Patients randomized to as-needed treatment with bevacizumab received more injections (mean, 7.7) than did those given as-needed ranibizumab (mean, 6.9). The mean decrease in central retinal thickness was greater in the monthly ranibizumab group than in the as-needed bevacizumab group (196 μm vs 152 μm, respectively). There was a significantly higher percentage of eyes without fluid seen on OCT with ranibizumab therapy than with bevacizumab therapy at 1 month (27.5% vs 17.3%). There also was a difference in the percentage of eyes that had an absence of fluid on OCT at 1 year, with 43.7% of eyes in the monthly ranibizumab group and 19.2% of eyes in the as-needed bevacizumab group being free of fluid on OCT. Analysis of FA results showed the lesions to be slightly larger in the as-needed treatment groups than in the monthly dosing groups.

Safety. Analysis of adverse events revealed no difference in the rates of ocular side effects (eg, endophthalmitis) between the groups of patients taking either medication for 1 year. The rates of death, arterial thrombotic events (ATEs), venous thrombotic events, myocardial infarction, and stroke also were similar among patients taking ranibizumab or bevacizumab. However, there was a greater incidence of serious systemic adverse events (mostly hospitalizations) in the bevacizumab group than in the ranibizumab group (24.1% vs 19.0%). Specifically, among those receiving bevacizumab, there was a higher rate of patients with gastrointestinal (GI) disorders (P = 0.02). There was no increase in adverse events in the groups receiving bevacizumab or ranibizumab once a month compared with the groups treated with these drugs as needed.

Cost. There was a substantial difference in the cost of the medications, with ranibizumab being significantly more expensive than bevacizumab. Ranibizumab costs about $1,950 per dose, compared with $50 for one dose of bevacizumab. The difference in the total cost of treatment throughout 1 year was magnified in the monthly treatment groups versus the as-needed groups.

Thus, when given along the same schedule, use of ranibizumab or bevacizumab yielded equivalent effects on visual acuity after 1 year of therapy. In addition, when ranibizumab was given on an as-needed basis, the effects on visual acuity were the same as when the drug was administered monthly.

Two-Year Study Results

In the second year of the CATT study, patients initially randomized to receive monthly injections of ranibizumab or bevacizumab were re-randomized to monthly or as-needed dosing without changing the treatment drug. Patients continued to be evaluated every 4 weeks regardless of their study group.

A total of 1,107 of the 1,185 patients from the first year were followed for 2 years. Of 284 patients in the monthly ranibizumab group, 146 patients continued monthly therapy and 138 were switched to as-needed ranibizumab. Of 266 patients initially receiving monthly bevacizumab, 135 patients remained on monthly bevacizumab and 131 were switched to receive the drug as needed.

Efficacy. Regarding the primary outcome (mean change in visual acuity), no statistical difference between ranibizumab and bevacizumab therapy was found after 2 years (Figure 1). The mean increase in visual acuity from baseline was 8.8 letters in the monthly ranibizumab group, 7.8 letters in the monthly bevacizumab group, 6.7 letters in the ranibizumab as-needed group, and 5.0 letters in the bevacizumab as-needed group. In most cases, greater improvement in visual acuity occurred during the first year than it did during year 2. However, the mean gain in visual acuity was 2.4 letters greater for those dosed on a monthly basis than for those given the drug as needed (Figure 1). Mean visual acuity was similar among all treatment groups at the end of 2 years of treatment. The percentage of patients finishing the study with a visual acuity ≥ 20/20 or ≤ 20/200 also was similar among all four groups.

When evaluating the secondary outcomes, patients receiving bevacizumab as needed required more injections than did those receiving ranibizumab as needed (14.1 vs 12.6). There was a large difference in the proportion of patients demonstrating an absence of fluid on OCT at 2 years, with 45.5% being fluid-free in the monthly ranibizumab group and 13.9% being fluid-free in the bevacizumab as-needed group. In addition, mean retinal thickness was significantly smaller in the patients treated monthly than in those treated as needed.

The authors also evaluated a switch in dosing regimens from monthly to
Treatment of Exudative AMD: Data from the CATT and IVAN Trials

Matthew T. Witmer, MD

Mean change in visual acuity score from baseline (number of letters)

FIGURE 1 Mean change in visual acuity among the four treatment groups in patients that were treated with the same dosing regimen throughout the 2 years of the Comparison of Age-Related Macular Degeneration Treatments Trial (CATT). Adapted, with permission, from Martin et al.6

Ranibizumab

Mean change in visual acuity score from baseline (number of letters)

Bevacizumab

Mean change in visual acuity score from baseline (number of letters)

FIGURE 2 Mean change in visual acuity throughout the Comparison of Age-Related Macular Degeneration Treatments Trial (CATT) in patients grouped by dosing regimen: monthly, as needed, or switched from monthly to as-needed dosing at year 1 (left, ranibizumab; right, bevacizumab). The improvement in mean gain in visual acuity in patients administered monthly medication versus as-needed medication for the first year was lost when these patients were switched to as-needed dosing in year 2. Adapted, with permission, from Martin et al.6
ranibizumab group (31.7%; Figure 4). As in the first year of the trial, the rate of GI disorders in patients given bevacizumab was higher than among those given ranibizumab. There was no difference in ocular-related adverse events, such as endophthalmitis, in either drug group. However, 10 of the 11 cases of endophthalmitis occurred in the groups receiving bevacizumab or ranibizumab monthly.

**Cost.** Two-year costs varied from $705 in the as-needed bevacizumab group to $44,800 in the monthly ranibizumab group.

**Summary.** Two-year data from the CATT study tended to confirm the 1-year finding that the effects of ranibizumab and bevacizumab are similar in terms of mean changes in visual acuity. However, there were several statistically significant differences in outcomes between ranibizumab and bevacizumab, particularly in the incidence of adverse events that favor ranibizumab (Table 1), and between monthly and as-needed dosing of each drug (Table 2).

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**FIGURE 3** Mean change in total foveal thickness in patients grouped according to medication and dosing regimen (left, ranibizumab; right, bevacizumab). The difference in the decrease of retinal thickness seen in patients administered monthly medication versus as-needed dosing in year 1 was lost when these patients were switched to as-needed dosing in year 2. Adapted, with permission, from Martin et al.6

**FIGURE 4** Kaplan-Meier analysis demonstrating the proportion of patients in the Comparison of Age-Related Macular Degeneration Treatments Trial (CATT) with serious systemic adverse events as a function of time by medication administered. Adapted, with permission, from Martin et al.6
TABLE 1  
CATT Trial 2-Year Results: Ranibizumab vs Bevacizumab

- Treatment with either ranibizumab or bevacizumab resulted in a similar mean improvement in visual acuity ($P = 0.21$).
- A higher percentage of patients on monthly ranibizumab therapy, compared with those on monthly bevacizumab, had no evidence of fluid leakage on OCT ($P = 0.0003$).
- Monthly ranibizumab therapy resulted in a greater decrease in the mean size of the CNV lesion, as determined by FA, than did monthly treatment with bevacizumab ($P = 0.006$).
- Patients given ranibizumab as needed required fewer injections (mean, 12.6) than did patients receiving bevacizumab as needed (mean, 14.1; $P = 0.01$).
- Patients receiving bevacizumab were 1.30 times more likely to have a serious systemic adverse event than those treated with ranibizumab ($P = 0.005$).
- Ranibizumab therapy led to fewer gastrointestinal tract reactions than did bevacizumab therapy ($P = 0.005$).
- Treatment with either ranibizumab or bevacizumab resulted in similar rates of death ($P = 0.62$), arterial thrombotic events ($P = 0.89$), and venous thrombotic events ($P = 0.054$).
- Ranibizumab therapy was significantly more expensive than bevacizumab therapy.

CATT = Comparison of Age-Related Macular Degeneration Treatments Trial; OCT = optical coherence tomography; CNV = choroidal neovascularization; FA = fluorescein angiography
Source: Martin et al

TABLE 2  
CATT Trial 2-Year Results: Monthly vs As-Needed Dosing

- Visual activity improved more with monthly dosing than with as-needed dosing ($P = 0.046$).
- Mean foveal thickness on OCT decreased more with monthly dosing than with as-needed dosing ($P = 0.046$).
- A higher percentage of patients were fluid-free on OCT with monthly rather than as-needed dosing ($P < 0.0001$).
- A higher percentage of patients had no evidence of fluid leakage on FA with monthly rather than as-needed dosing ($P = 0.002$).
- Monthly dosing resulted in smaller CNV lesions on FA when compared with as-needed dosing ($P = 0.0003$).
- The risk of having a serious systemic adverse event tended to be less with monthly rather than as-needed dosing ($P = 0.08$).
- The risk of developing new geographic atrophy lesions was higher with monthly rather than as-needed dosing ($P = 0.007$).
- The majority of patients (91%) who developed endophthalmitis were receiving monthly injections.
- Switching from monthly to as-needed dosing at 1 year significantly decreased mean visual acuity (mean, −2.2 letters; $P = 0.03$) and the proportion of eyes without fluid on OCT ($P < 0.0001$).
- Switching from monthly to as-needed dosing at 1 year yielded a change in mean visual acuity similar to that observed in patients randomized to as-needed treatment from the beginning of the trial.

