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Article

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One year after receiving FDA approval, ranibizumab (Lucentis, Genentech) has already established itself as by far the predominant first-line treatment for the wet form of age-related macular degeneration (AMD). The drug has brought new hope for improved vision to patients who had little hope before and has given retina specialists a potent new weapon with which to fight the anticipated increase in wet AMD cases as the huge baby boomer generation enters its senior years.

The numbers speak for themselves. Ranibizumab is on track to produce approximately $800 million in first-year sales for Genentech. The competing AMD drug pegaptanib sodium (Macugen, OSI Pharmaceuticals/Pfizer) recently recorded quarterly US sales of $7 million and verteporfin for injection (Visudyne, QLT/Novartis), is currently tracking US sales at about $8.4 million per quarter.

DOCTORS SEE DRAWBACKS

Though retina specialists are quick to praise ranibizumab as an effective and practice-transforming therapy, recent interviews with retina specialists conducted by this publication point to concerns about ranibizumab, primarily centering on too-frequent patient visits for repeat injections, unrealistic patient expectations, and the major financial issues that stocking and billing the drug entails. Indeed, doctors interviewed by *Retinal Physician* for this article would like to see a wet AMD drug approved in the next 5 years that requires fewer injections and is less expensive. Longer term, they see the ideal treatment for the disease as an oral or topical therapy.

Retina specialists' mixed feelings about ranibizumab are clearly demonstrated in the following 2 quotes from Andrew Antoszyk, MD, who has served as lead investigator in the longest duration study of the safety and efficacy of ranibizumab, following some patients for as long as 3.8 years.

"Lucentis ranks up there with other milestones in the management of various medical disorders," says Dr. Antoszyk. "It has been capable of not only preventing severe vision loss in patients with wet AMD but has allowed many individuals to experience a significant degree of visual improvement. I definitely consider Lucentis a practice-transforming therapy."

"Lucentis has several drawbacks. One, it requires a patient to come back on a relatively frequent basis (every 4 to 6 weeks), which places a tremendous burden either on the patients themselves and/or their families. In addition, there are financial concerns involved with these repeat treatments that not only include the cost of the drug but the associated ancillary testing and clinical exams required to monitor the therapy. One of the problems with Lucentis is having to carry a large inventory, which is a significant cost.

"Although there are also theoretical drawbacks to the use of pan-VEGF-A blockade, these are yet to be proven. The potential increased risk of cerebrovascular events in patients receiving intravitreal Lucentis is of concern, although the rate is low and not above what is expected for this age group."

TOO MANY PATIENT VISITS

Of the several drawbacks to ranibizumab mentioned by retina specialists, it is dealing with the day-to-day disruptions of increased patient flow that distresses them the most.

"The need for multiple treatments at 4-week intervals with no definite endpoint is a significant drawback," says Sharon Fekrat, MD.

"Frequency of patient visits is definitely an issue with Lucentis, says Henry Hudson, MD. "Even if you use OCT (optical coherence tomography) to determine the timing of retreatments, you may not be giving a patient injections every month but you are still scheduling the visits to monitor disease progression."

For its part, Genentech says it recognizes the burden the repeated treatments puts on physicians and their practice and is working with the retina community to evaluate less frequent dosing regimens.

Dr. Hudson also cites unrealistic patient expectations for ranibizumab treatment.

"Expectations are very high now. Everyone who comes in for treatment knows someone who has done well with Lucentis," he notes. "Some patients, who don't see improvement after the first injection, want to be switched to another therapy. It is a concern, but then again, patients also had high expectations when PDT (photodynamic therapy) was first introduced."

Generally, retina specialists now see ranibizumab as the standard of care for first-line treatment of wet AMD. Physicians who previously used bevacizumab (Avastin, Genentech) to treat wet AMD patients have cut back sharply on their use of that drug because ranibizumab is an approved therapy that is more easily reimbursed.

