MAYO CLINIC

Ophthalmology Update

Ophthalmology News From Mayo Clinic

Vol. 1, No. 3, 2011

Bevacizumab Expands Treatment Options for Patients With Age-Related Macular Degeneration

INSIDE THIS ISSUE

Sophie J. Bakri, MD

First-year results from a National Eye Institute–funded study of neovascular age-related macular degeneration (AMD) treatments indicate that bevacizumab (Avastin), a drug commonly used off label to treat new blood vessel growth due to wet AMD, is as effective as ranibizumab (Lucentis) for the treatment of AMD when given at the same dosing schedule.

Researchers participating in the Comparison of AMD Treatments Trials (CATT) report that Avastin and Lucentis are equally effective in halting eye damage that leads to blindness. Avastin costs approximately $50 per treatment. Lucentis, the US Food and Drug Administration–approved treatment for wet AMD, costs $2,000. Both drugs were developed by Genentech.

The Mayo Clinic Department of Ophthalmology is one of the major centers participating in CATT. Sophie J. Bakri, MD, the study principal investigator at Mayo Clinic, says that based on first-year results, patients at Mayo Clinic will be given the choice of either drug. Dr Bakri notes, however, that subgroup analyses being performed by the CATT group may confirm whether patients with specific lesion types respond better to one drug vs the other.

CATT Compares Drugs and Dosing

CATT investigators compared the effects of both drugs and of 2 different dosing regimens: monthly use vs an as-needed regimen. Results show that monthly use of either bevacizumab or ranibizumab results in the same visual acuity outcome, the primary outcome measure for CATT. Researchers also observed equivalent visual-acuity outcomes with both the monthly and the as-needed regimens of ranibizumab.

Although the results of the as-needed regimen with bevacizumab are similar to those of the as-needed regimen with ranibizumab, the as-needed bevacizumab regimen compares less favorably with monthly regimens for either bevacizumab or ranibizumab.

"In Mayo's collaborative model of care, patients are actively involved in their health care decisions," says Dr Bakri. "CATT demonstrates that the less expensive drug and as-needed dosing are viable treatments. These trial results allow us to provide patients with AMD with more choices and help them to make better-informed decisions about their treatment options."

Investigators for CATT will continue to monitor patients through a second year of treatment. The additional data will provide information on longer-term effects of the drugs on vision and safety.

"AMD is the leading cause of vision loss and blindness in older Americans," says George B. Bartley, MD, chair emeritus of the Department of Ophthalmology. "The CATT results allow Mayo Clinic to add valuable treatment options for patients with AMD. Mayo, in turn, adds value to multicenter randomized clinical trials because of the excellent quality of the data it contributes. Such data are a result of Mayo's integrated medical record, which was the world's first and is now fully electronic. Additionally, the superb study coordinators at Mayo ensure that every *i* is dotted and every *t* is crossed."

Learn More About CATT

Visit www.clincialtrials.gov (NCT00593450) or contact the Mayo Clinic clinical trials office at 507-538-7623.

Read about CATT in the May 19, 2011, issue of *The New England Journal of Medicine* at www.nejm.org.

View video of Dr. Bakri discussing macular degeneration on YouTube at www.youtube.com/watch?v=WshDIMKs7W8.

Current Assessment and Management of Intermittent Exotropia

Intermittent exotropia is one of the most common forms of childhood strabismus, affecting up to 10 in every 1,000 children. Nevertheless, the debate continues on when to treat intermittent extropia and which treatments are effective.

Assessment of severity of intermittent exotropia is challenging because the deviation is sometimes present and sometimes absent. The frequency of the manifest deviation is often termed *control*, but until recently, control has mainly been assessed subjectively: parents are asked what proportion of the day they see the child's eye drift outward. Unfortunately, parental report can be unreliable, so new control measures are needed.

