

A comparative debate on the various anti-vascular endothelial growth factor drugs: Pegaptanib sodium (Macugen), ranibizumab (Lucentis) and bevacizumab (Avastin)

Manish Nagpal, FRCS; Kamal Nagpal, MS; P N Nagpal, MS, FACS

Wet age-related macular degeneration and diabetic retinopathy are pathological consequences of vascular endothelial growth factor (VEGF) release as a reaction to deficiency of oxygen and nutrients in the macular cells. Conventional treatment modalities have been constrained by limited success. Convincing evidence exists that targeting VEGF signaling is a significant approach for the therapy of these ocular angiogenesis-dependent disorders. We have come a long way since the approval of the first angiogenesis inhibitors in medicine. The clinical use of these drugs has provided enormous tempo to clinical and pharmacological research. It has also significantly altered patient outcome and expectations. In the following brief, we will discuss the development and emergence of these drugs as well as the anticipated future course based on evidence.

Key words: Angiogenesis, diabetic retinopathy, vascular endothelial growth factor, wet age-related macular degeneration

Indian J Ophthalmol 2007;55:437-9

Last decade witnessed vast research on angiogenesis, as it applies to the physiology and pathology of the human body and its relevance to the human eye. This has been a fast-paced, critically significant 'translational research' - transforming basic science and biotechnology into new dynamic therapeutic approaches. Human vascular endothelial growth factor (VEGF) is a powerful mediator of vascular permeability as a potent endothelial cell mitogen and angiogenic factor. Targeting VEGF therefore, allows a double hit strategy: antiangiogenesis and antipermeability.^{1,2} These two pathogenic mechanisms are in part responsible for severe vision loss in neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME), the two leading causes of visual disability in the adult population, world-over. Because of the sheer numbers involved, anti-VEGF drugs have a potential of enormous socio-economic implications. Following is a brief comparative debate on the various anti-VEGF drugs commonly in use today, such as pegaptanib sodium (Macugen, Pfizer United States, Eyetech Pharmaceuticals Inc.; Pfizer, Inc.), ranibizumab (Lucentis, Genentech, Switzerland) and bevacizumab (Avastin, Genentech, Switzerland)

Pegaptanib Sodium^{3,4}

History: The US Food and Drug Administration (FDA) announced the approval of pegaptanib sodium injection in December 2004, which at that time was a "new therapy to slow vision loss in people with the eye disease neovascular (wet) AMD" It was said that "Pegaptanib provides a needed addition to the treatment of patients with this disease." It was

the first approved drug in this category. More than 50,000 patients with wet AMD were treated with pegaptanib sodium in the United States last year. Pegaptanib's approval represented a major milestone. It validated VEGF as a major regulator of aberrant and excessive blood vessel growth and permeability in the eye and is the first anti-angiogenic therapy indicated for the treatment of neovascular AMD. It is the first aptamer to be successfully developed as a therapeutic agent in humans. Pegaptanib sodium is an aptamer binding VEGF165, the isoform most frequently identified with pathological angiogenesis in the retina and thus has a selective anti-VEGF action. The strength of pegaptanib sodium lies in the following aspects.

- Because of the structural specificity (by only targeting the 165 isoform of VEGF), pegaptanib sodium might help in preventing major systemic vascular accidents. Ranibizumab and bevacizumab on the other hand target all the isoforms of VEGF. The patient population suffering from AMD is likely to have co-morbid systemic vascular conditions such as ischemic heart and cerebro-vascular disorders, hypertension, diabetes and lipid disorders. Although systemic absorption of ranibizumab and bevacizumab, if given intravitreally appears to be minimal, long-term studies are essential to completely shelve this issue.
- Pegaptanib sodium may in future be available through other systemic routes of administration, because it spares all other VEGF isomers.