CATT = Comparison of Age-Related Macular Degeneration Treatments Trial; OCT = optical coherence tomography; FA = fluorescein angiography; CNV = choroidal neovascularization
Source: Martin et al

IVAN TRIAL

Based on a presentation by Usha Chakravarthy, MD, Professor, Department of Ophthalmology and Vision Sciences, Queen’s University, and Consultant and Directorate, Department of Ophthalmology, Royal Victoria Hospital, Belfast, Ireland, UK

The IVAN trial is an ongoing head-to-head comparison of the efficacy and safety of bevacizumab and ranibizumab in patients with exudative AMD.

The study is being conducted at 23 clinical centers in the United Kingdom and is sponsored by the National Institute for Health Research. The investigators had a target of 600 patients for enrollment, with only one eye per patient included in the study. The primary outcome is best corrected visual acuity after 2 years of treatment; an interim analysis was slated for 1 year. The data will be analyzed on an intention-to-treat basis, with a threshold of 3.5 letters used to determine noninferiority (as opposed to the 5-letter criterion used in the CATT study). The secondary outcomes to be measured include near visual acuity, reading speed, contrast sensitivity, characteristics of the CNV lesion on FA, presence of fluid and retinal thickness on OCT, serum VEGF levels, cost, and quality of life; ocular and systemic safety data also will be analyzed.

A computer-generated system randomized the patients to one of four treatment groups: (1) 0.5 mg of ranibizumab monthly (continuous dosing); (2) 1.25 mg of bevacizumab monthly (continuous dosing); (3) 0.5 mg of ranibizumab monthly for the first 3 months, followed by an interruption in treatment with monthly review to detect disease relapse/progression (discontinuous dosing); or (4) 1.25 mg of bevacizumab monthly for the first 3 months, followed by an interruption in treatment with monthly review to detect disease relapse/progression (discontinuous dosing).

Unlike the CATT trial, all patients in the IVAN study received three injections of the anti-VEGF medication at the outset of the trial. Patients subsequently were followed monthly; if they met retreatment criteria, they once again were given three monthly doses of their assigned medication for 3 months. There was no limit to the number of cycles of treatment that could be given. The retreatment criteria included the presence of subretinal fluid, an increase in intraretinal fluid, persistent intraretinal fluid with a decrease in visual acuity, or the presence of fresh blood in the CNV lesion.

One-Year Study Results

Primary outcome. The 1-year results included data from 693 patients. The mean change in visual acuity across all four treatment groups was similar, with improvements of between one and two lines on a standard vision test for all groups. Continuous monthly doses of bevacizumab yielded a mean change in visual acuity that was 0.2 letters worse than that noted with continuous monthly doses.
of ranibizumab. Given the confidence intervals of these analyses, however, the difference between the two medications in terms of visual acuity was characterized by the investigators as inconclusive. When comparing the discontinuous use of both drugs with their continuous use, the mean change in visual acuity was determined to be equivalent. However, there was a 1.58-letter difference (statistically superior) favoring continuous, monthly administration of these medications.

**Secondary outcomes.** An examination of secondary outcomes showed that ranibizumab was superior to bevacizumab in increasing mean near-distance visual acuity. There was no difference between the two medications in terms of contrast sensitivity or any characteristics visible using FA. Bevacizumab decreased serum VEGF levels more than ranibizumab, particularly with continuous use.

A median of seven injections was administered in the discontinuous therapy groups throughout the year. There was no difference in the incidence of death or ATEs among the four treatment groups; however, similar to the findings from the CATT study, serious systemic adverse events occurred more frequently with the use of bevacizumab than with ranibizumab.

**Cost.** The cost analysis revealed that treatment with ranibizumab was more expensive than bevacizumab therapy. In addition, expenses were much higher when either medication was used in a discontinuous rather than discontinuous manner. The authors of the study concluded that the National Health Service could save an estimated £84.5 million per year (based on administration of 17,295 injections) by switching from ranibizumab to bevacizumab and administering the medication discontinuously on an as-needed basis.

**Summary.** There were no clinically important differences in visual acuity or any secondary functional outcomes between patients using the two medications after 1 year (Table 3). The investigators also found no significant difference in mean visual acuity with the use of continuous or discontinuous dosing regimens (Table 4).

### TABLE 3

**IVAN Trial 1-Year Results: Ranibizumab vs Bevacizumab**

- No conclusive difference in mean visual acuity
- No difference in contrast sensitivity
- No difference in any characteristics of the CNV lesion on FA
- No difference in mortality
- No difference in arterial thrombotic events
- Serum VEGF levels decreased to a greater extent with bevacizumab than with ranibizumab.
- The risk of a serious systemic adverse event was higher with bevacizumab than with ranibizumab.
- Ranibizumab was significantly more expensive than bevacizumab.

IVAN = Inhibition of VEGF in Age-Related Choroidal Neovascularization; CNV = choroidal neovascularization; FA = fluorescein angiography; VEGF = vascular endothelial growth factor

**Source:** Chakravarthy et al

### TABLE 4

**IVAN Trial 1-Year Results: Continuous vs Discontinuous Treatment**

- Continuous monthly dosing yielded equivalent mean visual activity, but statistically superior results (1.58-letter increase) when compared with discontinuous, as-needed dosing.
- Continuous monthly dosing and discontinuous, as-needed dosing resulted in a similar mean change in visual acuity in both ranibizumab- and bevacizumab-treated patients.

IVAN = Inhibition of VEGF in Age-Related Choroidal Neovascularization

**Source:** Chakravarthy et al

### CONCLUSION

The outcomes of these two prospective, randomized clinical trials yield clinical information that is important to both physicians and their patients with exudative AMD. The 2-year CATT and 1-year IVAN trial results are significant and may have important implications for the healthcare systems in both the United States and the United Kingdom; about 250,000 patients in the United States are treated for exudative AMD over 2 years. We anxiously await a comparison of the 2-year IVAN trial results with the CATT results. Additional information may further clarify the impact of treating patients with exudative AMD with these novel medications.

### REFERENCES


8. Chakravarthy U, IVAN Investigators. The Inhibition of VEGF in Age-Related Choroidal Neovascularization (IVAN) trial: 1-year interim analysis. Presented at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO); May 6, 2012; Fort Lauderdale, Florida.

9. Evans JR, Fletcher AE, Wormald RP. Age-related macular degeneration causing visual impairment in people 75 years or older in Britain: an add-on study to the Medical Research Council Trial of Assessment and Management of Older People in the Community. *Ophthalmology.* 2004;111:513–517.
Current Controversies in the Management of Neovascular Age-Related Macular Degeneration

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Abstract Intravitreal injection of vascular endothelial growth factor inhibitors has become the gold standard in managing neovascular age-related macular degeneration. The dramatic results demonstrated during initial phase III clinical trials of ranibizumab required monthly injections. Attention now has turned to dosing regimens that may allow equivalent outcomes without the burden of monthly injections. In addition, clinical researchers have been focusing on the safety and efficacy of other agents that can be given less frequently (eg, aflibercept) or that are less expensive (eg, bevacizumab). At the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology, investigators presented data on how ranibizumab is optimally administered, patients who do not respond may be predicted and treated, and use of other drugs compares with ranibizumab therapy under various dosing protocols. Long-term outcomes, safety, and patient quality of life also were discussed.

The Anti-Vascular Endothelial Growth Factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization (CNV) in Age-Related Macular Degeneration (ANCHOR) trial1 and the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)2 firmly established intravitreal anti-VEGF injection using ranibizumab as the standard of care in treating exudative age-related macular degeneration (AMD). Before the introduction of ranibizumab, loss of visual acuity was the norm, with only a small fraction of affected patients regaining a significant amount of vision. With monthly intravitreal injections of ranibizumab, 95% of AMD patients maintained their initial visual acuity, and 34%–40% of patients actually gained 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters.1,2

As expectations rose, so did frustrations with the burden of monthly injections. The focus of clinical trials shifted to alternative dosing regimens, either less frequently (PIER study),3 on an “as-needed” basis (PrONTO study),4 or with successive extension of the between-injection interval (“treat-and-extend” protocol).5,6 Investigators sought new drugs that targeted VEGF apart from ranibizumab based primarily on a less-frequent dosing regimen, such as every-other-month dosing with aflibercept.7,8 At the same time, the cost of ongoing monthly treatment with ranibizumab became prohibitive for some patients, and interest shifted to less expensive alternatives, culminating in the head-to-head trial of ranibizumab versus bevacizumab in the Comparison of AMD Treatment Trial (CATT).9

As we enter the second decade of the 21st century, clinicians and researchers have set their sights on the two thirds of patients who, despite treatment, never regain a significant amount (ie, > 3 lines) of vision. In addition, the international retina community is still trying to determine the best dosing regimen that maximizes outcomes with a lower burden of patient visits and injections. Also, despite the publication of the first-year CATT results this past year,9 it is still unclear how bevacizumab use compares with ranibizumab administration, especially when the drugs are given as needed.

