The Pharmacist Activist

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Editorial

More Profits or More Blindness?

Genentech Should Rescind its Action Against Compounding Pharmacies!

Age-related macular degeneration (AMD) is a common cause of blindness in older adults, and is diagnosed in more than 150,000 Americans each year. The neovascular ("wet") type of AMD accounts for approximately 10% of the cases of AMD, but is more severe and rapidly progressive than the non-neovascular ("dry") type. The approval and marketing of ranibizumab (Lucentis) in 2006 represented an important advance in the treatment of wet AMD. In the clinical studies, 90% of patients maintained their vision over a period of 24 months of treatment with the drug. But even more noteworthy was the finding that approximately one-third of the patients experienced improved vision. When I reviewed Lucentis as a new drug, I gave it my highest rating of 5, using the New Drug Comparison Rating system with a scale of 1 to 5.

Vascular endothelial growth factor (VEGF) is a protein that is involved in the occurrence and worsening of wet AMD. When VEGF is overexpressed, it promotes angiogenesis (blood vessel growth) and increased vascular permeability (leakage). Lucentis is a monoclonal antibody fragment that binds to human VEGF-A and prevents its interaction with its receptors. By acting as a VEGF antagonist, it reduces vascular leakage and new blood vessel formation, and is effective in the treatment of wet AMD. It is administered by intravitreal injection, usually once a month.

Avastin

In 2004, bevacizumab (Avastin) was marketed for the treatment of metastatic carcinoma of the colon or rectum, and it has subsequently been approved for the treatment of certain types of non-small cell lung cancer. Its beneficial effects in the treatment of these cancers are attributed to its VEGF antagonist action; however, it has not been formally evaluated for the treatment of wet AMD. Lucentis is actually a component of the Avastin molecule that is less than 50% of the size of the larger molecule. This and several other features of the molecule and its formulation were intentionally included in the research and development of the product/formulation that was intended for injection into the eye. Both Lucentis and Avastin act as VEGF antagonists.

When Avastin became available in 2004 (approximately two years before the availability of Lucentis), many ophthalmologists, particularly those treating retinal problems, who were aware of its mechanism of action, thought this drug would be of value in the treatment of their patients with wet AMD, as well as certain other ocular disorders. Working with compounding pharmacists who used Avastin supplied in vials intended for intravenous use to prepare formulations appropriate for ophthalmic injection, the drug has been used "off-label" for the treatment of patients with wet AMD. The experience with this off-label use of Avastin has been highly successful to the point that it is now widespread, even after Lucentis, that was specifically developed and studied for ophthalmic use, became available in 2006.

When used in the dosages needed to treat the cancers for which it is indicated, Avastin is a very expensive treatment. However, the dosage of Avastin that is appropriate for the treatment of wet AMD is much smaller, with the result that compounding pharmacists can prepare many "ophthalmic doses" from one vial of Avastin. The approximate cost of a dose of Avastin for the treatment of wet AMD is $50, whereas the approximate cost of a dose of Lucentis is $2,000. Both Avastin and Lucentis are manufactured by Genentech.

Genentech's Action

In a letter addressed to members of the Retinal Community and dated October 11, 2007, Genentech announced that, "As of November 30, 2007, Genentech will no longer allow compounding

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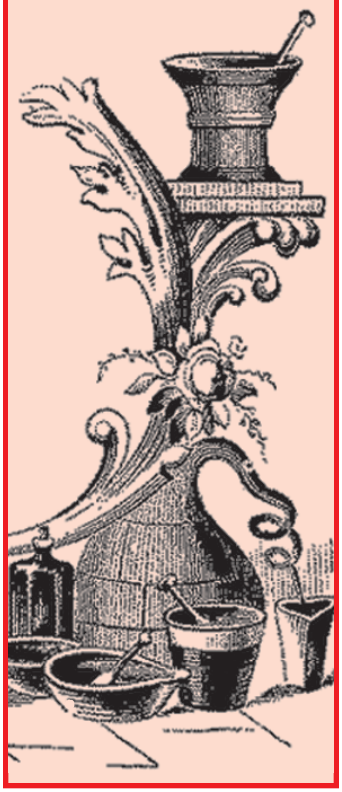

