Targeted Therapy For the Treatment of Macular Degeneration

Based on the proceedings of an expert advisory panel, Miami, March 10, 2006

HIGHLIGHTS

• Overview of Age-Related Macular Degeneration
• Treatments for Age-Related Macular Degeneration
• PANEL DISCUSSION: Ranibizumab Therapy in the Managed Care Market
• Considerations for Managed Care Decision Makers

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FACULTY PRESENTATIONS

Overview of Age-Related Macular Degeneration ........................................3
Pravin U. Dugel, MD
Retina Consultants of Arizona

Treatments for Age-Related Macular Degeneration .............................7
Pravin U. Dugel, MD

PANEL DISCUSSION

Ranibizumab Therapy in the Managed Care Market ......................16
Pravin U. Dugel, MD
Gary L. Johnson, MD, MBA, Group Health Cooperative
Robert LoNegro, MD, Tufts Health Plan
Glenda S. Owens, RPH, MHA, Arcadian Health Plan
Balakrishna R. Pai, MD, Health Alliance Plan
Sherman Poolosky, MD, Vista Healthplan
Albert J. Rezoli, MD, Presbyterian Health Plan
Charles A. Stemple, DO, MBA, Humana
Bret S. Yarczower MD, Geisinger Health Plan

MANAGED CARE CONSIDERATIONS

Points To Ponder .................................................................20

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The National Health Interview Survey found that about 3 percent of Americans 50 years of age or older reported having been told by a doctor that they have AMD, with the prevalence ranging from 1 percent in people ages 50–64 to nearly 5 percent in the 65-or-older age group (Saaddine 2004). Another recent study has estimated that advanced AMD affects about 1.75 million Americans (Friedman 2004). This number includes people with either neovascular AMD (the focus of this supplement) or geographic atrophy (a well-defined round or oval area of retinal de-pigmentation). In a population-based study, the incidence of advanced AMD in patients age 65 was 5.5 percent (Klein 2002). Owing to the aging of the population in the United States, the number of people with advanced AMD is expected to increase to nearly 3 million by 2020 (Friedman 2004). In the absence of an effective means of treating or preventing AMD, this disease will present an ever-larger economic and social burden as the population ages.

Neovascular AMD is commonly called wet AMD because it is associated with leakage of blood or serum from new blood vessels that develop in the choroid, the vessel-rich tissue between the retina and sclera. No such leakage occurs in atrophic (avascular) AMD, which is therefore known as dry AMD. Both wet and dry AMD can result in loss of vision. Wet AMD is much less common than dry AMD, but the wet form accounts for about 75 to 90 percent of the severe vision loss associated with AMD (Ferris 1984, Klein 1997).

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weeks, but the more frequent path is for visual acuity to deteriorate slowly and to stabilize within 3 years, usually to between 20/250 and 20/400 (Fine 2000).

The appearance of *drusen* — tiny packets of extracellular debris that slowly accumulate between the retinal pigment epithelium (RPE) and Bruch’s membrane — is a sign of early AMD. (The RPE is a layer of cells that maintains the adjacent photoreceptors, or rods and cones; Bruch’s membrane is a thin collagenous structure that separates the RPE from the choroid.) Based on the presence of drusen, nearly every person over the age of 50 can be said to have some amount of macular degeneration. Progression of drusen tends to be very slow, but the more drusen a patient has, the higher the risk for neovascular bleeding.

Having at least one druse with a diameter ≥125 µm is a risk factor for progressing to neovascular AMD. An estimated 7 million Americans over age 40 have at least one druse of this size, and this number is predicted to increase by an additional 6.4 million by 2020 (Friedman 2004). For patients with at least one large druse, there is an estimated 6 percent risk of progressing to neovascular AMD within 5 years. With 10 or more such drusen, the 5-year risk increases to 14 percent. The prevalence of neovascular AMD remains low until people reach their 70s, but prevalence increases sharply after the age of 80. After age 80, the prevalence of neovascular AMD in women is more than triple that of men.

Various risk factors for neovascular AMD have emerged (Table 1). However, the etiology is poorly understood. Oxidative stress, trauma to Bruch’s membrane, inflammation, hypoxia, and nutrient deprivation are among the factors implicated as initiating events (Roth 2004, Zarbin 2004).