Expert presentations delivered during various poster sessions at this year’s annual meeting of the Association for Research in Vision and Ophthalmology (ARVO) focused primarily on the best schedule for administering ranibizumab therapy, the prediction and treatment of patients who do not respond to anti-VEGF therapy, and the comparison of VEGF-inhibitor treatments under various dosing protocols. In addition, now that anti-VEGF agents have been used clinically for several years, attention also is being paid to the long-term safety profiles of these drugs, the initial dramatic gains seen in treated patients, and the long-term outcomes of anti-VEGF therapy.

CATT Trial Update

During the delay awaiting US Food and Drug Administration (FDA) approval of

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ranibizumab following publication of the dramatic ANCHOR and MARINA data, clinicians began using bevacizumab in an off-label fashion to treat neovascular AMD. Because results with use of bevacizumab appeared to be comparable to those found with ranibizumab therapy, and bevacizumab was significantly less expensive than ranibizumab to use, a head-to-head trial of the two was conducted with funding from the National Institutes of Health.

One-Year Results

One-year (primary endpoint) outcomes of the CATT study results showed that visual acuity was better in the ranibizumab group than in the bevacizumab group, but there was no statistically significant difference between the two (ie, bevacizumab use was noninferior to ranibizumab therapy) if they were given on a monthly dosing schedule. The data did not allow investigators to determine whether as-needed dosing of bevacizumab was inferior or noninferior to as-needed ranibizumab use or to monthly dosing of either drug.

Thus, after the 1-year results of the CATT trial were released, the international retina community was left with several unanswered questions. Would the results demonstrating the equivalence of monthly ranibizumab and bevacizumab (and of monthly and as-needed ranibizumab dosing) continue to hold true at the 2-year mark? Is as-needed bevacizumab use comparable to as-needed (or monthly) ranibizumab therapy? Would the apparently increased rate of adverse events experienced by the bevacizumab group during the first year continue to be found through the second year, or was this simply a statistical aberration?

Two-Year Results

With regard to the questions of efficacy and safety, the 2-year CATT results demonstrated persistent equivalence of the two drugs from the 1-year time point through the 2-year mark. That is, bevacizumab use remained noninferior to ranibizumab therapy in terms of visual acuity at the 2-year study point. However, the rate of adverse events in the bevacizumab group (treated either monthly or as needed) remained higher than that in the ranibizumab group (treated either monthly or as needed). The reason for this difference is still unclear, especially because patients who received as-needed dosing (and, consequently, fewer drug injections) continued to have higher rates of adverse events than did patients who received either ranibizumab or bevacizumab monthly. The rates of death or arterial thrombotic events that could be linked pathophysiologically to anti-VEGF treatment were comparable between the groups. Because of the lack of specificity to conditions associated with VEGF inhibition, interpretation of the relationship between bevacizumab therapy and higher rates of serious adverse events is unclear.

With regard to the effect of the dosing regimen on visual acuity outcome, a pooled analysis of the 2-year CATT results demonstrated that as-needed dosing with either ranibizumab or bevacizumab was statistically inferior to monthly dosing with either drug. However, the CATT study was initiated in the days of time-domain optical coherence tomography (TD-OCT), and treatment decisions were based upon a decrease in visual acuity and the presence of fluid on TD-OCT. More recent as-needed regimens have much stricter criteria for retreatment, including the presence of any fluid on spectral-domain OCT (SD-OCT). Thus, it is not known how much small amounts of fluid not seen with TD-OCT affect visual outcomes.

Visual Acuity According to Retinal Morphology

The CATT investigators also attempted to correlate retinal morphology with visual acuity among CATT participants. This endeavor was of particular interest, since patients receiving ranibizumab had a greater reduction in central subfoveal thickness than did those receiving bevacizumab, despite the equivalence in visual acuity outcomes. Specifically, the investigators looked at the presence of fluid (either intraretinal fluid [IRF], subretinal fluid [SRF], or subretinal pigment epithelium fluid [SRPEF]), the thickness of the central foveal region, and how these variables correlated with visual acuity outcomes.

All four treatment regimens (monthly or as-needed ranibizumab and monthly or as-needed bevacizumab) decreased the amount of IRF, SRF, and SRPEF and overall subfoveal thickness from baseline. More eyes treated with ranibizumab than those injected with bevacizumab were free of any fluid at 52 weeks, yet the majority of patients in all four treatment groups still had persistent fluid at that point. Those receiving monthly ranibizumab had the lowest rate of persistent fluid (55%) when compared with the other three groups (74%–80%), with IRF being most common. At every time point, eyes with residual IRF had worse visual acuities than did eyes without IRF, whereas the presence of SRF or SRPEF did not appear to affect visual acuity. By 4 weeks after the first injection was given, retinal thickness decreased; however, a greater decrease was seen with the use of ranibizumab than with bevacizumab therapy, and the greatest reduction in retinal thickness was noted among the group given monthly ranibizumab treatments.

AFLIBERCEPT

Some of the ongoing concerns with ranibizumab therapy involve pharmacokinetics and duration of action, resulting in the need for monthly therapy as long as exudative lesions remain active. Therefore, ophthalmologists were excited that the results of the VIEW 1 and VIEW 2 trials showed equivalency between every-other-month treatment with aflibercept, also known as VEGF Trap-Eye, and monthly ranibizumab administration, introducing the prospect of fewer injections for patients and fewer patient office visits for retina specialists.

Efficacy According to Subgroups

Ho et al presented a subgroup analysis of the efficacy of aflibercept for neovascular AMD as noted during the VIEW 1 and VIEW 2 trials. In all, 2,457 patients were randomized to receive ranibizumab...
monthly, 0.5 mg of aflibercept monthly, 2 mg of aflibercept monthly, or aflibercept every other month. The main outcomes were the percentage of patients maintaining vision (ie, losing < 15 ETDRS letters) and the mean change in best-corrected visual acuity.

Regardless of how the cohort was subdivided, results of a noninferiority analysis showed no statistical difference in outcomes among the four treatment groups. Subgroups were divided based on several criteria: age, initial visual acuity, lesion type, lesion size, and central retinal thickness. No subgroup was at a disadvantage by using any one of the treatment regimens.

### Time to Change in Visual Acuity

In a separate study presented by Roth et al,13 the cohorts from the VIEW 1 and VIEW 2 studies were analyzed with regard to the time until a gain or loss of 15 letters occurred (simple event) and the time until a sustained gain or loss was noted (sustained event, defined as that degree of gain or loss over two consecutive visits).

Gain of vision occurred equally rapidly between groups, and there was no difference among the four treatment groups with regard to the time until sustained vision gain of > 5 letters, > 10 letters, or > 15 letters. Time to a gain of > 5 letters was 12 weeks, and time to a gain of > 10 letters was 28 weeks in all four groups.

#### DIFFERENT DOSING REGIMENS AND LONG-TERM RESPONSE

Several researchers presented data at ARVO 2012 on the efficacy of different anti-VEGF dosing regimens for treating neovascular AMD.

### As-Needed Maintenance Therapy Following Three Loading Doses of Ranibizumab

Rees and colleagues14 reported on their experience with long-term structural and functional outcomes after three loading doses of ranibizumab were given to patients with neovascular AMD; further treatment was given as needed. Outcomes were visual acuity and the presence of SD-OCT image abnormalities after the initial three injections were given and at 12 and 24 months afterward.

After three injections, 97.1% of patients maintained their vision (lost < 15 ETDRS letters), and 20% gained ≥ 15 letters (mean gain from baseline, +6.2 ± 10.9 letters). At 12 months, 88.6% of patients maintained visual acuity, and 31.4% gained 15 letters (mean gain, +6.9 ± 17.6 letters). At 24 months, 88.6% maintained acuity, and 51.4% gained 15 letters (mean gain, +11.2 ± 20.1 letters). Macular fluid was present on SD-OCT in 93% of eyes at baseline, in 66% of eyes after three injections, in 69% of eyes at 12 months, and in 59% of eyes at 24 months. These results demonstrate that patients can continue to experience improvements in visual acuity for a long time after ranibizumab therapy is initiated. Further, the improvement in visual acuity seen early in the treatment course is not necessarily indicative of the maximal effect that may be expected, even when an as-needed dosing regimen is used.

### As-Needed Retreatment with Ranibizumab

Gaucer et al15 reported on their experience with as-needed retreatment using a series of three intravitreal ranibizumab injections. Each patient received initial induction with three monthly doses of ranibizumab. When signs of activity were present, patients then received as-needed dosing based on the PrONTO retreatment criteria.4 All patients were followed monthly for best-corrected visual acuity and with OCT when not receiving injections of ranibizumab. They were retreated when visual acuity decreased by at least five letters or when OCT showed signs of exudation.

At 2 years, patients made a mean of three office visits annually and received a mean of five injections annually. Using this treatment paradigm, visual acuity stabilized in 65.6% of eyes and improved in 28.8% of eyes with a relatively low burden of patient visits and injections, although there was no mean gain in visual acuity over the 2 years of this study (year 1, 53.18 letters; year 2, 54.18 letters).