pharmacies to purchase this product (Avastin) directly from wholesale distributors." There is no information to suggest that Genentech had any discussions with the retinal community or compounding pharmacists prior to announcing this action. The letter goes on to say: "Despite the availability of Lucentis, an FDA-approved treatment for neovascular (wet) age-related macular degeneration (AMD), some ophthalmologists are using Avastin for the unapproved treatment of this and other ocular indications. Avastin is not FDA-approved for ocular uses and is not manufactured to meet US Pharmacopoeia (USP) ophthalmic standards. This change will not go into effect until November 30, 2007 to allow for physicians and compounding pharmacies to adjust to this change in distribution."

In an attempt to justify its action, Genentech essentially employs a "blame the FDA" strategy. It refers to a FDA warning letter to a compounding pharmacy regarding the sterility and repackaging of Avastin for ocular use, and concerns voiced by FDA inspectors during a routine visit to a Genentech manufacturing facility. However, the FDA has not required or suggested that Genentech take the action it did. This decision was made by Genentech, and Genentech alone.

In addition to communicating with the retinal community, Genentech sent letters to patients who had signed up on its website to receive information about their condition or for whom they had addresses through other programs. Patients were informed that the company would no longer be supplying Avastin to compounding pharmacies and that the ophthalmic use of Avastin was unapproved, and were provided with information that included a list of complications associated with the intravenous use of Avastin. Numerous patients contacted their ophthalmologists with concerns about their treatment and questions such as whether they were participants in an "experiment" without their approval. Genentech is one of many companies that take steps to learn the identity and contact information of patients who are treated with medications they make, for the positive purpose of providing educational information regarding the patient's medical condition and drug therapy. However, Genentech's communication with patients about Avastin is a blatant abuse of the privilege of its being able to contact patients and a betrayal of the health professionals involved in their care. This situation provides cause to re-evaluate whether the identity of individual patients should be available to pharmaceutical companies.

Outrage

The response to Genentech's actions from compounding pharmacists and the retinal community has been one of outrage. The American Society of Retinal Specialists (ASRS) and the American Academy of Ophthalmology (AAO) have vehemently protested Genentech's action and asked that it be rescinded. Others have noted that Genentech's reference to the ophthalmic standards of the USP is misleading, if not inaccurate. The intensity of the response resulted in a meeting on October 26 of several top executives of Genentech with representatives of the ASRS and AAO. However, the only specific outcome of that meeting that is known is that the date on which Genentech will discontinue supplying Avastin to compounding pharmacies has been changed from November 30, 2007 to January 1, 2008. This is still unacceptable. Genentech should rescind its action! To my knowledge, the executives of Genentech have not met with compounding pharmacists.

Genentech also has noted that it will reinstate its supply of Avastin to compounding pharmacies if the FDA gives the company legal and regulatory authorization to do so. "Disingenuous" is probably the mildest response to this offer. The action was taken by Genentech and was not requested or suggested by the FDA. Off-label use of a medication is legal and is common with many medications, and there is no need for the FDA to provide legal and regulatory authorization. This is just another ruse to attempt to suggest that the FDA has a responsibility for Genentech's misguided action, and Genentech apparently has not even requested such authorization from the FDA.

What is Genentech's motivation?

To respond to the growing and increasingly public concerns, Genentech made an "open letter" available on October 29, 2007 (updated on October 31), in which it addressed a number of issues. It anticipated, correctly so, that some would accuse it of making profit its priority. However, it notes in its letter: "Genentech's decision was not motivated by a desire for increased profits. We did not and do not expect that this change in policy toward compounding pharmacies will lead to any increase in Lucentis sales."

