In patients with age-related macular degeneration (AMD), bevacizumab (Avastin; Genentech) and ranibizumab (Lucentis; Genentech) had equivalent effects on visual acuity when administered in the same dosing regimen. This was according to the 1-year results of the Comparison of AMD Treatment Trials (CATT), presented by Daniel F. Martin, MD, at the ARVO annual meeting in Fort Lauderdale, Florida. These data were made available online ahead of print in the *New England Journal of Medicine*.1

The multicenter, single-masked, noninferior CATT, conducted at 43 US clinical sites, included 1,185 patients aged 50 years or older who had neovascular AMD and visual acuities between 20/25 and 20/320. Participants were randomized to one of four treatment groups: ranibizumab monthly, ranibizumab as needed (PRN) with monthly evaluation, bevacizumab monthly, or bevacizumab PRN with monthly evaluation. The primary outcome measure was the mean change in visual acuity at 1 year, with a noninferiority limit of five letters on the eye chart. The confidence interval used for the study was 99.2%.

At 1 year, the mean gain in visual acuity was equivalent in the groups receiving monthly treatment with bevacizumab and ranibizumab (8.0 letters and 8.5 letters gained, respectively). PRN bevacizumab and ranibizumab were also equivalent, with 5.9 letters and 6.8 letters gained, respectively. PRN ranibizumab was equivalent to monthly treatment with that agent, although the comparison between PRN bevacizumab and monthly bevacizumab was inconclusive.

"For the last 5 years, ophthalmologists and patients have been confronted with the choice every day of which drug to use and how often," Dr. Martin said. "These results inform that decision, which is what our primary goal was from the onset of this study. [Ranibizumab] and [bevacizumab] were equivalent, in fact, virtually identical, for visual acuity at all time points when administered at the same dosing regimen. We produced a very good PRN result, but it was achieved, I would argue, by the diligent follow-up that we gave and the number of injections that we gave over that period of time."

The mean decrease in the central retinal thickness was greater in the ranibizumab-monthly group (196 µm) than in the other groups (152-168 µm; \( P = .03 \) by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for both drugs (\( P > .20 \)). The proportion of patients with serious systemic adverse events, primarily hospitalizations, was higher among subjects assigned to bevacizumab than ranibizumab (24.1% vs 19.0%). Excess events were broadly distributed in disease categories not identified in previous studies as areas of concern.

"Both drugs produced an immediate and substantial decrease in fluid," Dr. Martin said. "Neither drug eliminated fluid in the majority of eyes, although more eyes were completely dry with [ranibizumab] monthly. There was no difference in death, stroke, myocardial infarction, or hypertension between drugs at 1 year, and death, stroke, and myocardial infarction were the primary prespecified adverse events we were interested in. There were nongeneric [systemic adverse event] differences detected; the significance of those is unknown and requires additional study."

Following the results of the CATT study, the AAO released a statement saying the data will help physicians fully understand the potential benefits and risks associated with each treatment.

"The initial results of the CATT study affirm the position of the [AAO] that both Lucentis and Avastin should be available for the treatment of AMD," AAO CEO David W. Parke II, MD, said in the statement. "The ophthalmic community is fortunate to have these two highly effective drugs for treating this devastating condition. The treatment plan must be selected by the ophthalmologist and the patient, taking into account a host of complex factors. This important study provides critically important information that further empowers ophthalmologists to make evidenced-based decisions in choosing the treatment option that provides the best care for their patients."

Patients will be observed for a second year, during which an additional randomization of patients will occur. Half of the patients originally assigned to the two monthly treatment groups will be switched to PRN dosing, while the other half will continue on the monthly regimen, Dr. Martin said.
The outcomes considered in year 2 will include whether the visual acuity findings at 1 year remain throughout the second year and if the anatomical differences observed will have long-term visual consequences, according to Dr. Martin. The investigators will also assess whether the use of spectral-domain optical coherence tomography will result in the detection of more fluid and, thus, the need for more injections and, lastly, if there are genetic findings that predict outcomes, durability response, and the number of injections required.

A separate study, sponsored by Genentech, shows that the risk of systemic and ocular adverse events, including death, may be higher among patients treated with bevacizumab compared with ranibizumab. During a session at ARVO, Emily Gower, MD, of the Johns Hopkins University, presented the results of the safety analysis.

To conduct the analysis, Dr. Gower and colleagues obtained Medicare claims data for 77,886 individuals who had at least one treatment claim for wet AMD between 2005 and 2009. Overall, their results showed that patients receiving bevacizumab had an 11% increased risk of death and a 57% increased risk of hemorrhagic stroke compared with patients receiving ranibizumab.

“Our data do show an increased risk of all-cause mortality, hemorrhagic stroke, intraocular inflammation, and cataract surgery when using bevacizumab compared to ranibizumab,” Dr. Gower said. “There is a suggestion of an increased risk of ocular hypertension or glaucoma in ranibizumab users. I do want to highlight that, due to uncontrolled confounding and the other limitations we’ve discussed here, we can’t establish causality based on these treatments. I really view this study as hypothesis-generating as opposed to formulating final opinions on this analysis.”