### Retreatment with Sequential Ranibizumab Injections

Ceklic et al16 used a variation of this as-needed protocol involving three sequential injections. After dose induction with ranibizumab, patients were monitored monthly, including with OCT. If signs of exudation were present, a series of three monthly injections was administered. If the macula remained dry, the patient continued to receive ranibizumab injections on a quarterly basis.

Using this modified protocol, in which patients who remained dry still received low-frequency injections of ranibizumab, mean best-corrected visual acuity improved by seven letters at 12 months and eight letters at both 24 and 36 months when compared with baseline. These gains were achieved with a mean of 7.4, 12.1, and 16 injections at each time point, respectively.

### Treatment of Worsening Neovascularization

A different maintenance strategy was used by Dyer and colleagues.17 Initially, either ranibizumab or bevacizumab was administered until there was no leakage on fluorescein angiography and/or no fluid was found on OCT. Thereafter, maintenance therapy with 0.3 mg of pegaptanib was administered every 6 weeks. Retreatment with ranibizumab was given for signs of worsening neovascularization at the investigator’s discretion. Induction therapy to achieve a dry macula required a mean of 3.5 ± 1.3 injections.

A mean of 11.4 ± 2.4 maintenance injections were given over 24 months. Seventy-nine percent of patients main-
tained visual acuity, 26% gained > 15 letters, and 40% required retreatment with ranibizumab for breakthrough activity despite pegaptanib maintenance therapy. Because pegaptanib has the advantage of being more selective than other VEGF inhibitors for VEGF<sub>165</sub>, treatment with this drug theoretically may cause fewer arterial thrombotic adverse events. This supposition, however, remains to be verified in practice.

Benefits of the Induction Phase

Most as-needed ranibizumab protocols currently being advocated begin with a mandated induction phase involving three monthly injections before the as-needed portion of the protocol is begun. Kloeckener-Gruissem and colleagues<sup>18</sup> evaluated the benefits of the induction phase in a retrospective analysis. In addition, they examined the predictive value of the initial rise in visual acuity as it pertains to visual acuity 12 and 24 months later and the effect of polymorphisms in the gene for complement factor H (CFH) in regard to response to ranibizumab and final visual acuity.

Eyes showing an initial gain in visual acuity tended to retain improvement over the course of the study period. Patients who were homozygous for the rs1061170 single-nucleotide polymorphism at CFH were more likely to belong to the group of poor responders. However, whether or not patients received an induction phase of three monthly injections of ranibizumab before beginning as-needed maintenance therapy did not affect their long-term visual acuity at either 12 or 24 months.

Ranibizumab for Treatment-Naïve Subfoveal CNV

Suner et al<sup>19</sup> presented first-year data from the HARBOR study, which evaluated the efficacy and safety of 2.0 mg versus 0.5 mg of ranibizumab given for treatment-naïve subfoveal CNV from AMD. In this study, 1,097 patients were randomized to one of four different groups given ranibizumab: 0.5 mg of ranibizumab dosed monthly, 0.5 mg given as needed (with monthly monitoring), 2.0 mg dosed monthly, or 2.0 mg given as needed. Three loading doses were given in the as-needed protocol arms.

All four groups experienced improved visual acuity at the 12-month primary endpoint, with 95% maintaining vision (range, 93.4%–97.8%). About one third of all patients gained 15 letters. Patients given 0.5 mg monthly gained a mean of 10.1 letters (mean, 11.3 injections), the 2.0 mg-monthly group gained +9.2 letters (mean, 11.2 injections), the 0.5 mg-as-needed group gained +8.2 letters (mean, 7.7 injections), and the 2.0 mg-as-needed group gained +8.6 letters (mean, 6.9 injections). In a pooled analysis, the as-needed protocols did not meet the noninferiority endpoints when compared with monthly dosing at either dosage (ie, as-needed therapy was inferior to monthly dosing), and 2.0 mg of the drug was not superior to 0.5-mg dosing.

Thus, monthly injections of 0.5 mg of ranibizumab appeared to be at the top of the curve for treatment-naïve neovascular AMD. Increasing the dosage to 2.0 mg monthly added no further benefit, although as-needed dosing with monthly monitoring still resulted in clinically meaningful gains in visual acuity.

Long-Term Ranibizumab Therapy

Bhisitkul and others<sup>20</sup> presented the most long-term data available for neovascular AMD patients receiving ranibizumab. All of these patients initially had been enrolled in the ANCHOR and MARINA registration trials and then participated in the HORIZON extension study, where they were randomized to receive long-term ranibizumab maintenance therapy. Thus, these patients began receiving ranibizumab 7–8 years ago—longer than any other AMD study participants have been exposed to the drug.

In this study, the Seven-Year Observational Update (SEVEN UP) study, the first cohort of patients was re-evaluated with a complete ophthalmologic examination, fundus photography, autofluorescence, fluorescein angiography, SD-OCT, and serum collection for genetic analysis. The primary endpoint was the percentage of neovascular AMD patients with a visual acuity ≥ 20/70. Sixty-three patients were included in the analysis.

The investigators found that 35% of patients had a visual acuity of ≥ 20/70, 23% of patients had a visual acuity of ≥ 20/40, and 37% had a visual acuity of ≤ 20/200. Altogether, 27% of the original study eyes had active leakage at the time of the SEVEN UP study visit, 54% of the eyes had recent CNV activity in the 6 months before the study visit, and 52% of the eyes needed some treatment for disease activity during the previous 6 months. In the interim, 51% of patients had developed exudative AMD in the other eye, and 6% of patients were now legally blind (visual acuity ≤ 20/200 in both eyes). Since exiting the HORIZON study, only 25% of eyes required no interim ranibizumab injections because of either disease quiescence or therapeutic futility, and 25% of eyes required ≥ 11 injections. Only a minority of study eyes had excellent visual outcomes, whereas the majority demonstrated ongoing disease activity and poor visual outcomes. Therefore, clinical vigilance and prolonged treatment may be required for these patients.

### PREDICTING RESPONSE AND THE PROBLEM OF NONRESPONDERS

The majority of patients with wet AMD receiving anti-VEGF therapy maintain their pretreatment visual acuity—that is, they lose < 15 ETDRS letters when compared with their presenting visual acuity—and only one third gain a significant amount of vision (usually defined as a gain of ≥ 15 ETDRS letters). Because most patients do relatively well, attention has turned to predicting who will not benefit from anti-VEGF therapy alone and how best to approach the management of these patients. Apart from the CFH gene polymorphism data noted previously,<sup>18</sup> several other researchers also reported on the prediction, identification, and management of nonresponders.

Lesion Characteristics

Caprani and colleagues<sup>21</sup> described the baseline lesion characteristics of ranibizumab nonresponders. In a retrospective
Analysis, all patients were treated with three monthly ranibizumab injections; outcomes at month 4 were evaluated. Patients were divided into three groups: those gaining at least one line of vision (responders), those losing at least one line of vision (nonresponders), and those staying within one line of the initial presenting visual acuity (stable group).

Overall, patients in the responder group had significantly smaller lesions than did patients in the other two groups (P < 0.05). The presence of intraretinal fluid at baseline, which correlated with poor visual acuity in other studies, did not predict a poor prognosis. Initial presenting visual acuity likewise did not predict whether a patient would gain or lose vision on ranibizumab therapy.

**Maintaining a Good Response**

In patients who initially responded to ranibizumab therapy, Saldanha and Blyth22 attempted to ascertain the likelihood of maintaining this good response over a long period. Patients were categorized as full responders, partial responders, nonresponders, and those with structural damage based on visual acuity and OCT findings. Patients were treated with three monthly ranibizumab doses and then followed an as-needed dosing protocol.

Of patients categorized as being full responders at 16 weeks (ie, 4 weeks after receiving the initial three loading doses), 73% remained full responders at 52 weeks, and 63% remained full responders at 104 weeks. Only 3% of patients were deemed nonresponders at 52 weeks, and 7% of patients were by 104 weeks. Structural damage occurred in 12% of patients at 52 weeks and in 17% of patients at 104 weeks. Thus, a good response at 16 weeks was associated with continued positive outcomes at 52 and 104 weeks.

**Fluid Status on OCT**

In their subgroup analysis of data from the VIEW 1 and VIEW 2 studies, Ho and colleagues12 observed indications that the fluid status on OCT at the end of the first year of treatment may help predict the number of ranibizumab or aflibercept injections that might be needed during the second year of treatment. In both of these studies, patients were injected monthly (ranibizumab) or every other month (aflibercept) throughout the first year before switching to an as-needed regimen during the second year.

Schrader et al13 studied how the number of ranibizumab or bevacizumab injections required during the first year of treatment according to an as-needed dosing schedule (with three monthly loading doses) might be used to predict the number of injections that a patient might require in future years of treatment. They compared the final visual acuity and the annual number of injections required for those patients who received four or fewer injections in the first year with those of patients given more than four injections.

The number of injections required during the first year of treatment predicted neither the final visual acuity nor the number of injections needed in future years in a statistically significant way. However, insurance companies in Germany generally require a loss of ≥ 5 ETDRS letters for retreatment. This requirement might be associated with a less favorable result than repeated therapy based upon the presence of fluid on OCT.