These observations raise several questions:
If Genentech implements its action to discontinue providing Avastin to compounding pharmacies, how will the patients with AMD who are now treated with Avastin prepared by these pharmacists subsequently be treated, if they are not switched to Lucentis (which would presumably increase its sales)? Will Genentech make Lucentis available free of charge to patients with AMD currently treated with Avastin prepared by compounding pharmacists, if it does not expect to see any increase in Lucentis sales as a result of its policy? Will the restricted distribution of Avastin not result in some patients not being treated with either Avastin or Lucentis, thereby increasing the potential and rate of the occurrence of blindness?

One very likely consequence of Genentech's action is that fewer patients with AMD will be treated with Avastin. Some of these patients will not be able to afford treatment with Lucentis, notwithstanding the availability of The Lucentis Commitment support program. The result will be that more patients will become blind or will become blind sooner if they cannot receive treatment from which they could benefit.

In its letter of October 29, Genentech notes that it expects that physicians will continue to prescribe Avastin for ocular conditions. The retinal specialists/ophthalmologists have the wisdom to have compounding pharmacists with the needed expertise, equipment, and facilities to prepare the doses of Avastin that they will administer, rather than doing it themselves in their offices or surgical suites. By discontinuing the distribution of Avastin to compounding pharmacies, Genentech encourages the preparation of the drug for ophthalmic use in the physicians' offices by individuals who have not been trained for this responsibility. This will only increase the possibility of contamination and error.

There is one other action described in Genentech's letter that I find particularly puzzling. Reference is made to concerns of FDA inspectors (although the FDA did not request or suggest any specific action). The letter states: "In order to resolve the concerns raised by the FDA, we destroyed four batches of Avastin deemed unsuitable for use in the eye due to a higher visual inspection standard. (These lots would have been entirely suitable for its approved use as an intravenous cancer medication.) The action resulted in the loss of more than 350,000 vials of Avastin with a market value of more than $200 million."

As noted earlier, the observation that the product was suitable for intravenous use but not for use in the eye has been challenged. But beyond that, identifying a market value for the destroyed product as being more than $200 million is sensationalism and many, many times greater than its actual value to Genentech. The data mentioned is just one more reminder of how expensive Avastin is (approximately $570

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New Drug Review

Lapatinib
(Tykerb – GlaxoSmithKline)
Antineoplastic Agent

New Drug Comparison Rating (NDCR) = 4
(significant advantages) in a scale of 1 to 5, with 5 being the highest rating

Indication:
In combination with capecitabine (Xeloda) for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline (e.g., doxorubicin [e.g., Adriamycin]), a taxane (e.g., docetaxel [e.g., Taxotere]), and trastuzumab (Herceptin).

Most important risks/adverse events:
Decreased left ventricular ejection fraction (should be determined at baseline and during treatment; patients should be advised to report symptoms such as shortness of breath and palpitations); interstitial lung disease and pneumonitis (should be discontinued if patients experience severe pulmonary symptoms); QT interval prolongation (caution must be observed in patients at risk [e.g., hypomagnesemia and/or hypokalemia should be corrected before initiating treatment]); severe diarrhea; may cause harm to a fetus and should not be used during pregnancy; is a substrate for CYP3A4 and its action may be increased by the concurrent use of a CYP3A4 inhibitor (e.g., clarithromycin [e.g., Biaxin]), and decreased by the concurrent use of a CYP3A4 inducer (e.g., rifampin [e.g., Rifadin]).

Most common adverse events:
Diarrhea (65%), palmar-plantar erythrodysesthesia (i.e., hand-foot syndrome; 53%), nausea (44%), rash (28%), vomiting (26%).

