Promising Therapies for Choroidal Neovascularization in Age-related Macular Degeneration: A Literature Review

Michele Lomelino

Writer's Comment: In the midst of applying to optometry schools, working in a vision science research lab, and interning at a private practice optometry office, I developed a real appreciation for scientific literature, especially that which focused on new therapies and methods for treating eye diseases. Because of all my exposure to the vision science field, I decided to write my literature review on different therapies for treating aging macular degeneration, a prevalent ocular disease that can lead to irreversible blindness. I also wrote this paper during a time when two of the most popular forms of treatment, bevacizumab and ranibizumab, were being hotly debated in the pharmaceutical field because of differences in cost, effectiveness, and also FDA approval. By writing this paper, I hoped to shed light not only on the seriousness of the disease, but also the tremendous effort by vision research labs to find a cure.

—Michele Lomelino

Instructor's Comment: Michele wrote this literature review for my UWP 102B (Writing in the Biological Sciences) class last fall (2007). She faced a tough choice in how to organize this material, whether by the four treatments that she discusses for macular degeneration or by the various methods for evaluating the treatments. I felt she made a good choice in organizing around the methods for evaluating the treatments, because the reader gets a clear idea for each method as to which treatments do a better job. This literature review will make a great example in discussions with future students about organizational choices. In addition to the clear organization, Michele

integrates and explains the information well, and she writes at a level of technicality that should be readily understandable to the target audience.

—Jared Haynes, University Writing Program

Introduction

Age-related macular degeneration, or AMD, is an eye disease involving the macula, a highly sensitive portion of the retina responsible for our precise central vision. AMD has become the leading cause of blindness in the US for people age fifty and older (Bressler *et al.*, 2003). Specifically, AMD can develop into a form known as wet macular degeneration where fragile, new blood vessels grow, break, and bleed over the macula through a process known as choroidal neovascularization. Because wet macular degeneration is becoming more prevalent, researchers are testing new therapies to combat this disease. One treatment, photodynamic therapy (PDT) with verteporfin, was the first treatment to gain FDA approval for the treatment of choroidal neovascularization in wet macular degeneration. A new family of drugs, anti-vascular endothelial growth factor antibodies (anti-VEGF), mainly administered to treat colon and lung cancers, are now being researched as effective therapies for breast cancer and wet macular degeneration. Anti-VEGF antibodies help halt blood vessel proliferation and cell division, both of which can lead to the development of cancerous tumors or wet macular degeneration. While intravitreal pegaptanib, an anti-VEGF antibody treatment, was approved by the FDA to treat wet macular degeneration shortly after the approval of PDT with verteporfin, two newer drugs, bevacizumab and ranibizumab, both anti-VEGF-A antibodies, are becoming popular therapy options for wet AMD. Both manufactured by Genentech, ranibizumab has recently gained FDA approval to treat macular degeneration while bevacizumab is becoming a more popular treatment protocol amongst ophthalmologists although lacking FDA approval for the treatment of ocular disease. However, ongoing studies comparing older, FDA-approved treatments with the newer anti-VEGF therapies will determine which of these drugs will prove most effective. To compare these four therapy options, researchers use similar parameters to measure the effectiveness of each therapy: best corrected visual acuity (BCVA), central retinal thickness also known as foveal thickness, greatest linear

dimension of the macular lesion, also any adverse systemic and ocular effects from the drug administration.

Best Corrected Visual Acuity (BCVA)

Intravitreal bevacizumab has been shown to significantly increase visual acuity, as subjects treated with 1.25 mg of 0.05ml of bevacizumab showed a substantial gain in visual acuity, and some subjects were even able to gain more than 15 letters on the Snellen visual acuity chart across the nine-month follow-up period (Cleary *et al.*, 2007). Bashshur *et al.* (2007) compared the intravitreal bevacizumab therapy and routine verteporfin PDT in patients diagnosed with wet AMD across three and six month follow-up visits; they showed a significant increase in BCVA in the group receiving intravitreal bevacizumab injections, while the PDT group showed a decrease in BCVA at both three- and six-month follow-ups. While bevacizumab was able to increase visual acuity up to 20/40 or better, PDT was not able to reach this acuity and actually decreased BCVA to 20/200 (Bashshur *et al.,* 2007).

Pegaptanib therapy has gained enough support to become a standard treatment for wet AMD. Studies performed before its FDA approval exhibited promising results. Gragoudas *et al.* (2004) treated subjects with different dosages of pegaptanib and compared them with subjects receiving sham (placebo) injections. Visual acuity for the intravitreal pegaptanib group increased much more than the placebo group and remained higher throughout the study (Gradougas *et al.,* 2004). In addition, this study showed that subjects treated with intravitreal pegaptanib were also less likely to decrease visual acuity and maintain or gain letters as compared with the group treated with sham injections (Gradougas *et al.,* 2004). While pegaptanib exhibited promising results, similar anti-VEGF-A therapies like bevacizumab and ranibizumab are now arising as perhaps more effective therapeutic treatments (Bashshur *et al.,* 2007).

