Intraocular Pressure Should Be Monitored in Eyes Receiving Ranibizumab

Retrospective analysis of intraocular pressure (IOP) data from two phase III trials indicates that IOP should be monitored in patients with age-related macular degeneration (AMD) who receive ranibizumab, a recombinant humanized monoclonal antigen binding fragment that neutralizes all active isoforms of vascular endothelial growth factor (VEGF) A.

The two pivotal studies — the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) trials — demonstrated that intravitreal administration of ranibizumab significantly improves and maintains visual acuity in patients with wet AMD.

Although there were no meaningful differences in the mean pre-injection IOP at baseline or at any of the monthly follow-up visits in MARINA or ANCHOR, several publications have since reported long-term sustained elevation of IOP in a small subset of patients who received intravitreal injections of anti-VEGF agents for the treatment of neovascular (wet) AMD.

IOP characterization over time
Sophie J. Bakri, M.D., with the Department of Ophthalmology at Mayo Clinic’s campus in Rochester, Minnesota, led a team comprising colleagues from across the United States to analyze data from MARINA and ANCHOR. The goal was to compare the incidence of pre-injection IOP increases in the ranibizumab versus the sham or photodynamic therapy (PDT) groups and characterize further the pre-injection IOP over time during the 24-month treatment period. Results of the team’s post hoc analysis were published in Ophthalmology in 2014.

“...there were limitations for using these phase III studies to evaluate IOP events,” says Dr. Bakri. “The design of inclusion and exclusion criteria in these studies was not guided by specific needs likely to be present in an IOP-focused or a glaucoma-specific protocol.” The limitations resulted from:

• Multiple techniques for measuring IOP
• Nonstandardized time of measurement for baseline and subsequent IOPs
• No stratification at baseline for pre-existing IOP or glaucoma risk factors and medications
• No central corneal thickness measurements, gonioscopy, visual fields, nerve fiber layer assessments or detailed optic nerve examinations

One eye of each patient, the study eye, was treated in MARINA and ANCHOR. In their
Combination Therapy Offers Rapid Improvements in Vision and CST in Patients With Macular Edema Due to RVOs

In patients with branch retinal vein occlusions (BRVOs) and central retinal vein occlusions (CRVOs), the second-most-common retinal disorders, decreased blood flow through the retinal vasculature results in tissue ischemia, upregulates vascular endothelial growth factor (VEGF), breaks down the blood-retinal barrier and causes vision loss, primarily because of macular edema.

“Impressive results from the pivotal phase III registration trials led to the approval of ranibizumab and aflibercept for the treatment of macular edema due to CRVO and ranibizumab for BRVO,” says Michael W. Stewart, M.D., with the Department of Ophthalmology at Mayo Clinic’s campus in Jacksonville, Florida. “Compared with ranibizumab and aflibercept, however, bevacizumab is generally more available, is less expensive and produces comparable gains in vision — but level I evidence for the use of bevacizumab in the treatment of retinal vein occlusions is not available.”

Dr. Stewart’s team conducted a six-month pilot study that explored the effects of combined anti-VEGF (bevacizumab) and corticosteroid (dexamethasone implant) therapy on eyes with macular edema due to BRVO and CRVO, and compared them with bevacizumab monotherapy. Results appeared in Clinical Ophthalmology.
2014. “Our intent was to determine if intravitreal bevacizumab combined with the dexamethasone intravitreal implant 0.7 mg improves visual acuity and macular thickness more than does bevacizumab monotherapy in eyes with macular edema due to branch and central retinal vein occlusions,” says Dr. Stewart.

Thirty subjects were enrolled in the study. Eligible patients had macular edema of less than one year’s duration due to BRVO or CRVO, with central subfield thickness (CST) > 250 μm. Best corrected visual acuity scores at baseline were > 24 and < 20/80 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, or > 20/230 and < 20/25 Snellen equivalents. Subjects were randomly assigned to one of two study groups:

• The monotherapy group (15 eyes) received intravitreal bevacizumab 1.25 mg at baseline followed by a sham dexamethasone implant injection at the time of randomization one week later. Additional bevacizumab injections were given at monthly intervals when the CST measured > 250 μm.

• The combination therapy group (15 eyes) received intravitreal bevacizumab 1.25 mg at baseline followed by an intravitreal dexamethasone implant 0.7 mg (DEX) injection at the time of randomization one week later. Bevacizumab injections were repeated monthly when the CST measured > 250 μm. Re-injections of DEX or sham DEX (in the monotherapy group) were performed at month four or month five (one week after the repeat bevacizumab injection) if the CST measured > 250 μm.