"Prior to Lucentis approval, Avastin was our standard (wet AMD) treatment," says Robert Avery, MD. "After approval, many patients elected to be treated with Lucentis due to its FDA approval and its impressive benefit demonstrated by well-done randomized controlled clinical trials. What has changed in the exam lane is a longer discussion of the differences between well-studied Lucentis and lower-cost Avastin. After the discussion, I let the patient decide upon which agent to use. Those who choose Avastin often do so for financial reasons or because they have done well with it in the past and do not want to change."

Though there is now anecdotal data that ranibizumab can be effective in treating other retinal diseases, particularly diabetic macular edema (DME), doctors are not using it for other retinal diseases because it is not approved for other indications and is too expensive to use without the possibility of reimbursement. However, trials are continuing using ranibizumab to treat DME and vein occlusions.

COMBINATIONS BEING TRIED

"I only use Lucentis in combination if the patient does not appear to be responding to Lucentis alone," says Paul Sternberg Jr., MD. "In most cases, I have tried PDT."

A number of other retina specialists have recently begun using so-called "triple therapy" — a combination of ranibizumab, reduced-fluence PDT, and dexamethasone that is now the subject of several ongoing studies.

Ranibizumab retreatment schedules are being determined by several methods. Some physicians report that they follow the recommended dosing schedule of retreatment every 4 weeks. Others, such as Allen Ho, MD, use a combination of examination, visual acuity measurement, OCT monitoring, and sometimes fluorescein angiography to determine when retreatment is necessary.

"Fluorescein angiography helps to look for leakage not identified on OCT and for increasing size of the neovascularization," adds Dr. Antoszyk. "We are continuing to monitor and observe for evidence of progression of the dry component of AMD. It is highly likely that this (the dry) will continue to progress, even in the presence of inhibited neovascularization."

LOOKING AHEAD

In regard to the need for other therapies that are alternatives to Lucentis becoming available in the next 5 years, some respondents point to VEGF Trap (Regeneron), which is now moving into a phase 3 trial. Although significantly more testing is required, VEGF Trap may offer the potential to improve vision with a regular dosing regimen that is less frequent than monthly.

However, Dr. Ho believes that there is only a small chance that a new monotherapy will supplant ranibizumab in the next 5 years, though he notes that new treatment combinations that include ranibizumab may prove to be more effective than Lucentis alone.

Retina specialists are also eager to see the ranibizumab/bevacizumab head-to-head, sponsored by the National Institutes of Health, commence.

"I think that this study is outstanding and needs to be done," says Dr. Fekrat. "I hope it gets funded."

"It's a very important study," adds Dr. Ho. "But it's too slow to get going."

"If the 2 drugs are proven to be of equal benefit, Avastin would be the choice because it's much cheaper," notes Dr. Hudson."

Finally, practices are still wrestling with the economic aspects of stocking ranibizumab and receiving equitable reimbursement.

"Numerous financial headaches have been highlighted by the rapid adoption of Lucentis therapy," says Dr. Avery. "Many practices are losing money on the handling of the drug as the 6% profit spread has been reduced to 4%, and this may not cover the cost of collections and unpaid claims.

"Of course this depends upon the payer mix and the efficiency of the practice, but in my experience, for most primary payers other than Medicare, the effort required by my billing staff has been excessive this first year. I expect this to improve when there is a J code for Lucentis in the future. Regardless, there will be a problem with certain HMOs or IPAs who do not want to pay for expensive therapies. Certain states have a tax on medical reimbursements which cut into the slim 'profit margin,' and even universities must carve the payments out of the dean's tax. Fortunately, Genentech has tried to help with generous plans for the uninsured patients."

Despite these problems, by any reasonable measure, having ranibizumab approved and widely available to treat wet AMD for the past 12 months has overall been a major plus for the retina community and for patients. Whether ranibizumab retains its dominance or yields its place to a more effective, more efficient, or less costly therapy will be determined in the months and years ahead. **RP**

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