Ranibizumab and Bevacizumab

History: The US FDA approved of ranibizumab for the treatment of macular degeneration on June 30, 2006 after a priority review (six-month). In the FDA release, it was said that 'Ranibizumab is the first treatment which, when dosed monthly, can maintain the vision of more than 90 percent of patients with wet AMD'

Retina Foundation, Ahmedabad, India

Correspondence to Dr. Manish Nagpal, Retina Foundation, Shahibag, Ahmedabad - 4, Gujarat, India. E-mail: drmanishnagpal@yahoo.com

Manish Nagpal, 11-03-07, Ranibizumab, 11-05-07

Bevacizumab was approved by the US FDA in 2004 for the treatment of colorectal cancer. Limited visual results of pegaptanib sodium and unavailability of ranibizumab prompted Rosenfeld and coworkers at the Bascom Palmer Eye Institute to try systemic and subsequently intravitreal bevacizumab as an off-label indication in wet AMD with exceptional results.

Basic science: Ranibizumab is derived from a full-length "affinity matured" antibody whereas bevacizumab is only the Fab (antigen binding domain) of bevacizumab. The company claims that the binding constant for ranibizumab is five to 10 times more potent to all VEGF isoforms than is bevacizumab.⁵ Its low molecular weight as compared to bevacizumab (approximately one-third) aids penetration of the full-thickness retina, which was questioned in an animal model for bevacizumab.⁶ However, in a recent study on albino rabbits, it was shown that full-thickness retinal penetration of bevacizumab was present at 24h and was essentially absent at four weeks based on confocal immunohistochemistry. It was nontoxic to the retina based on electrophysiologic studies.⁷ Further, bevacizumab has two binding sites per molecule and the edematous state of the diseased retina, as in eyes with choroidal neovascular membrane (CNVM) might further enhance penetration. However, as the retinal edema decreases during treatment, perhaps, the penetration advantage of ranibizumab may be useful. Given its larger molecular weight, bevacizumab likely has a longer half-life in the vitreous and therefore may require less frequent re-injections.

Major clinical results: Ranibizumab has been shown to have remarkable results following extensive, stringent clinical trials. MARINA⁸ and ANCHOR⁹ are both Phase III, multi-center, randomized, double-masked trials which showed visual improvements in patients with wet AMD. In a significant proportion of patients, unlike pegaptanib, not only is there a prevention of visual loss but also an improvement in visual acuity. The FDA approval imparts huge advantages pertaining risk evaluation, safety, insurance coverage and relative immunity from patient litigation. All clinical trials¹⁰⁻¹² with bevacizumab have been uncontrolled and, therefore anecdotal and short-term. Initially, bevacizumab was used to treat patients not doing well on other therapies such as pegaptanib sodium or photodynamic therapy (PDT), visually or on optical coherence tomography (OCT) scans, with monthly re-injections. No significant ocular or systemic side-effects were observed. Bevacizumab has potentially better visual results than either pegaptanib sodium or photodynamic therapy. Very few problems and side-effects have been found in its anecdotal experience. It is freely available and could be used immediately for several indications including diabetic retinopathy, CNVM associated with high myopia and other causes of macular leakage. The off-label use of bevacizumab is responsible for its cost being miniscule compared to those developed directly for intraocular use. Single dose of pegaptanib sodium costs \$1,000 and ranibizumab is priced at \$2,000 per injection. The cumulative cost of monthly or six-weekly injections for several months to years becomes foreboding.

The dilemma

- Pegaptanib sodium is probably out of the main race for AMD treatment since both bevacizumab and ranibizumab have raised the bar of patients' expectations by actually consistently showing visual improvement, as compared

to near stabilization with pegaptanib sodium.