### Role of VEGF in neovascular AMD

The existence of some Factor X was once thought to be responsible for the stimulation of neovascularization in AMD. The identity of Factor X appears to have been discovered — a secreted glycoprotein known as vascular endothelial growth factor-A (VEGF-A). VEGF-A is an important mediator of angiogenesis, the process by which both physiologic vascularization and pathologic neovascularization occur (Figure 1).

VEGF-A is a member of the VEGF gene family. Among the other members of this family, which are involved in lymphangiogenesis and inflammation, are VEGF-B, -C, -D, and -E, along with placental growth factor (Ferrara 2003). For the remainder of this article and in the fol-

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**TABLE 1** Emerging risk factors for neovascular AMD

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Friedman 2004</td>
</tr>
<tr>
<td>Smoking</td>
<td>Khan 2006, Klein 1993</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Buch 2005</td>
</tr>
<tr>
<td>Family history</td>
<td>Buch 2005</td>
</tr>
<tr>
<td>Variation in other genes</td>
<td>Haines 2006</td>
</tr>
</tbody>
</table>
In addition to promoting angiogenesis, VEGF is a potent enhancer of vascular permeability. It was initially called “vascular permeability factor,” but it was renamed upon being purified and cloned by Ferrara (Senger 1983, Ferrara 1989, Leung 1989). As an enhancer of vascular permeability effect, VEGF is 50,000 times more potent than histamine. In fact, VEGF is more powerful as a permeability factor than as an angiogenesis factor, but the two concepts are interrelated. If angiogenesis is likened to a new branch growing from a tree, some kind of breakage must occur in the trunk to permit the new branch to emerge. Without an increase in vascular permeability, whether physiologic or pathologic, angiogenesis cannot occur.

VEGF is secreted by a variety of cells in response to local tissue stress, most commonly hypoxia/ischemia, as well as changes in pH (Ferrara 2003). VEGF is upregulated by other growth factors and hormones, including epidermal growth factor, transforming growth factors α and β, basic fibroblast growth factor, platelet-derived growth factor, keratinocyte growth factor, insulin-like growth factor-1, interleukins 1α and -6, and estrogen.

VEGF exists in at least six isoforms, all arising from alternative splicing of mRNA transcribed from a single gene (Gaudreault 2005). These variations encode protein molecules consisting of 121, 145, 165, 183, 189, or 206 amino acids. In addition, any of these six isoforms can be cleaved by plasmin into an isoform of 110 amino acids. VEGF165 is the predominant isoform and is found in normal eyes of rats, monkeys, and humans, along with VEGF121. However, the precise role of each isoform in AMD has not been determined.

VEGF binds to a VEGF receptor, of which there are two subtypes — VEGFR1 and VEGFR2 — both found on the surface of endothelial cells. The angiogenic, mitogenic, and permeability-enhancing properties of VEGF are mediated by VEGFR2.

To establish that VEGF drives retinal neovascularization, VEGF was injected into the eyes of healthy monkeys (Figure 2) (Toletalino 2002). The injections were continued every 3 days for up to 78 days. Neovascular glaucoma developed by day 19, and at the time of vitrectomy at day 80, intraretinal neovascularization was noted. VEGF alone was sufficient to induce vascular dilation and tortuosity, microaneurysm formation, intraretinal hemorrhages, and intraretinal vascular proliferation.

| TABLE 2 Ocular neovascular diseases associated with increased levels of VEGF |
|----------------|----------------|
| Disease                  | Reference |
| AMD                      | Otani 2002 |
| Proliferative diabetic retinopathy | Wilkinson-Berka 2004 |
| Diabetic macular edema    | Funatsu 2003 |
| Retinopathy of prematurity | Cooke 2004 |
| Iris neovascularization   | Pe’er 1997 |
| Central and branch retinal-vein occlusion | Pe’er 1998 |
| von Hippel-Lindau syndrome | Harris 2000 |
| Intraocular melanomas and retinoblastomas | Stitt 1998 |
In addition to neovascular AMD, VEGF has been implicated in many other neovascular diseases of the eye (Table 2, page 5). Therefore, it has become an attractive therapeutic target. In the following article, I will review the treatments for neovascular AMD — notably, those aimed at blocking the effects of VEGF.