**Factors That Predict Treatment Failure**

Droege and others24 took a different approach to understanding the long-term course of patients receiving intravitreal anti-VEGF injections for exudative AMD. They examined factors that affected patient adherence to the intravitreal treatment regimen using the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25) and a 22-item questionnaire that specifically pertained to perceptions about intravitreal injections.

Of the initial 96 patients, 14 did not attend the final follow-up visit. Factors that most predicted failure to follow through with the treatment regimen were distance from the hospital (41.7% [3 of 14 patients continued their care with an ophthalmologist closer to home]), fear regarding possible disease relapse (16.7%), no subjective benefit (11.5%), loss of motivation (10.4%), visit frequency (7.7%), and problems with insurance (2.1%).

**Treating Unresponsive AMD**

Several researchers also presented results of various studies on how best to manage patients who fail to respond, or respond suboptimally, to standard treatment regimens.

**Varied dosing intervals.** Chen and colleagues25 presented 2-year results of the Superdose Anti-VEGF (SAVE) trial, an open-label study of 2.0 mg of ranibizumab in patients with refractory neovascular AMD. Enrolled patients received an average of 24 prior injections. All patients were injected with 2.0 mg of ranibizumab once a month; they were randomized to receive monitoring either monthly or every 6 weeks after being given an initial series of three monthly injections.

A higher dose of ranibizumab appeared to promote and maintain improvements in both visual acuity at month 18 (6.5 ETDRS letters in the monthly-as-needed cohort; 4.1 ETDRS letters in the 6-week-as-needed cohort) and in central macular thickness. These results are distinctly different from the findings of the HARBOR study, in which dosing with 2.0 mg of ranibizumab had no added benefit when compared with 0.5-mg doses. However, the HARBOR study evaluated the efficacy of superdose ranibizumab in treatment-naïve patients, whereas the SAVE trial evaluated its efficacy in patients who derived no benefit from previous conventional treatment.

**High-dose therapy.** Fung et al26 reported on the outcomes of the High-Dose Ranibizumab for Pigment Epithelial Detachment (HiPED) study, which evaluated the efficacy of 2.0-mg injections of ranibizumab in the treatment of pigment epithelial detachment (PED) refractory to usual dosing (ie, persistent PED after six monthly injections of 0.5 mg of ranibizumab). In this open-label study, patients were randomized to receive either mandated monthly injections of 2.0 mg of ranibizumab or monthly examinations with as-needed injections after three initial loading doses. A 12-month analysis of this
24-month study showed that visual acuity improved by 4.5 letters at 6 months and by 8 letters at 12 months. Nearly all patients in the as-needed groups required at least one injection for persistence or recurrence of disease activity over the course of the first year of the study.

**Inadequate later response.** A different approach was taken by Hirji and colleagues, who retrospectively identified patients with neovascular AMD who initially responded to bevacizumab but then demonstrated an inadequate response (ie, a gain of less than one ETDRS line) to bevacizumab on two consecutive visits and immediately were switched to monthly treatment with ranibizumab.

Best corrected visual acuity and central macular thickness on OCT were compared after the final dose of bevacizumab (prior to the switch) and after the initial three monthly doses of ranibizumab were given. Visual acuity increased by a mean of 10 ± 2 letters, with 46.5% of patients gaining > 10 letters. Central macular thickness likewise decreased by a mean of 22.35 ± 7.3 5 µm. Thus, ranibizumab was effective in patients with neovascular AMD who showed an inadequate response to bevacizumab.

### LONG-TERM SAFETY

**The LUMINOUS Program**

The first-year data from the European LUMINOUS program was presented by Bandello and others. The LUMINOUS program retrospectively pooled safety data from four European registries of neovascular AMD patients: the WAVE program in Germany, HELIOS in the Netherlands and Belgium, and a Swedish registry. A total of 4,444 patients treated with ranibizumab were included.

The mean number of ranibizumab injections ranged from 4.3 to 5.7 over 12 months. The most significant adverse events reported were endophthalmitis (0.11%), retinal detachment (0.02%), myocardial infarction (0.11%), arterial thromboembolic events (0.59%), and venous thromboembolic events (0.11%). This ongoing, prospective, multicenter study is planned to continue for 5 years.

**Systematic Review of Clinical Trials**

Schmucker et al compared the safety of bevacizumab therapy for neovascular AMD with that of ranibizumab by systematically reviewing the results of randomized clinical trials of both agents through a search of MEDLINE, EMBASE, and The Cochrane Library. Three clinical trials were available for direct comparison, six were available for indirect comparison, and three evaluated bevacizumab alone.

In the trials available for direct comparison, 1-year safety data showed a significantly higher rate of serious ocular adverse events among patients treated with bevacizumab compared with those who were given ranibizumab (relative risk [RR], 4.90; 95% confidence interval [CI], 1.67–14.35). The rate of serious systemic adverse events was also higher among patients receiving bevacizumab (24.1% vs 19.0% for patients given ranibizumab; RR, 1.25; 95% CI, 1.01–1.66) in this direct comparison; however, the rate of arterial thrombotic events was similar in the two treatment groups (2%–3%). Attempts at indirect comparisons were hampered by too many methodologic limitations in the bevacizumab studies to rule out any major safety concerns.

**RANIBIZUMAB IN PATIENTS WITH ADVANCED AMD**

The Lucentis in Advanced Macular Degeneration (LAMA) trial evaluated the efficacy of 3 or 6 months of monthly injections of ranibizumab followed by as-needed injections of the drug among patients who had well-advanced AMD on presentation.

MacKeen et al showed that even patients with profoundly decreased visual acuity from neovascular AMD (visual acuity ≤ 20/400) could still benefit from intravitreal injections, with the majority showing improvements in reading speed and accuracy, low contrast, and a timed test of activities of daily living. Microperimetry findings also improved in most patients after ranibizumab treatment.

Sanislo et al evaluated the effect of ranibizumab treatment on VFQ-25 scores in the LAMA cohort. Among all patients, treatment with ranibizumab in this severely visually impaired cohort did not improve overall VFQ-25 scores when compared with baseline. However, when the study eye was the better-seeing eye, VFQ-25 scores improved by 16 points at 3 months and by 6 points at 6 months. This subgroup especially experienced large improvements in near- and distance-vision activities subscores. Thus, patients with decreased acuity secondary to exudative AMD in the better-seeing eye might particularly benefit from intravitreal ranibizumab.

Rung and Adrian likewise assessed VFQ-25 scores in treatment-naïve patients with neovascular AMD who received ranibizumab on an as-needed basis following an initial induction period of three monthly injections. VFQ-25 scores at baseline and at a mean of 37 ± 7 months after initiation of ranibizumab therapy were compared; these scores were then compared with clinical and imaging findings. Following the initial series of three monthly injections of ranibizumab, distance visual acuity improved from 53 ± 14 letters to 61 ± 14 letters; however, it subsequently declined to 44 ± 24 letters; both changes were statistically significant.

Despite the gradual decline in visual acuity, VFQ-25 subscores revealed no statistically significant concomitant increase in worrying and no decrease in mental health or in the performance of near-vision activities. There was, however, a statistically significant decrease in subscores relating to social functioning outside the home, independence, color vision, distance activities, and patients’ self-perceived general health. The lack of an increase in patients worrying about their visual functioning despite the objective decline in visual acuity was particularly interesting.

**CONCLUSION**

Taken together, the results of these studies seemed to support monthly treatment with ranibizumab or bimonthly dosing with aflibercept at the top of the curve in terms of patient outcomes. Use of other as-needed dosing regimens or substitution of bevacizumab also seemed to afford...
excellent patient outcomes. Increasing the ranibizumab dose provided no advantage in treating new-onset exudative AMD, but it could be helpful in treating patients who do not respond to conventional 0.5-mg dosing. Switching to ranibizumab might be beneficial in patients on bevacizumab therapy who do not experience improved vision. Although their use is safe in the long-term, VEGF inhibitors apparently must be given continuously over many years to maintain disease quiescence. That said, patient quality of life does improve with continued injections. At the end of the day, that must be our primary goal.

REFERENCES

19. Suen JJ, Yao L, Lai P. HARBOR study: one-year results of efficacy and safety of 0.5 mg versus 0.5 mg ranibizumab in patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration. Presented at the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO); May 6–10, 2012; Fort Lauderdale, Florida. Abstract S167.


32. Rung L II, Adrian MKL. Despite deterioration in visual acuity, patients treated with ranibizumab for wet, age-related macular degeneration did not demonstrate any raise in worrying related quality of life related items. Presented at the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO); May 6–10, 2012; Fort Lauderdale, Florida. Abstract 4429.
The Evolving Landscape for Treatment of Diabetic Macular Edema

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**Abstract** Diabetic macular edema (DME) is a significant cause of vision loss among patients with diabetic retinopathy. Although the focal/grid macular laser has long been the standard of care for treating edema, the results of several recent trials underscored the importance of treatment using vascular endothelial growth factor inhibitors, particularly ranibizumab, in improving visual outcomes. At the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), experts in ophthalmology presented the results of important research that may change the management of DME.