Several studies (Bhatnagar *et al.,* 2007; Heier *et al.,* 2006; Brown *et al.,* 2006) have examined ranibizumab therapy, its effectiveness in treating wet AMD, and its comparison with PDT therapy. Bhatnagar *et al.* (2007) showed that mean baseline visual acuity at 20/152 had significantly increased to 20/126 after three months, and that patients who had previously received bevacizumab injections also showed an increase in visual acuity from a baseline of 20/100 to 20/98 after treatment with ranibizumab. PDT in combination with ranibizumab injections has also

proven to be more effective than just PDT alone (Heier *et al.,* 2006). After two groups, one receiving intravitreal ranibizumab injections and the other receiving sham injections, underwent PDT seven days after the injection, more subjects receiving combination therapy showed an increase in visual acuity than those receiving PDT alone over 12 months (Heier *et al.,* 2006). Brown *et al.* (2006) showed that ranibizumab was more effective at increasing visual acuity and suggested a dose-dependent response, as patients who were given higher doses of ranibizumab exhibited higher increases in visual acuity. Those treated with PDT alone in this study showed a decrease in visual acuity and were more likely to lose more than 15 letters, whereas the ranibizumab group were less likely to lose more than 15 letters of visual acuity also in a dose-dependent manner (Brown *et al.,* 2006).

Central Retinal (Foveal) Thickness

A decrease in central retinal thickness can indicate the dissolution of the leaky blood vessels and reduction in subretinal bleeding and macular scarring characterized in wet AMD. Bevacizumab is effective in greatly decreasing foveal thickness at three- and six-month follow-ups (Cleary *et al.* 2007). Foveal thickness started at a mean baseline of 291μm and decreased to 282.7μm and 249.7μm at three and six months, respectively, in subjects receiving intravitreal bevacizumab (Cleary *et al.*, 2007). Similar findings indicate that bevacizumab is not only effective at decreasing central retinal thickness but also significantly better than PDT with verteporfin at doing so (Bashshur *et al.,* 2007). Joeres *et al.* (2007) compared bevacizumab and pegaptanib and found that bevacizumab is much better at reducing foveal thickness than pegaptanib therapy, which did not show any decrease in foveal thickness from mean baseline three months after treatment. Additional research from Bhatnagar *et al.* (2007) has shown that ranibizumab may also decrease central retinal thickness as reported in an improvement from a mean baseline of 278μm to 211μm at three months.

Greatest Linear Dimension

Bashshur *et al.* (2007) demonstrated that intravitreal bevacizumab is more effective than PDT with verteporfin at decreasing the greatest linear dimension of the macular lesion. Their results show the mean base-

line dimension in the bevacizumab improved from 2801μm to 2593μm after six months, while the mean baseline for the PDT group improved from 2871μm to 2366μm at three months, but worsened to 3377μm at six months (Bashshur *et al.,* 2007). Likewise, a study done to compare ranibizumab with PDT also indicated that the greatest linear dimension increased with PDT therapy as well as with ranibizumab, though less dramatically (Brown *et al.,* 2006).

Adverse Effects

Adverse effects should always be monitored in any study involving potential therapeutic drugs. With intravitreal injections, there is always a risk of endophthalmitis, a common complication observed in several studies after the administrations of bevacizumab, pegaptanib, and ranibizumab (Bashshur *et al.,* 2007; Cleary *et al.,* 2007; Brown *et al.,* 2006; Heier *et al.,* 2006; Gragoudas *et al.,* 2004). Retinal detachment and lens damage are also known risk factors with intravitreal injections of bevacizumab and pegaptanib (Bashshur *et al.,* 2007; Gragoudas *et al.,* 2004). Tears in the retinal pigment epithelium (RPE) were common in subjects undergoing intravitreal bevacizumab therapy, as well as pegaptanib therapy (Clearly *et al.,* 2007; Chang *et al.,* 2007). Chang *et al.* (2007) noticed this trend between RPE tears and pegaptanib and undertook a study to further investigate this adverse effect. Six out of twenty-two eyes exhibited extremely similar RPE tears after pegaptanib injections, an indication that further research is necessary to decrease complications with this therapy (Chang *et al.,* 2007). Another trend was found between the administration of ranibizumab and the occurrence of intraocular inflammation (Heier *et al.,* 2006; Brown *et al.,* 2006). While Brown *et al.* (2006) found that intraocular inflammation occurred much more often in subjects receiving ranibizumab therapy than in subjects receiving PDT, Heier *et al.* (2006) noticed that although the occurrence of intraocular inflammation related to ranibizumab was high, the affected subjects still had improved visual acuities and did not suffer any long-term injury. Other commonly observed adverse effects with ranibizumab included formation of cataracts (Brown *et al.,* 2006) and increased intraocular pressure (Brown *et al.,* 2006; Heier *et al.,* 2006); however, none of these seemed to pose any serious, long-term threat. Although systemic adverse events such as thromboembolism, hypertension, and proteinuria are listed as risks associated with intravitreal injection of anti-VEGF-A