References


As of early 2006, the treatments available for AMD were limited in their ability to improve visual acuity. These treatments included laser photocoagulation, photodynamic therapy (PDT) with verteporfin (Visudyne), combination therapy with PDT and steroids, and pegaptanib (Macugen), an aptamer against vascular endothelial growth factor. Vascular endothelial growth factor A (hereafter referred to as VEGF) has been implicated in neovascular AMD. This article will discuss the current therapies and then examine the evidence supporting a novel treatment for neovascular AMD, ranibizumab (Lucentis), a humanized monoclonal antibody fragment against VEGF.

Some treatments are appropriate only for patients with certain kinds of choroidal neovascularization (CNV). On the basis of its appearance in fluorescein angiography, CNV can be grouped into three categories: predominantly classic, minimally classic, and occult. In a predominantly classic, or well-defined CNV, more than half of the area of the choroidal neovascular lesion has distinct borders. A minimally classic lesion has some distinct borders but less than half of the area of the lesion is well defined. An occult lesion completely lacks well-defined borders.

Assessments of visual acuity are the primary tool for determining the efficacy of treatments for neovascular AMD. The familiar chart used for assessing visual acuity is the Snellen chart, named for the 19th century Dutch ophthalmologist who created it. On the Snellen scale, 20/20 represents normal visual acuity and 20/200 represents legal blindness. In modern research, the most commonly used tool for assessing visual acuity is the ETDRS eye chart, which was first used in the Early Treatment of Diabetic Retinopathy Study. The ETDRS chart consists of rows, or lines of letters, five letters to a line, with each line of type smaller than the one above it. The patient reads down the chart until he or she reaches a row where a minimum of three letters on a line cannot be read. Upon retesting, the loss of 15 letters (three lines of letters) is clinically considered a moderate loss of visual acuity; the loss of 30 letters (six lines) or more is considered a severe loss. The number of ETDRS letters a person can see is approximately equivalent to the following Snellen ranges: &gt;73 letters, 20/40; 73–54 letters, 20/40 to 20/80; 53–34 letters, 20/100 to 20/200; &lt;33 letters, &lt;20/200 (Ferris 1982).

Laser photocoagulation

Introduced in the early 1990s, laser photocoagulation was the first treatment used to treat neovascular AMD. Despite its high-tech name, it proved to be a rather crude tool — the clinical equivalent of a hand grenade. When laser photocoagulation achieves its intended result — burning new blood vessels — it also causes indiscriminate collateral damage to overlying photoreceptors, which results in significant and permanent vision loss wherever the laser is applied. Laser photocoagulation of an extrafoveal blood vessel creates a blind spot on that part of the retina, but the patient may be willing to accept that loss in the hope of preserving central vision. On the other hand, laser photocoagulation of a subfoveal blood vessel destroys central vision.

Strict criteria, therefore, are needed to minimize unwanted damage. Eligibility criteria used by the Macular Photocoagulation Study Group (MPS) have been adopted as guidelines for determining which kinds of CNV are suitable for treatment (MPS 1991). These guidelines recommend that only symptomatic, well-demarcated extrafoveal and juxtapfoveal lesions be treated. Occult lesions are not suitable for treatment as no treatment benefit for occult lesions has been shown.

In a small study, MPS criteria were applied to patients...
who were newly diagnosed with neovascular AMD, and only 13 percent (9/67) were eligible for laser coagulation (Freund 1993). Moreover, recurrence rates after laser photocoagulation are high — about half within 3 years (MPS 1994) — and the recurrences tend to be subfoveal. Because of the limitations of thermal laser photocoagulation, only a small percentage of people with neovascular AMD are likely to benefit from it.

The need for a new approach led to testing of an indirect laser treatment, or scatter photocoagulation, for occult lesions. In pilot trials of this technique, the treatment was not found to be beneficial (Arnold 1997, Bressler 1996, Cardillo Piccolino 1993).

**Photodynamic therapy with verteporfin**

Photodynamic therapy (PDT) with verteporfin, a light–activated drug, emerged in 2000 as a means of selectively ablating neovascular AMD lesions while minimizing thermal damage to overlying and underlying structures. Verteporfin is indicated for treatment of patients with predominantly classic subfoveal CNV; evidence is insufficient to indicate verteporfin for treatment of predominantly occult subfoveal CNV (verteporfin 2004).