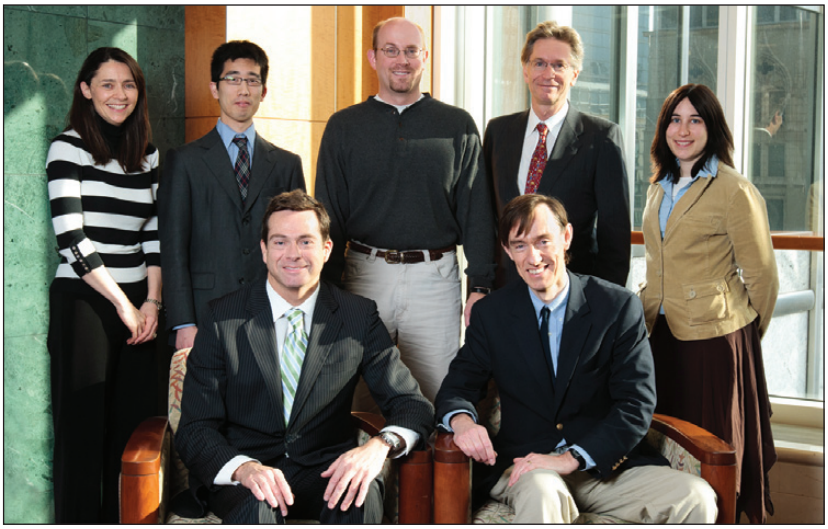
The strabismus team at Mayo Clinic in Rochester, Minnesota—Jonathan M. Holmes, MD, Brian G. Mohney, MD, and Michael C. Brodsky, MD; Tomohiko Yamada, OD; research orthoptists Sarah R. Mickow and Laura Lepor; and research technologist David A. Leske—has worked on new outcome measures for intermittent exotropia for several years.

Control Scale Documents Exotropia Severity

The team developed and validated a control scale that allows documentation of severity using a standardized observation and dissociation protocol. The child is observed for 30 seconds looking at a distance target, such as a video at the end of the examination room. A team member notes whether the exotropia is constant (grade 5) or is present >50% (grade 4) or <50% (grade 3) of the time. The assessment is repeated with the child looking at a near target. If no spontaneous tropia is present, the right eye is dissociated with a 10-second standard cover and time to refusion is noted. The dissociation is repeated, covering the left eye, and then repeated over the eye demonstrating the longest recovery. The worst recovery is scored: >5 seconds (grade 2), 1-5 seconds (grade 1), or <1 second (grade 0). A grade is assigned for distance and near fixation separately.

Using this new control scale, team members determined whether control varied through the day or whether a single assessment was sufficient. About 50% of the children studied had variable control (eg, excellent in the morning and poor in the afternoon), but sometimes control improved as the day went on. These data suggest that a single assessment of control does not necessarily represent severity of intermittent exotropia.

In a study published in the *American Journal of Ophthalmology* online in August, the strabismus team reported that the average of 3 control assessments during a single office examination best characterizes control of intermittent exotropia. Three assessments are now the standard at Mayo Clinic.



Left to right, back row, research orthoptist Sarah R. Mickow, Tomohiko Yamada, OD, research technologist David A. Leske, Michael C. Brodsky, MD, and research orthoptist Laura Lepor; front row, Brian G. Mohney, MD, and Jonathan M. Holmes, MD.

Quality-of-Life Questionnaire

To broaden the ability to assess severity of intermittent exotropia, the team developed a new quality-of-life instrument, the intermittent exotropia questionnaire. Based on a series of structured interviews with children who had intermittent exotropia and their parents, the validated questionnaire has 3 components:

- Child questionnaire
- Parallel proxy questionnaire (how the parent feels the condition affects the child)
- Parent questionnaire (how the child's condition affects the parent)

Initial studies revealed that the child is rarely bothered by the condition, but parents often express various types of worry. Since parental worry may drive surgical decisions, identifying and addressing parental concerns are an important aspect of managing intermittent exotropia.

New Methods Measure Distance Stereoacuity

Another facet of intermittent exotropia assessment is evaluation of stereoacuity, at both near fixation and distance fixation. The team designs, develops, and tests new methods to measure distance stereoacuity and has found that not all stereotests are equal. Some, such as Frisby-Davis 2, are relatively easy for children with intermittent exotropia, who can perform well despite poor control. Other tests, such as Distance Randot, are more challenging.