antibodies, there has been no strong, significant trend linking bevacizumab, pegaptanib, or ranibizumab to these occurrences (Bashshur *et al.,* 2007; Brown *et al.,* 2006; Heier *et al.,* 2006; Gragoudas *et al.,* 2004).

Conclusion

Anti-VEGF-A therapies are making their way to the forefront of pharmaceutical research and are continuing to prove themselves as effective treatments for neovascular disease. Of the two older FDA-approved treatments for wet macular degeneration, the anti-VEGF antibody pegaptanib seems to be more effective in occluding the choroidal neovascularization and improving visual acuity than PDT. With this in mind, similar anti-VEGF therapies like ranibizumab and bevacizumab are being sought after as more effective candidates. Bevacizumab seems to be the most promising of the group, providing substantial improvement in visual acuity and decreasing both central retinal thickness and greatest linear dimension, all with fewer side effects than ranibizumab and pegaptanib. This may be attributed to its characteristic of being a humanized antibody and its ability to suppress all isoforms of VEGF expressed by proliferating blood vessels. While intravitreal injection seems to have risks, the benefits appear to outweigh the costs. Although PDT seems to induce fewer adverse effects, it offers minimal improvement and dissolution of choroidal neovascularization in wet AMD in comparison to anti-VEGF therapies. With further research on anti-VEGF therapies, a promising future for the treatment of wet AMD could be in reach.

Literature Cited

Bashshur ZF, Schakal A, Hamam RN, El Haibi CP, Jaafar RF and Noureddin BN. 2007. Intravitreal bevacizumab vs verteporfin photodynamic therapy for neovascular age-related macular degeneration. *Archives of Ophthalmology* 125: 1357–61.

Bhatnagar P, Spaide RF, Takahashi BS, Peragallo JH, Freund KB, Klancnik JH, Cooney MJ, Slakter JS, Sorenson JA and Yannuzzi, LA. 2007. Ranibizumab for treatment of choroidal neovascularization secondary to age-related macular degeneration. *Retina* 27: 846–50.

Bressler NM, Bressler SB, Congdon NG, Ferris, FL, Friedman DS, Klein R, Lindblad AS, Milton RC and Seddon JM for the Age-Related Eye Disease Study Research Group. 2003. Potential public

health impact of AREDS results: AREDS report No. 11. *Archives of Ophthalmology* 121:1621–1624.

Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, and Schneider S. 2006. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *The New England Journal of Medicine* 355: 1432–44.

Chang LK, Flaxel CJ, Lauer AK, and Sarraf D. 2007. RPE tears after pegaptanib treatment in age-related macular degeneration. *Retina* 27: 857–63.

Cleary CA, Jungkim S, Ravikumar K, Kelliher C, Acheson RW, and Hickey-Dwyer M. 2007. Intravitreal bevacizumab in the treatment of neovascular age-related macular degeneration, 6- and 9-month results. *Nature*. Epub <http://www.nature.com/eye/journal/vaop/ncurrent/full/6702936a.html>. Downloaded 12/5/2007.

Gragoudas ES, Adamis AP, Cunningham ET, Feinsod, M and Guyer R. 2004. Pegaptanib for neovascular age-related macular degeneration. *The New England Journal of Medicine* 351:2805–2816.

Heier JS, Boyer DS, Ciulla TA, Ferrone PJ, Jumper JM, Gentile RC, Kotlovker D, Chung CY and Kim RY. 2006. Ranibizumab combined with verteporfin photodynamic therapy in neovascular age-related macular degeneration. *Archives of Ophthalmology* 124: 1532–42.

Joeres S, Kaplowitz K, Brubaker JW, Updike PG, Collins AT, Walsh AC, Romano PW, and Sadda SR. 2007. Quantitative comparison of optical coherence tomography after pegaptanib or bevacizumab in neovascular age-related macular degeneration. *Ophthalmology*. Epub. <http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VT2-4P5RVPC-2&_user=4421&_coverDate=07%2F12%2F2007&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000059598&_version=1&_urlVersion=0&_userid=4421&md5=f3327cc2a304c4c567b5c15dfdcc9d9b#>. Downloaded 12/5/2007.

◈