Verteporfin therapy comprises two steps: a 10-minute intravenous infusion of verteporfin, which accumulates somewhat preferentially in the neovascularature, including CNV, followed by activation of the drug with a nonthermal red laser (689 nm wavelength) 15 minutes after the beginning of the infusion. In the presence of oxygen, activated verteporfin generates reactive oxygen species that cause local damage to the neovascular endothelium, resulting in occlusion of the vessel.

PDT with verteporfin has been found to be most beneficial in patients with predominantly classic CNV at baseline. Two clinical trials of PDT showed that in this subgroup, 68 percent of verteporfin-treated patients lost <3 lines on the ETDRS chart, compared with 40 percent of the patients who received a placebo; after two years, 59 percent of the patients in the verteporfin group lost <3 lines versus 31 percent in the placebo group (verteporfin 2004). Severe vision loss (≥6 lines of visual acuity) occurred in 12 and 15 percent of verteporfin-treated patients at years 1 and 2, respectively, compared with 34 and 36 percent of placebo–treated patients. PDT is increasingly used in conjunction with intravitreal triamcinolone, but that combination increases the risk of glaucoma and cataracts (Gillies 2004).

**Pegaptanib anti-VEGF treatment**

In December 2004, pegaptanib became the first anti-VEGF therapy approved by the U.S. Food and Drug Administration for the treatment of neovascular AMD. Pegaptanib is an aptamer, a short strand (28 bases) of synthetic RNA that binds to and inhibits the VEGF<sub>165</sub> isoform. Pegaptanib is delivered as an intravitreal injection containing 0.3 mg of drug every 6 weeks. In clinical trials, injections were given over a period of 48 weeks (nine injections).

Two concurrent phase 3 clinical trials of pegaptanib were conducted: one trial enrolled 586 patients in the United States and Canada and the other enrolled 622 patients in Europe, Israel, Australia, and South America (Gragoudas 2004). The study population ranged in age from 52 to 92 years (mean, 77) and included patients with all angiographic subtypes of CNV (predominantly classic, minimally classic, and occult with no classic CNV) in roughly equal proportions (Table 1). Patients were excluded if they had a history or evidence of severe cardiac disease (myocardial infarction within 6 months, ventricular tachyarrhythmias, or unstable angina); history or evidence of peripheral vascular disease; clinically significant impaired renal or hepatic function; stroke within 12 months of study entry; or previous therapeutic radiation to the eye, head, or neck.

In both trials, pegaptanib treatment was compared to sham treatment. To maintain patient masking, a syringe lacking a needle was pressed against the anesthetized eyeball.

Patients with a history of PDT with verteporfin were allowed in the study; 8 percent of the pegaptanib 0.3 mg group and 6 percent of the sham group reported such a

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**TABLE 1** Demographics and baseline characteristics of subjects in pegaptanib phase 3 trials

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sham (n=298)</th>
<th>Pegaptanib 0.3 mg* (n=295)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>Age, mean (years)</td>
<td>75.7</td>
<td>76.4</td>
</tr>
<tr>
<td>Mean VA (ETDRS letter score)</td>
<td>52.7</td>
<td>52.8</td>
</tr>
<tr>
<td>Mean lesion size (DA)</td>
<td>4.2</td>
<td>3.7</td>
</tr>
<tr>
<td>CNV classification (% of subjects)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occult with no classic</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Minimally classic</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>Predominantly classic</td>
<td>26</td>
<td>24</td>
</tr>
</tbody>
</table>

CNV=choroidal neovascularization, DA=optic-disc area (equal to 2.54 mm²).
ETDRS=Early Treatment of Diabetic Retinopathy Study, VA=visual acuity.
*These phase 3 trials also included arms for pegaptanib 1.0 and 3.0 mg, but they are excluded because results were similar to those for pegaptanib 0.3 mg, the FDA-approved dose. No benefit was associated with the higher doses.

Sources: Gragoudas 2004, Pegaptanib 2004
history at baseline. At the discretion of the physician, who was masked to treatment assignment, PDT was permitted in patients with predominantly classic lesions as per the verteporfin label. The incidence of prior PDT use was slightly greater in the North American trial (13 percent) than in the other (predominantly European) trial (3 percent), possibly reflecting variations in clinical practice (pegaptanib 2004). The percentage of patients receiving PDT from study investigators at baseline (5–10 days before the study began) was similar in the pegaptanib 0.3 mg group (12 percent) and sham group (13 percent). After baseline, however, slightly more sham-treated patients received PDT than patients who were treated with 0.3 mg of pegaptanib (21 versus 17 percent, respectively). Overall, the percentage of subjects who received PDT was higher in the sham group (25 percent, or 75/296) than in the pegaptanib 0.3 mg group (20 percent, 58/294) (pegaptanib 2005).