At each visit, best corrected ETDRS visual acuities were measured and slit-lamp examinations, intraocular pressure measurements, fundus examinations and time-domain optical coherence tomography were performed. Fluorescein angiography was performed at baseline and at month six.

**Secondary end points met**
The team identified the study’s primary end point as visual acuity in the combination group compared with visual acuity in the bevacizumab group at six months. Secondary end points included mean changes in CST, proportions of eyes with CST < 250 μm and number of bevacizumab injections required by each group.

At six months, several secondary end points were met. Patients receiving combined therapy:

• Required fewer bevacizumab re-injections than did those receiving monotherapy (two versus three; \( P = 0.02 \))
• Experienced greater mean reductions in CST from randomization (- 56 μm versus + 45 μm; \( P = 0.01 \))
• Were more likely to have resolved all edema (CST < 250 μm) (7/11 versus 2/14; \( P = 0.02 \))

The primary end point was not met. Mean visual acuity changes from baseline were similar in the two groups (\( P = 0.75 \)).

“This pilot trial suggests that, compared with bevacizumab monotherapy, combining bevacizumab with the dexamethasone implant leads to more rapid improvements in vision and CST in patients with macular edema due to RVOs, while requiring fewer bevacizumab injections,” says Dr. Stewart. “For patients who are already pseudophakic and who are not steroid responders, adding DEX to a regimen of bevacizumab injections is unlikely to significantly increase the risk of complications, and for those patients who are unable to visit physicians’ offices monthly, less frequent treatments with combination therapy may be a palatable alternative to the more frequently administered bevacizumab monotherapy.”

**For more information**

**Residents Receive VitreoRetinal Surgery Foundation (VRSF) Research Awards**
Lauren A. Dalvin, M.D., and Harish Raja, M.D., with the Department of Ophthalmology at Mayo Clinic’s campus in Rochester, Minnesota, received 2014 VRSF Research Awards.

**Reimbursement Policy Creates a Conflict of Interest for Patients and Physicians**
In 2009, the Centers for Medicare & Medicaid Services (CMS) modified the reimbursement policy for blepharoplasty and blepharoptosis repair, the two most commonly performed eyelid operations, to prohibit separate payment for blepharoplasty and blepharoptosis repair if both are performed on an ipsilateral upper eyelid within a 90-day period. The National Correct Coding Initiative (NCCI) mandate was intended to prevent “bundling”—improper payment for procedures that are considered to be components of a more comprehensive process.

Elizabeth A. Bradley, M.D., with the Department of Ophthalmology at Mayo Clinic’s campus in Rochester, Minnesota, speculated whether such changes in physician reimbursement,
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The 198 physicians who participated in the survey represented office-based practices, freestanding ambulatory surgical centers, academia, nonprofit community hospitals and for-profit community hospitals. They reported receiving productivity-based payment, a combination of salaried and productivity-based payment, salaries only, and other self-employment, and retirement. Their responses indicated practice change:

- Before the CMS reimbursement policy change, 77 percent of ocuoplastic surgeons performed blepharoplasty and blepharoptosis repair in the same sitting, whereas 37 percent did so after the policy change.
- Compared with before the policy change, more surgeons performed the two procedures at least three months apart (4 percent before vs. 29 percent after).
- Compared with before the policy change, surgeons billed patients for a cosmetic blepharoplasty more often (5 percent before vs. 12 percent after).

The data support the speculation that changes in physician reimbursement may alter physician behaviors,” says Dr. Bradley. “These surgeons made a significant change in the delivery of ptosis and blepharoplasty surgical services after the bundling of payment for these two procedures by the CMS. This change is not desirable to most of the patients surveyed.”

In 2013, the CMS implemented the Bundled Payments for Care Improvement initiative, enrolling select organizations that receive bundled payments for acute and post-acute care episodes. “Our study also indicates that such changes may ultimately mitigate the health care savings from bundling,” says Dr. Bradley. “We estimate the CMS saves approximately $287 with the new bundling reimbursement for each case performed. If a physician performs a blepharoplasty and blepharoptosis repair 90 days apart, however, the cost increase to the CMS is approximately $1,500. Unbundling a single case negates the cost savings of approximately five bundled cases.”

Physician practice habits
A five-question Web-based survey was distributed to 510 unique physician email addresses obtained from the American Society of Ophthalmic Plastic and Reconstructive Surgery in 2010. The survey represented office-based practices, freestanding ambulatory surgical centers, academia, nonprofit community hospitals and for-profit community hospitals. They reported receiving productivity-based payment, a combination of salaried and productivity-based payment, salaries only, and other self-employment, and retirement. Their responses indicated practice change:

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