The FAME study consisted of two identical, double-masked, sham-controlled, multicenter, phase 3 studies, trial A and trial B, and included a total of 956 patients with DME. Participants were randomized 2:2:1 to receive 0.2 µg Iluvien (n = 376), 0.5 µg Iluvien (n = 395), or placebo (n = 185). The primary endpoint was the proportion of patients who gained 15 letters or more in BCVA at month 24. As previously reported, the prespecified primary endpoint for the FAME study was met for low-dose Iluvien in both trial A and trial B.

“The FAME trial showed that it did meet its primary readout, but the question arose, ‘Was there a particular subgroup of patients with DME that had a greater benefit-to-risk ratio?’” Dr. Antoszyk said. “The ideal subgroup would have to have a statistically significant visual acuity result at months 24 and 36, a greater benefit-to-risk ratio, and should be identifiable prior to administration of the Iluvien implant.”

The subgroup consisted of 536 patients who had had DME for 3 years or more and 416 patients who had had DME for less than 3 years. Of the Iluvien-treated patients with DME for 3 years or more, 33.6% in trial A and 42.4% in trial B achieved an improvement in BCVA of 15 letters or more at month 30. At month 36, 31.8% of the patients in trial A and 36.4% of the patients in trial B had an improvement in BCVA of 15 letters or more.

Of the patients who received the control treatment, 13.6% in trial A and 13.2% in trial B had an improvement in BCVA of 15 letters or more at 36 months. No statistically significant improvement in BCVA was observed in the subgroup of patients with DME of less than 3 years’ duration. Consistent with the full patient population, approximately 75% of the patients treated with Iluvien received only one insert during the 36-month study.

At 36 months, the IOP had increased to 30 mm Hg or more at any time point in 14.8% of Iluvien-treated patients in the subgroup versus 18.3% of Iluvien-treated patients in the full patient population. In addition, 5.3% of Iluvien-treated patients in the subgroup underwent an incisional surgical procedure to reduce elevated IOP compared with 4.8% in the full patient population. In the subgroup, the incidence of cataracts among Iluvien-treated patients who had a natural lens at baseline was 86%, with 85% undergoing a cataract operation, compared with 80% and 74.9%, respectively, in the full patient population.

Based on the results of the FAME study, Alimera has submitted a new drug application to the FDA for regulatory approval of low-dose Iluvien.


2. Gower EW, Cassard S, Chu L, et al. Adverse event rates following intravitreal injection of Avastin or Lucentis for treating macular edema (FAME) study, presented by Andrew N. Antoszyk, MD, at ARVO.1
Merck to Acquire Inspire Pharmaceuticals for $430 Million

In a move to expand its ophthalmology business in the United States, Merck & Co., Inc. (Whitehouse Station, NJ), announced it will acquire Inspire Pharmaceuticals, Inc. (Raleigh, NC), for $430 million.

Under the terms of the agreement, Merck, through a subsidiary, will commence a tender offer for all outstanding common stock of Inspire at a price of $5 per share in cash. That represents a 26% premium to the closing price of Inspire’s common stock on April 4, 2011. The transaction has been unanimously approved by the boards of directors of both companies. Warburg Pincus Private Equity IX, LP (New York, NY), which owns approximately 28% of the outstanding shares of Inspire, has agreed to tender all of its shares into the offer, according to Merck.

Inspire’s key product is AzaSite (azithromycin ophthalmic solution 1%), a treatment for bacterial conjunctivitis. AzaSite’s revenues increased 22% to $42.7 million in 2010, according to Inspire. AzaSite is also being developed as a treatment for blepharitis. A recent study published in Cornea showed that the drug produced a significant improvement in the signs and symptoms of blepharitis after 4 weeks of treatment compared with baseline. The improvement persisted in a 4-week follow-up period.1

Merck will also acquire Inspire’s rights to royalties on sales of the dry eye drug Restasis (topical cyclosporine 0.05%) and Elestat (epinastine) for allergic conjunctivitis (both from Allergan, Inc.).

Merck’s ophthalmology business includes the proposed glaucoma treatment Saflutan (tafluprost), which the FDA is reviewing. Merck’s ophthalmic portfolio includes the glaucoma drugs Cosopt (timolol-dorzolamide) and Trusopt (dorzolamide HCl). Merck lost US marketing exclusivity on both products in 2008, and sales of those products declined 4% in 2010 to $484 million. The deal with Inspire can help fill the void created when the company lost its US rights to those products.

“Since Cosopt went off-patent, we’ve had a very small presence in ophthalmology in the United States,” said Ian McConnell, a spokesman for Merck’s Scientific Affairs, Research and Development, and Licensing and Partnerships, in an interview with Advanced Ocular Care. “We haven’t really had a sales force, but with Saflutan progressing and having been filed with the FDA, it was important that we reestablish our presence [in ophthalmology], and reestablish a strong sales force.”

Despite paying a 26% premium for Inspire based on the stock price the day the deal was announced, Merck may have been opportunistic in its timing of the purchase.