- The popularity of the 'off-label' bevacizumab use has placed this genre of treatment in a unique situation. It was neither developed and formulated, nor studied and approved for intraocular use. Yet, it has been widely adopted. Although, off-label use of drugs is not illegal (intravitreal triamcinolone, tissue plasminogen activators, intracameral vancomycin or lignocaine are off-label treatments), it does raise ethical issues and safety concerns.
- The paradox, that the same company (Genentech) developed both bevacizumab and ranibizumab might obstruct FDA approval for bevacizumab for this use.
- All the published reports of bevacizumab are uncontrolled, non-randomized and have short follow-ups. Many studies used Snellen charts, which are not as precise or reproducible as the ETDRS charts.
- Although it seems unlikely that systemic toxicity, such as thromboembolic events and gastrointestinal problems, will develop this risk must be studied with both bevacizumab and ranibizumab.

The real issue: Ranibizumab versus bevacizumab:

In the absence of controlled studies comparing bevacizumab to ranibizumab, no definite assumptions can be made; however, the two drugs appear very similar in their visual results profile. When looking at the various studies, stability or improvement of visual function has been encountered in about 90 to 95% of eyes treated with either drug. Even the percentage of eyes showing a particular number of lines of improvement, when treated by either of the drugs appears similar. Recently a head to head trial has been funded by the NIH (USA) to directly compare ranibizumab and bevacizumab, results of which might take us closer to resolving the issue.

Currently, most retinal surgeons are happy injecting bevacizumab because of its cost-effectiveness, which remains a crucial parameter. As far as the approval status is concerned, we don't think that patients are too concerned. Having been approved, ranibizumab is establishing a role in those for whom cost is not a big issue and those under insurance cover. Recently, Genentech the founder company for ranibizumab and bevacizumab has given a warning about a potential stroke risk with 0.5 mg ranibizumab injections in predisposed patients - having preexisting history of myocardial infarction or stroke and thus pegaptanib sodium is being recommended for this category of patients because of its specificity in targeting the pathologic VEGF molecule. Complete counseling and discussion about benefits and risks with the patients is mandatory.

We are in a very interesting era of anti-VEGF therapy and whether or not we find an answer to which one of them is the overall best in efficacy and safety, our patients are finally benefiting from a treatment for a condition which previously was crippling for them. The future holds even better news for them as many such molecules will see its way with better efficacy.

References

1. Ferrara N. Vascular endothelial growth factor basic science and clinical progress. *Endocr Rev* 2004;25:581-611.
2. Ferrara N. VEGF and the quest for tumour angiogenesis factors. *Nat Rev Clin Oncol* 2003;3:705-802.

3. VEGF Inhibition Study in Ocular Neovascularization (VISION) Clinical Trial Group, Chakravarthy U, Adamis AP, Cunningham ET, Goldbaum M, Guyer DR, *et al.* Year 2 efficacy results of 2 randomized controlled clinical trials of pegaptanib for neovascular age-related macular degeneration. *Ophthalmology* 2006;113:1508.e1-25.
4. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR; VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;351:2805-16.
5. Ferrara N, Damico L, Shams N, Lowman H, Kim R. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy of neo-vascular age-related macular degeneration. *Retina* 2006;26:859-70.
6. Mordenti J, Cuthbertson RA, Ferrara N, Thomsen K, Berleau L, Licko V, *et al.* Comparisons of the intraocular tissue distribution, pharmacokinetics and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. *Toxicol Pathol* 1999;27:536-44.
7. Shahar J, Avery RL, Heilweil G, Barak A, Zemel E, Lewis GP, *et al.* Electrophysiologic and retinal penetration studies following intravitreal injection of bevacizumab (Avastin). *Retina* 2006;26:262-9.
8. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, *et al.* Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419-31.
9. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, *et al.* Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1432-44.
10. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. *Ophthalmology* 2005;112:1035-47.
11. Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ. Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Ophthalmology* 2006;113:363-72.
12. Spaide RF, Laud K, Fine HF, Klanck JM Jr, Meyerle CB, Yannuzzi LA, *et al.* Intravitreal bevacizumab treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 2006;26:383-90.

Source of Support: Nil, Conflict of Interest: None declared.