Recent studies suggest that near random dot stereoacuity is almost always preserved in intermittent exotropia, so the philosophy of early surgery to preserve good near stereoacuity is difficult to justify.

Strabismus Trials Enroll Patients

This Mayo team helps to lead 2 national randomized clinical trials, conducted through the Pediatric Eye Disease Investigator Group network, that are actively enrolling patients:

- Intermittent Exotropia Study 2 compares patching 3 hours a day with observation alone. It will provide information about the natural history of the condition and whether patching reduces the deterioration rate
- Intermittent Exotropia Study 1 compares 2 common surgical approaches for intermittent exotropia: bilateral lateral rectus recessions and unilateral recess-resect procedures

Based on evidence available in 2011, this team's philosophy is conservative. Team members monitor children who have intermittent exotropia without surgery until there is evidence of deterioration (loss of near stereoacuity or constancy of the deviation at both distance and near). Other reasons for surgery include social concern, which is more common in older children, and symptoms of diplopia or strain. Management of intermittent exotropia will evolve in the next few years on the basis of these and other ongoing studies.

Clinical Trials Seek Participants

For more information, access http://clinicaltrials.mayo.edu/ and search for *strabismus* or visit www.clinicaltrials.gov.

Intermittent Exotropia Study 1 (IXT1)
A randomized trial of bilateral lateral rectus recession vs unilateral lateral rectus recession with medial rectus resection for intermittent exotropia, NCT01032603

Intermittent Exotropia Study 2 (IXT2)
A randomized clinical trial of observation vs occlusion therapy for intermittent exotropia, NCT01032330

The Role of Fluctuation in the Relationship Between Intraocular Pressure Variability and Glaucoma Risk

Research conducted over the past 7 years about intraocular pressure (IOP) and glaucoma risk has led Arthur J. Sit, MD, with the Department of Ophthalmology at Mayo Clinic to focus on a fundamental issue: understanding why IOP varies.

"IOP is the primary risk factor for glaucoma and the only risk factor that can be treated," says Dr Sit, "but we don't fully understand how IOP is involved with glaucoma, especially the fluctuations."

Conflicting Results

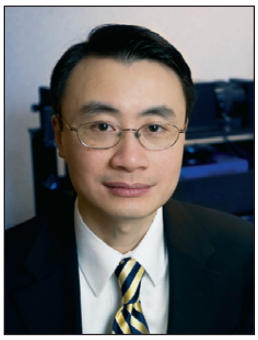
In recent years, several studies have addressed the importance of IOP fluctuations (the change within 24 hours) and variations (the change during periods longer than 24 hours) as independent risk factors for glaucoma progression:

- The Advanced Glaucoma Intervention Study (AGIS) suggests that IOP variability between visits is a more important predictor of glaucoma progression than mean IOP, particularly in patients with low IOP.
- The Diagnostic Innovations in Glaucoma Study (DIGS) and the Early Manifest Glaucoma Trial (EMGT) suggest the opposite: IOP variability between visits is not predictive of glaucoma progression, but mean IOP is the important risk factor.

Differences in patient populations, study design, data collection, and data analysis may account for the seemingly conflicting results. Increasing evidence, however, also suggests that incremental reduction of IOP may be subject to the principle of exponentially diminishing benefit.

Results from AGIS, EMGT, and the Collaborative Initial Glaucoma Treatment Study suggest that at low IOP, each incremental reduction in pressure contributes less to reducing progression risk because of exponentially diminishing benefit. IOP variability would therefore manifest as a risk factor for glaucoma. At higher IOP, the benefit may be linear, and IOP variability would not appear to be a risk factor. It is the subset of patients with low IOP who appear to be at risk from IOP variability. "The exponentially diminishing benefit at low IOP may explain the conflicting study results," says Dr Sit.

Dr Sit suggests that the method of measuring IOP variability may also be inaccurate. The use of standard deviation of the mean IOP as a measure of variability captures only the absolute changes above and below baseline, which may underestimate the risk at low IOP and overestimate the risk at high IOP. Instead, measuring percentage variation may be better at capturing the risk associated with IOP variability.