In January, Inspire suffered a blow to its pipeline when its cystic fibrosis drug denufosol failed in a phase 3 study (TIGER-2). The setback caused Inspire’s stock price to drop 55%. Adrian Adams, president and CEO of Inspire, said, based on an extensive analysis of various strategic options since the results of the TIGER-2 clinical trial were announced, the deal with Merck provides “a compelling and timely opportunity for our shareholders to realize the value of their investment in Inspire.”


Alcon and Novartis Complete Merger and Form New Alcon Division

Shareholders of both Alcon, Inc. (Huenenberg, Switzerland), and Novartis AG (Basel, Switzerland) have approved the merger of the two companies, completing the biggest takeover in Swiss corporate history and reshaping the global eye care market. Alcon will become a newly formed division within Novartis and will continue to be headquartered in Fort Worth, Texas, with operations in 75 countries, according to an Alcon news release.

After more than a year and a half of negotiations, the deal was completed, calling for Novartis to pay $12.9 billion for the 23% of Alcon it does not already own. The deal, which was reached in December 2010, brings the total acquisition price to $51.6 billion and gives Novartis control of 70% of the global eye care market. Under the terms of the agreement, Alcon shareholders will receive 2.9228 Novartis shares, which include the dividend adjustment, and $8.20 in cash for each share of Alcon, for a total consideration of $168 per share. In a statement, Novartis Chief Executive Joseph Jimenez said Novartis expects its now-bolstered eye care division to have annual revenues of $9 billion and to produce an annual cost savings of $300 million.

With the Alcon acquisition, Novartis will add eye care as a fifth growth platform, alongside innovative pharmaceuticals, generics, vaccines and diagnostics, and consumer health, according to Novartis.

(Continued on page 14)
Coronary Artery Bypass Rates Declined Significantly

The number of patients undergoing coronary artery bypass graft (CABG) surgery decreased dramatically between 2001 and 2008, according to a study in the Journal of the American Medical Association.¹

Researchers from the University of Pennsylvania conducted a study of patients undergoing CABG surgery or percutaneous coronary interventions (PCIs) between 2001 and 2008 in US hospitals in the Healthcare Cost and Utilization Project’s Nationwide Inpatient Sample, which reports inpatient coronary revascularizations. These data were supplemented by Medicare outpatient hospital claims.

A 15% decrease in the annual rate of coronary revascularizations was observed between 2001 to 2002 and 2007 to 2008. The annual CABG surgery rate decreased steadily from 1,742 CABG surgeries per million adults per year in 2001 to 2002 to 1,081 CABG surgeries per million adults per year in 2007 to 2008. There was, however, no significant change in PCI rates. Between 2001 and 2008, the number of hospitals providing CABG surgery increased by 12%, and the number of hospitals providing PCI increased by 26%. The median CABG surgery caseload per hospital decreased by 28%, and the number of hospitals providing fewer than 100 CABG surgeries per year increased from 23 in 2001 to 62 in 2008.

“Our data imply a sizeable shift in cardiovascular clinical practice patterns away from surgical treatment toward percutaneous, catheter-based interventions,” study author Peter W. Groeneveld, MD, MS, said in a news release. “This is concerning given that recent data from a national trial indicated CABG surgery remains the better choice for patients with previously untreated three-vessel or left main coronary artery disease.” □


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Bausch + Lomb, Technolas Announce Agreement to Distribute Femtosecond Laser

Bausch + Lomb (Rochester, NY) and Technolas Perfect Vision GmbH (Munich, Germany) announced an agreement in principle to globally distribute the first femtosecond laser capable of performing both cataract and refractive procedures on one platform. Financial terms were not disclosed.

Under the arrangement, Technolas will develop and manufacture its femtosecond cataract and refractive laser system from its facilities in Munich, and maintain the product through its current worldwide service organization, according to Bausch + Lomb. Technolas will continue to commercialize the refractive portfolio.

In an interview with Eyetube.net, Robert E. Grant, CEO and president of Bausch + Lomb Surgical, said the key selling point for the company’s acquiring the rights to distribute the platform was the laser’s ability to perform both cataract and refractive procedures.

“We’ve done research in this industry and looked at the impact that femtosecond will have on the market,” Mr. Grant said. “We believe strongly that this is going to significantly transform the industry and be much better for patients, and it’s going to help us move the industry toward 20/20 vision.”

He added, “The industry has changed a lot over the past 20 years. With the advent of excimer laser technology, the whole refractive and cataract specialties really split apart, and the interesting thing coming back [to San Diego] in 2011, is what’s going to bring the industry and these subspecialties back together again is actually the advent of femtosecond technology.”

Technolas was established in 2009 through a joint venture between Bausch + Lomb and 20/10 Perfect Vision AG to develop advanced refractive and cataract technologies. The company specializes in both femtosecond and excimer laser businesses, with current innovations focused on laser cataract surgery and the correction of presbyopia. Commercialization of the laser platform is expected to begin in the second half of 2011. Technolas previously announced that it filed for 510(k) clearance in the United States. □

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