Clinically significant diabetic macular edema (DME) is a major cause of vision loss in patients with diabetic retinopathy. As the prevalence of diabetes grows worldwide, the potential loss of vision from DME poses significant quality-of-life and socioeconomic concerns.

The treatment of DME using focal/grid macular laser therapy was established by the Early Treatment Diabetic Retinopathy Study (ETDRS). However, this standard eventually was challenged in a study by the Diabetic Retinopathy Clinical Research Network (DRCR.net), in which focal/grid macular laser therapy combined with intravitreal injection of a vascular endothelial growth factor (VEGF) inhibitor resulted in improved visual outcomes.

The RESTORE trial was the first large, randomized clinical trial to compare macular laser treatment alone, ranibizumab alone, and ranibizumab in combination with laser therapy. The RESTORE results demonstrated that ranibizumab used alone or with focal/grid macular laser therapy provided superior visual acuity outcomes over focal/grid macular laser treatment alone in patients with DME.

At 1 year, no differences were detected between the ranibizumab and the ranibizumab/laser arms.

The seeds of the DRCR.net trial in 2010 and the RESTORE trial in 2011 have grown into many diverse studies and randomized clinical trials that are trying to determine the best practices for managing DME. At the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) held in Fort Lauderdale, Florida, a growing collection of research showed that the standard of care as established by the ETDRS over 20 years ago will continue to evolve in the years ahead.

**Factors Predicting Bevacizumab Success in DME Therapy**

Certain patient characteristics apparently may help to predict better visual acuity outcomes when bevacizumab is used to treat DME.

**Levels of Blood Markers**

Rusu et al evaluated the effect of hemoglobin A1c (HbA1c) level on bevacizumab response during DME treatment. Their retrospective chart review evaluated the effect of HbA1c level on the visual characteristics of 28 patients with DME who were given two consecutive intravitreal injections of bevacizumab 53 days apart.

Using regression modeling, they found that central foveal thickness, as assessed by optical coherence tomography (OCT), improved among patients in the bevacizumab arm as compared with controls not receiving bevacizumab. Patients with worse diabetic control (as assessed by higher HbA1c levels) were less likely to respond to bevacizumab therapy. Thus, clinicians must consider the HbA1c level when they contemplate using bevacizumab to treat patients with DME. This finding likely will be evaluated further in larger prospective trials.

**Prediction of Fellow-Eye Response**

In another study, Karth et al performed a retrospective chart review of 28 DME patients to predict patient response to intravitreal bevacizumab. By assessing OCT central thickness of one eye of a DME patient treated with bevacizumab, they attempted to predict the success of treating the fellow eye.

Using regression analysis, they found that 21% of the reduction in central thick-
ner in the fellow eye might be explained by the response of the first treated eye. However, further validation in larger prospective trials is needed before treatment efficacy can be gauged according to initial treatment of one eye.

**RANIBIZUMAB MONOTHERAPY AND DME: RISE AND RIDE TRIAL RESULTS**

VEGF plays a role in the creation of retinal ischemia and increased vascular permeability, which results in macular edema.\(^\text{10,11}\) Smaller trials have demonstrated the superiority of ranibizumab monotherapy over laser therapy alone in treating DME.\(^\text{7}\)

The RISE and RIDE trials\(^\text{12,13}\) were double-masked, sham-controlled, multicenter, phase III trials that evaluated the impact of monthly ranibizumab injections on DME. The trials had a parallel design that compared the use of 0.3 or 0.5 mg of ranibizumab given monthly for 24 months with sham therapy in patients who underwent macular laser therapy. After 3 months of injection therapy, grid macular rescue laser therapy could be applied if central foveal thickness > 250 μm or if a 50-μm worsening from the prior month occurred.

For the RISE trial, 377 patients were randomized to receive sham therapy (n = 127) or 0.3 mg (n = 125) or 0.5 mg (n = 125) of ranibizumab; patient characteristics were similar across the three arms. At 24 months, gains of > 15 ETDRS letters occurred in 18.1% of patients given sham injections, 44.8% of those injected with 0.3 mg of ranibizumab, and 39.2% of those given 0.5 mg of ranibizumab.

In the RIDE cohort, 382 patients were randomized to receive sham therapy (n = 130) or 0.3 mg (n = 125) or 0.5 mg (n = 127) of ranibizumab; again, the groups had similar baseline characteristics. Gains of > 15 ETDRS letters were noted in 12.3% of sham patients, 33.6% of those given 0.3 mg of ranibizumab, and 45.7% of patients given 0.5 mg of the drug.

Significant improvements in macular edema were noted on OCT in both ranibizumab arms of both trials. Retinopathy was less likely to worsen in treated patients. In the RISE cohort, panretinal photocoagulation eventually was needed for eventual progression to proliferative diabetic retinopathy in 11% of the sham group, 0% of the group given 0.3 mg of ranibizumab, and 0.8% of those given 0.5 mg of ranibizumab. For the RIDE cohort, panretinal photocoagulation was needed by 12.3%, 1.6%, and 1.6% of patients, respectively. In both trials, ranibizumab-treated patients underwent significantly fewer macular laser procedures. Over 24 months, a mean of 1.8 procedures were needed in the sham treatment groups and 1.6 were needed in the ranibizumab therapy cohorts.

The risk of endophthalmitis from repeated intraocular injections is a concern, especially in a diabetic population. In both trials, endophthalmitis occurred in four ranibizumab patients after a total of 10,584 injections, which is a reassuringly low rate. The total mortality from vascular or unknown causes, nonfatal myocardial infarctions, and nonfatal cerebrovascular accidents was 4.9%–5.5% in sham-injected patients and 2.4%–8.8% in ranibizumab-treated patients.

The results of both the RISE and RIDE trials helped to establish monthly ranibizumab monotherapy as an efficacious and sustainable treatment for DME, which was associated with low rates of ocular and systemic complications. In August 2012, the US Food and Drug Administration approved the use of ranibizumab for the treatment of DME.

**Changes in Visual Function**

The relationship between DME and diabetes was established in epidemiologic studies,\(^\text{12,13}\) but the impact of disease beyond visual acuity still must be assessed. Turpçcu et al.\(^\text{14}\) presented data to help validate one such metric, the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25), as it relates to vision gains in diabetic patients in the RISE and RIDE trials.

The NEI VFQ-25, which evaluates patient-reported visual function in daily activities, was given to patients in the RISE and RIDE cohorts at baseline and at 6, 12, 18, and 24 months. Results from each trial were evaluated separately; investigators reported on the 12-month results.

The subgroup of ≥ 15 letters gained was evaluated via regression modeling. It corresponded with an NEI VFQ-25 composite score of 8.7 points (95% confidence interval [CI], 5.9–11.5) for the RIDE cohort and 8.3 points (95% CI, 5.8–10.7) for the RISE cohort.

The endpoint of ≥ 15 letters gained remains a meaningful vision outcome that has become a standard in randomized clinical trials of retinal disease since the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization (CNV) in Age-Related Macular Degeneration (AMD; ANCHOR) trial\(^\text{15}\) and the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA).\(^\text{16}\) The NEI VFQ-25, which provides a consistent and validated patient-reported metric to evaluate outcomes, may be another important outcome metric to be applied in future clinical trials.

**Impact on Legal Blindness**

Another study evaluated the theoretical impact of monthly ranibizumab injections on reducing legal blindness and visual impairment among non-Hispanic white and Hispanic individuals with center-involving DME in the United States.\(^\text{17}\) The model evaluated the effect of ranibizumab treatment on the development of legal blindness from DME over 2 years.

Legal blindness was defined as a visual acuity letter score ≤ 38 in the better-seeing eye (approximate Snellen equivalent, 20/200 or worse). Visual impairment was defined as a visual acuity letter score ≤ 68 in the better-seeing eye (approximate Snellen equivalent, worse than 20/40). Incident cases of DME were estimated based on the population of the United States in 2011, the prevalence of diagnosed diabetes, and the 1-year incidence of clinically significant DME with visual impairment.

The impact of ranibizumab therapy was based on the results of the RISE and RIDE clinical trials. The model predicted 17,007 incident cases of DME with visual impairment in 2011. Without ranibizum-
Higher-Dose Ranibizumab Therapy and DME

As the evidence continues to grow that ranibizumab effectively treats DME, investigators are testing use of higher doses of medication and varied treatment intervals when managing affected patients.

0.5 mg vs 1 mg

Ferrone and Jonisch compared 0.5 mg of ranibizumab with 1 mg of ranibizumab for the treatment of DME. After receiving a loading dose of three consecutive monthly injections, patients were reevaluated every other month according to an as-needed treatment protocol during the first year. During the second year, patients were seen every month and received as-needed monthly injections of ranibizumab. In all, 42 eyes (0.5 mg, 20 eyes; 1 mg, 22 eyes) with similar baseline characteristics were evaluated.