Usual dosage:
Should be administered at least one hour before or one hour after a meal, and the daily dose should not be divided; 1,250 mg (Five tablets) once a day on Days 1-21 continuously in combination with capecitabine 2,000 mg/m^2/day (administered orally in two doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle; in patients with severe hepatic impairment, a reduction in dosage to 750 mg/day should be considered; if it is necessary to use a strong CYP3A4 inhibitor concurrently, a reduction in dosage to 500 mg/day should be considered; if it is necessary to use a strong CYP3A4 inducer concurrently, the dosage may be gradually increased up to 4,500 mg/day based on tolerability.

Product:
Tablets – 250 mg.

Comparable drugs:
Trastuzumab (Herceptin).

Advantages:
- May be effective in some patients with advanced breast cancer who do not respond or no longer respond to other therapies;
- Cross-resistance does not appear to exist;
- Is effective following oral administration (trastuzumab is administered intravenously);
- Is less likely to cause hypersensitivity reactions.

Disadvantages:
- Is not indicated for first-line use;
- Data are not yet available to demonstrate prolongation of survival;
- Is associated with a greater risk if used during pregnancy;
- Is only available through a restricted distribution program.

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per vial) when used for treating patients with cancer. And because Genentech considered these lots of Avastin suitable for use for cancer, why did it destroy them? Could it not have used these lots in supplying hospitals and oncologists with the medication, or made them available on a charitable basis to patients and institutions with great financial need? This decision to destroy the medication is absolutely baffling!

Over the years Genentech has enjoyed an excellent reputation as a company that develops important and innovative medications, and is very profitable. However, its explanations/excuses on this issue don't fly, leading to the inescapable conclusion that the motivation for its action is even greater profit. It is destroying its credibility by the action it has announced and its attempts to explain and justify it. It must rescind this action as the first step to restore its credibility!

Daniel A. Hussar

New Drug Review (cont.)

Comments:

Many women with metastatic breast cancer have tumors that overexpress the human epidermal growth factor receptor 2 (HER2) protein that is associated with more aggressive disease. Trastuzumab is a monoclonal antibody that selectively binds to the extracellular domain of the HER2 protein, and is administered intravenously for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein. However, some patients with HER2 positive breast cancers do not benefit from its use, and some others no longer receive the benefit that was experienced when therapy was initiated.

Lapatinib is a kinase inhibitor of the intracellular tyrosine kinase domains of both Epidermal Growth Factor Receptor (EGFR [ErbB1]) and of Human Epidermal Receptor 2 (HER2 [ErbB2]) receptors. Whereas trastuzumab is a large protein molecule that targets the part of the HER2 protein on the outside of the cell (i.e., the extracellular domain), lapatinib is a small molecule that enters the cell (i.e., the intracellular domain) and blocks the function of the HER2 protein as well as other proteins. The new agent has been effective in some patients who have not responded or are no longer responding to trastuzumab or other agents. An additive effect has been demonstrated when lapatinib is used in combination with capecitabine. In the clinical studies, a combination regimen of lapatinib and capecitabine was compared with capecitabine alone. The median time to tumor progression (or death related to breast cancer) for the combination regimen was 27 weeks compared with 19 weeks for capecitabine alone. In addition, the tumor response rate was higher with the combination regimen (24% compared with 14%). Data are not yet available to determine if the lapatinib-containing regimen prolongs survival; however, its approval represents significant progress in extending the treatment options for patients whose conditions are refractory to previous therapies.

The use of lapatinib has been associated with the occurrence of serious adverse events including decreased left ventricular ejection fraction, prolongation of the QT interval, interstitial lung disease, and severe diarrhea, and treatment must be closely monitored. In addition, it is a substrate for CYP3A4 and may interact with numerous other medications that inhibit or induce this metabolic pathway. If it is necessary to use one of these agents concurrently, consideration should be given to adjusting the dosage of lapatinib. Administration with food increases systemic exposure to lapatinib, but to an unpredictable extent. To increase the predictability of absorption and activity, it is recommended that it be administered at least one hour before or one hour after a meal.

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