Arthur J. Sit, MD

Mayo Clinic
Ophthalmology Update

Medical Editors:
George B. Bartley, MD
Jay C. Erie, MD

Contact Us

Mayo Clinic welcomes inquires and referrals, and a request to a specific physician is not required to refer a patient.

Arizona
866-629-6362

Florida
800-634-1417

Minnesota
800-533-1564

Resources

mayoclinic.org/medicalprofs

- Clinical trials
- CME
- Grand Rounds
- Scientific videos
- Online referrals

The Fluctuation Factor

"None of the major glaucoma studies addressed short-term IOP fluctuation as a risk factor for glaucoma progression," notes Dr Sit, "but long-term IOP variability may reflect differences in natural history of the disease, as well as the effect of therapy changes."

The question of whether IOP fluctuation during diurnal and nocturnal periods predicts glaucoma progression must also be considered, but to do so, a continuous IOP measurement device is needed. "There is a lack of evidence to suggest that long-term IOP variability is an appropriate surrogate measure for diurnal and nocturnal fluctuation in a 24-hour period," says Dr Sit. "It is possible that circadian IOP fluctuations may be of greater predictive value than long-term IOP variability, but there are no clinical tools currently available to assess that possibility."

Mayo Clinic researchers have tried to develop a contact lens–based system to measure IOP over 24 hours. "It's difficult because the system must measure at the surface of the eye, which is a constantly changing environment," notes Dr Sit. "We're most interested in tracking 24-hour variability. There is a clear, circadian rhythm to pressures. They're higher in morning and decrease over the day, and then there is a marked increase in IOP at night. The importance of these IOP patterns to glaucoma needs to be determined."

Next Steps

Other research conducted by Dr Sit's team focuses on the fundamental causes of the 24-hour IOP pattern. As well, their research demonstrates that many routine activities can cause pressures to fluctuate, but it is unclear how important those fluctuations are to glaucoma pathogenesis.

"There are defects in our knowledge base," says Dr Sit. "We need better tools to continuously measure IOP, so that we can begin to understand the impact of IOP fluctuations and variations on glaucoma and take appropriate therapeutic steps to prevent and treat the disease."

The paper "Intraocular Pressure Variability and Glaucoma Risk: Complex and Controversial," coauthored by Dr Sit and Kuldev Singh, MD, MPH, was published in the *Archives of Ophthalmology* in August (2011;129[8]:1080-1).

Continuous Professional Development

Retina Cases With Fluorescein Angiography and Imaging (Retina CFAN)

February 6-10, 2012, St. Maarten

Specialists present their experiences with rare cases or rare complications of common cases. For more information or to register, call 800-323-2688 (toll free), e-mail cme@mayo.edu, or visit www.mayo.edu/cme/ophthalmology.

Uveal Melanoma Treatment Study Recruits Participants

Mayo Clinic in Rochester, Minnesota, is recruiting patients for the National Cancer Institute-collaborative clinical trial Temozolomide or MEK Inhibitor AZD6244 in Treating Patients With Metastatic Melanoma of the Eye.

Nearly 160 men and women age 18 years and older with a histologically or cytologically confirmed diagnosis of metastatic uveal melanoma are needed for the randomized phase 2 trial, which will study temozolomide to see how well it works compared with MEK inhibitor AZD6244 in treating patients with metastatic melanoma of the eye.

"Drugs used in chemotherapy work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing," notes Jose S. Pulido, MD, coinvestigator for the study. "MEK inhibitor AZD6244 may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. It is not yet known whether temozolomide is more effective than MEK inhibitor AZD6244 in treating melanoma of the eye."

For more information or to refer patients for the trial, visit www.clinicaltrials.gov (NCT01143402) or contact the Mayo Clinic cancer clinical trials office at 507-538-7623.

MAYO CLINIC | 4500 San Pablo Road Jacksonville, FL 32224 | 200 First Street SW Rochester, MN 55905 | 13400 East Shea Boulevard Scottsdale, AZ 85259
mayoclinic.org

MC4294-1211