The group given 1 mg of ranibizumab demonstrated improvement in the number of letters gained over 2 years; the 0.5-mg group demonstrated a similar trend. The 1-mg group experienced an average gain of 10.4 ETDRS letters, and the 0.5-mg group gained an average of 7.0 ETDRS letters; the difference was not significant. The mean central foveal thickness was 192 µm in the 1-mg group and 216 µm in the 0.5-mg group, which also was not significantly different. An average of 12.0 injections was given to patients in the 1-mg group and 12.9 injections were given to those in the 0.5-mg group; this difference also was not significant.

These results suggested that patients with DME benefit from treatment with either 0.5 mg or 1 mg of ranibizumab. No significant difference in the ETDRS letters gained, percentage of patients gaining > 15 letters, central foveal thickness (as assessed by OCT), or average number of ranibizumab injections needed was seen among patients given the two doses.

0.5 mg vs 2 mg

The READ 3 trial evaluated the use of an even higher dose of ranibizumab versus the standard 0.5-mg dose given to manage DME. In all, 152 eyes with DME were randomized to receive 0.5 mg or 2 mg of ranibizumab in three consecutive monthly doses. Patients found to have a central foveal thickness > 250 µm were retreated.

Efficacy. Six-month data from the READ 3 trial demonstrated a mean change in best-corrected visual acuity (BCVA) from baseline to month 6—the primary endpoint—of +7.46 ETDRS letters in the 2-mg group versus +8.69 ETDRS letters in the 0.5-mg group. The mean reduction in OCT-determined central foveal thickness was –163.86 µm and –169.27 µm for the 2-mg and 0.5-mg groups, respectively. No serious ocular or systemic adverse events were reported in either treatment group.

These results show that monthly intravitreal injection of 0.5 mg or 2 mg of ranibizumab is similarly effective in managing DME.

Within-patient results. The READ 3 investigators also presented data for the fellow-eye subgroup. If the fellow eye contained clinically significant DME, it was randomized to receive the opposite dose of ranibizumab. A total of 44 patients were eligible for this study.

No notable differences on an inter- or intrapatient basis were noted between the 0.5 mg and 2 mg of ranibizumab with respect to BCVA or OCT-determined central foveal thickness. Longer trials should reveal whether these similarities in response persist.

Retreatment. Another READ 3 evaluation entailed the detection and retreatment of DME based on time-domain (TD) versus spectral-domain (SD) OCT. The study investigated treatment decisions made according to results obtained with different OCT modalities after the first 6 months of the trial.

Retreatment with ranibizumab was performed if a central foveal thickness > 250 µm was noted using the Stratus TD-OCT (Carl Zeiss Meditec; Dublin, CA) and/or if intraretinal or subretinal fluid was detected on Spectralis SD-OCT (Heidelberg Engineering GmbH; Heidelberg, Germany). DME could be present in eyes even when central foveal thickness was within the acceptable range on TD-OCT. SD-OCT could detect intraretinal and subretinal fluid missed by the TD-OCT system. Thus, SD-OCT may be a more sensitive imaging modality for guiding treatment decisions in DME. However, visual acuity outcomes were not evaluated between the TD-OCT and SD-OCT evaluations. Future trials should evaluate whether or not detection of DME using SD-OCT versus TD-OCT ultimately leads to better visual outcomes.

Ranibizumab and Laser Combination Therapy

Safety and Effectiveness at 24 Months

Two-year safety and efficacy data from the RESTORE Extension Study were presented at the 2012 ARVO meeting. A total of 240 patients from the RESTORE
cohort were treated with ranibizumab on an as-needed basis with or without laser therapy according to ETDRS guidelines. Patients were retreated if they experienced a decrease in BCVA because of DME progression that was confirmed by clinical evaluation, OCT, or other anatomic and clinical assessments. Patients were treated at monthly intervals until they again reached stable visual acuity.

The gains in BCVA that were observed during the first 12 months were maintained at month 24. No safety signals were noted in either arm. The average number of injections in the ranibizumab monotherapy arm was 3.9 and in the laser/ranibizumab arm was 3.5. As with the RISE and RIDE data, results from the extension study of RESTORE further emphasized both safety and continued efficacy of ranibizumab in treating DME at 24 months. However, the addition of laser therapy did not significantly lessen the burden of ranibizumab injection therapy.

Ranibizumab or Laser Alone vs Combination Treatment

The 12-month results of the REVEAL study further corroborated the results of the RESTORE trial. The REVEAL study followed an Asian cohort with DME to evaluate the safety and efficacy of 0.5 mg of ranibizumab alone in 133 patients, 0.5 mg of ranibizumab in combination with laser therapy in 132 patients, and laser treatment alone in 131 patients. After receiving three monthly injections, the patients were treated as needed if they experienced declines in BCVA and/or DME progression, as found on OCT.

As in the RESTORE trial, ranibizumab used alone and with laser therapy resulted in similar results (gains of 5.9 and 5.7 ETDRS letters, respectively); both treatments were superior to laser therapy alone (gain of 1.4 ETDRS letters). The mean number of injections needed was 7.8 in the ranibizumab monotherapy group and 7.4 in patients given combination therapy. Ranibizumab given alone or with laser therapy offered the best outcomes with respect to best-corrected central foveal thickness.

Together, these results helped to reaffirm that ranibizumab monotherapy or in combination with focal/grid macular laser therapy is superior to laser therapy alone in treating DME patients. Further, patients receiving ranibizumab experienced a durable 12- to 24-month clinical benefit of therapy. As in the RISE and RIDE trials, no significant ocular or systemic safety signals were detected. Furthermore, these trials showed that adding laser therapy to administration of ranibizumab did not lower the injection burden over time when compared with the use of ranibizumab alone.

Dexamethasone Intravitreal Implant and Aflibercept

The use of other promising treatment modalities in treating DME patients was the subject of other clinical trials.

Dexamethasone Intravitreal Implant

Zucchiatti et al assessed the efficacy and safety of dexamethasone intravitreal implants in patients with refractory DME. The retrospective trial evaluated a single intravitreal injection of the implant in nine eyes with DME that had previously been treated with intraocular VEGF inhibitors or with corticosteroid and/or laser therapy. Investigators used SD-OCT to further evaluate the retina.

Administration of the dexamethasone intravitreal implant improved the central foveal thickness until month 4 post injection. Improvements in BCVA were maintained until month 4 post injection. Cataract progression did not occur. One patient experienced an elevation in intraocular pressure, which was treated successfully with topical therapy. These results were promising, but larger cohorts and longer follow-up certainly are necessary to evaluate the safety and efficacy of the dexamethasone intravitreal implant in patients with recalcitrant DME.

Aflibercept

Aflibercept is an established therapy for exudative age-related macular edema, but its role in treating patients with DME has not yet been fully established. This drug is a recombinant fusion protein comprising the key VEGF-binding domains of human VEGF receptors 1 and 2. It possesses a higher binding affinity than does ranibizumab or bevacizumab and features a binding capacity for placental growth factors 1 and 2, which contribute to excessive vascular permeability and retinal neovascularization.

Promising results with use of aflibercept in patients with DME recently were reported from the DA VINCI trial. In all, 221 patients with center-involving DME were randomized to receive one of the following aflibercept regimens: 0.5 mg every 4 weeks, 2 mg every 4 weeks, 2 mg every 4 weeks for 3 months followed by 2 mg given every 8 weeks, 2 mg every 4 weeks for 3 months followed by 2 mg given as needed, or macular laser photocoagulation. The primary outcomes were BCVA at 24 weeks and at 52 weeks, the proportion of eyes that gained ≥ 15 letters, and the mean changes in central foveal thickness as assessed by OCT.

At 52 weeks, the mean improvements in BCVA were +11.0 letters in the group given 0.5 mg every 4 weeks, +13.1 letters in the group given 2 mg every 4 weeks, +9.7 letters in the group given 2 mg every 4 weeks for the initial loading doses, +12 letters in those given 2 mg as needed after the initial loading doses, and +1.3 letters for those who underwent laser therapy. Further, > 15 letters of visual acuity were gained in 40.9%, 45.5%, 23.8%, 42.2%, and 11.4% of patients, respectively. The mean reduction in central foveal thickness, as measured by OCT, were 165.4 μm, 227.4 μm, 187.8 μm, 180.3 μm, and 58.4 μm, respectively. No significant ocular or systemic safety signals were identified.

Aflibercept therapy has resulted in promising results when compared with laser monotherapy for treating patients with DME. Future randomized trials are needed to evaluate the safety and long-term efficacy of the approved 2-mg dose of the drug in treating DME. Future trials should mirror the ranibizumab DME trials and compare use of aflibercept monotherapy, aflibercept plus focal/grid macular laser treatment, or laser monotherapy. Given the abundance of efficacy data reported for ranibizumab therapy, a
head-to-head comparison of aflibercept with ranibizumab monotherapy would provide valuable information for clinicians treating patients with DME.

**CONCLUSION**

Focal/grid macular laser monotherapy, a DME therapy that has been used for more than 20 years, now may not represent best clinical practice. This treatment still is the official standard of care for DME, but enough separate and repeated Level 1 evidence has shown treatment with VEGF inhibitors, and especially ranibizumab, to improve visual acuity and reduce central foveal thickness, as assessed by OCT, in affected patients. Thus, ranibizumab should be a part of regular DME treatment.

Results of both the RESTORE and REVEAL trials showed that ranibizumab used alone and with laser therapy produced comparable results. However, the addition of laser therapy did not significantly decrease the treatment burden when compared with ranibizumab monotherapy.

The best VEGF-inhibitor injection protocol—that is, monthly injection, as-needed treatment, or a treat-and-extend paradigm—has yet to be established. Results from both the RISE and RIDE trials both provide evidence that monthly injections of ranibizumab alone are safe and effective against DME through at least 24 months of treatment. In the trials reported, ranibizumab monotherapy ultimately resulted in lower progression to proliferative retinopathy than did treatment that included sham laser therapy; this finding demands further evaluation.

When coupled with the reassuringly low systemic and ocular adverse event rate related to ranibizumab use, these findings seem to support the use of ranibizumab monotherapy as first-line DME therapy. Certainly, this theory must be evaluated in a large, prospective, randomized clinical trial.

In addition, data regarding HbA1c levels and the efficacy of anti-VEGF therapy must be evaluated further. Although the study described was retrospective and small, it demonstrated a declining efficacy of bevacizumab with higher HbA1c levels. Perhaps anti-VEGF monotherapy for DME may not be as effective in the presence of less optimized glycemic control in a given patient.

Since the majority of the RISE and RIDE cohorts had HbA1c levels < 8.0, the results of RISE and RIDE and the push toward recommending ranibizumab monotherapy as first-line therapy for DME may need to kept in perspective. The evidence for using a higher dose of ranibizumab was limited in terms of the size of the cohort and the length of follow-up, but maximum efficacy seemed to occur at the standard 0.5-mg dose widely used to treat exudative AMD.

SD-OCT may detect DME with a greater sensitivity than does TD-OCT. However, whether this difference is important, or not, to the ultimate clinical outcome still must be established.

The dexamethasone intravitreal implant may provide an additional complement in cases of refractory DME, based, so far, on little evidence. The role of aflibercept in treating DME remains unclear. Still, initial phase II data demonstrate promising efficacy and safety with the use of these agents.

The results of these trials likely will result in more questions and numerous research studies. However, they stress that treatment with focal/grid macular laser alone no longer is the only standard of care to treat DME. As the results of the ANCHOR and MARINA trials in 2006 shifted the therapeutic paradigm for neovascular AMD, the landscape of approaches to DME is changing also.

**REFERENCES**

and Ophthalmology (ARVO); May 6–10, 2012; Fort Lauderdale, Florida. Abstract 5739.
22. Mitchell P. 2-Year safety and efficacy outcome of ranibizumab 0.5 mg in patients with visual impairment due to diabetic macular edema: an interim analysis of the RESTORE Extension Study. Presented at the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO); May 6–10, 2012; Fort Lauderdale, Florida. Abstract 4667.
23. Ohji M, Ishibashi T Sr; REVEAL Study Group. Efficacy and safety of ranibizumab 0.5 mg as monotherapy or adjunctive to laser versus laser monotherapy in Asian patients with visual impairment due to diabetic macular edema: 12-month results of the REVEAL study. Presented at the 2012 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO); May 6–10, 2012; Fort Lauderdale, Florida. Abstract 404.
CME Post Test

Using these pages as a worksheet, select the best answer to each question based on your reading of the articles in this issue of *The Ophthalmology Report*, then complete the evaluation form on page 32 and see the instructions below it to obtain continuing medical education (CME) credit for completing this activity.

1. The recently completed RISE and RIDE trials demonstrated improvements in visual acuity and retinal thickness in patients with diabetic macular edema (DME) who were treated with ___________, when compared with those who received sham injections.
   a. Ranibizumab
   b. Bevacizumab
   c. Aflibercept
   d. Pegaptanib

2. Participants in the VIEW 1 trial with neovascular age-related macular degeneration (AMD) showed a significantly superior increase in visual acuity (number of letters gained) when given ___________ compared with 0.5 mg of ranibizumab monthly.
   a. 0.5 mg of bevacizumab monthly
   b. 0.5 mg of aflibercept monthly
   c. 2.0 mg of aflibercept monthly
   d. 2.0 mg of aflibercept every 2 months

3. Which of the following has been associated with monthly vascular endothelial growth factor (VEGF) inhibitor therapy in patients with neovascular AMD but not in those with DME or macular edema following retinal vein occlusion (RVO) receiving the same treatment?
   a. Persistent edema
   b. Increased geographic atrophy
   c. Endophthalmitis
   d. Retinal hemorrhage

4. An analysis of data from both the first and second years of the CATT study revealed that patients with neovascular AMD who were treated with bevacizumab had a higher rate of ___________ than did those who were given ranibizumab.
   a. Gastrointestinal disorders
   b. Arterial thrombotic events
   c. Stroke
   d. Death

5. One-year data from the IVAN trial of ranibizumab versus bevacizumab in patients with neovascular AMD demonstrated a greater:
   a. Improvement in visual acuity with bevacizumab than with ranibizumab
   b. Increase in contrast sensitivity with ranibizumab than with bevacizumab
   c. Decrease in serum VEGF levels with bevacizumab than with ranibizumab
   d. Frequency of serious systemic adverse events with ranibizumab than with bevacizumab

6. Which of the following treatment regimens led to the greatest gain in visual acuity (ie, number of letters gained from baseline) at the 2-year point in the CATT study?
   a. Bevacizumab monthly
   b. Bevacizumab as needed
   c. Ranibizumab monthly
   d. Ranibizumab as needed

7. Which of the following was not a finding of the CATT study at the 2-year point?
   a. Treatment with bevacizumab was noninferior to ranibizumab therapy in terms of improvement in visual acuity.
   b. The frequency of serious systemic adverse events was higher among patients treated with bevacizumab than among those treated with ranibizumab.
   c. Visual acuity improved more with monthly dosing of bevacizumab or ranibizumab than with as-needed dosing of either drug.
   d. Patients treated with bevacizumab as needed required fewer injections of the drug than did patients who were treated with ranibizumab as needed.
8. Which of the following baseline characteristics in patients with neovascular AMD was described by Caprani and colleagues as being a predictor of nonresponse to treatment with ranibizumab?
   a. Presence of intraretinal fluid
   b. Macular thickness
   c. Lesion size
   d. Initial presenting visual acuity

9. Repeated intraocular injections are associated with an increased risk of endophthalmitis in patients with a history of:
   a. Hypertension
   b. Diabetes
   c. Myocardial infarction
   d. Seizure disorder

10. Zucchiatti et al evaluated the use of a dexamethasone intravitreal implant in patients with refractory DME, finding that a single injection improved central foveal thickness and best-corrected visual acuity until:
    a. Month 1 post injection
    b. Month 2 post injection
    c. Month 3 post injection
    d. Month 4 post injection
Instructions for Obtaining CME Credit for Completing This Activity

To receive CME credit for this free educational activity and a certificate of participation from the University of Cincinnati:

- Study the educational material presented in this issue of The Ophthalmology Report.
- Using pages 30–31 as a worksheet, answer all of the post-test questions based on the content of the articles.
- Visit www.TheOphthalmologyReport.com on the Web by August 30, 2013, select this issue of The Ophthalmology Report, and click “CME Credit” to apply for credit online and complete the post test and evaluation.
- Complete the registration form, enter your post-test answers from the worksheet on pages 30–31, and respond to all of the questions on the evaluation form, then click the button to submit your answers. The full text of each article may be accessed at www.TheOphthalmologyReport.com, should you need to refer to it again.
- If you answer correctly at least 8 (80%) of the 10 post-test questions, you will immediately receive credit for this educational activity and can access your CME certificate online by clicking the “Certificate” button at the bottom of the evaluation form. Follow the on-screen instructions to print or e-mail your certificate.

Evaluation

Your candid and thorough completion of this evaluation will help the University of Cincinnati improve the quality of its CME activities. Thank you for your participation.

1. As a result of this activity, I am more knowledgeable about the…
   a. Use of vascular endothelial growth factor (VEGF) inhibitors and other therapies in patients with diabetic macular edema.
   b. Efficacy and safety of VEGF inhibitor therapy of neovascular age-related macular degeneration (AMD) at different doses and when given monthly versus as needed.
   c. Recent data from the CATT and IVAN trials comparing bevacizumab with ranibizumab in patients with neovascular AMD.
   d. Results of clinical trials of VEGF inhibition in treating macular edema following retinal vein occlusion.

   

2. I found the content of this educational activity…
   a. Clearly written and well organized.
   b. Accurate and timely.
   c. Related to its overall objectives.
   d. Free from commercial bias.
   e. Relevant to my own clinical practice.

   

3. Did the information you received from this CME activity:
   a. Confirm the way you currently manage your patients?
   b. Suggest new options for managing your patients that you might apply in the future?

   

4. I used the information in this CME activity for … (check all that apply)

   

5. Approximately how long (in hours) did it take you to complete this activity, including this evaluation?  

   

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