In a recent report of these combined phase 3 registry data, 70 percent of patients who received pegaptanib 0.3 mg lost <15 letters of visual acuity at 54 weeks, compared with 55 percent who received the sham injection (Table 2). Thirty-three percent of the pegaptanib group and 23 percent of the sham group reported maintenance or gain of visual acuity. During the second year of treatment, pegaptanib was less effective than during the first year. In the predominantly European study, 57 percent of patients in the pegaptanib 0.3 mg group and 57 percent in the sham group lost <15 letters from baseline to week 102; in the North American study, 61 percent of patients treated with pegaptanib 0.3 mg and 34 percent of sham-treated patients lost <15 letters in the same time period.

### Phase 3 trials of ranibizumab

Ranibizumab is a humanized monoclonal antibody fragment engineered to have high binding affinity for all isoforms of VEGF, thereby blocking the ability of VEGF to promote vessel permeability and angiogenesis. In human trials, administration of ranibizumab via intravitreal injection has been selected to maximize local VEGF inhibition in the retina while minimizing VEGF inhibition systemically. Results from two phase 3, 2-year trials of ranibizumab were recently reported: MARINA1 and ANCHOR2. MARINA was a sham-controlled trial of patients with minimally classic or occult CNV; ANCHOR was an active-controlled trial (PDT with verteporfin) enrolling patients with predominantly classic subfoveal lesions. Two-year data are available for MARINA, while 1-year data have been reported for ANCHOR.

#### MARINA

MARINA was a phase 3, randomized, multicenter, double-masked, sham-controlled study to evaluate the efficacy and safety of ranibizumab in subjects with minimally classic CNV or occult with no classic subfoveal CNV secondary to AMD (Rosenfeld 2006). MARINA enrolled a population that was not eligible for PDT.

The eligibility criteria were age \( \geq 50 \) years; minimally classic or occult with no classic CNV; Snellen-equivalent visual acuity ranging from 20/40 to 20/320; evidence of presumed recent disease progression (blood or recent growth shown by fluorescein angiography or recent loss in visual acuity); and lesion size \( \leq 12 \) disk areas. Patients were well-matched across all study groups in terms of demographics and ocular characteristics at baseline (Table 3, page 10). Exclusion criteria included prior sub-ranibizumab trial of the Anti-VEGF antibody ranibizumab in the treatment of Neovascular AMD.

#### ANCHOR

ANTI-VEGF antibody for the treatment of predominantly classic CHORoidal neovascularization in AMD.

### TABLE 2 Selected endpoints at week 54 in phase 3 trials of pegaptanib

<table>
<thead>
<tr>
<th></th>
<th>Sham (n=296)</th>
<th>Pegaptanib 0.3 mg (n=294)</th>
<th>P value vs. sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losing &lt;15 letters from baseline (primary endpoint)</td>
<td>55%</td>
<td>70%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Letter gain or loss from baseline (% of subjects)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gain ≥0 letters</td>
<td>23</td>
<td>33</td>
<td>.003</td>
</tr>
<tr>
<td>Gain ≥15 letters</td>
<td>2</td>
<td>6</td>
<td>.04</td>
</tr>
<tr>
<td>Loss ≥30 letters (severe loss)</td>
<td>22</td>
<td>10</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>VA ≤20/200 (legal blindness)</td>
<td>56</td>
<td>38</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean area of leakage, number of DAs (baseline)</td>
<td>5.2 (3.6)</td>
<td>4.3 (3.3)</td>
<td></td>
</tr>
</tbody>
</table>

DA = optic-disk area (equal to 2.54 mm²); VA = visual acuity.

SOURCE: GRAGOUDAS 2004
foveal laser treatment, PDT with verteporfin, and experimental treatments for wet AMD.

The primary endpoint was the current FDA standard in AMD trials: the proportion of subjects who lost <15 ETDRS letters of visual acuity at 12 months, compared to baseline, in the best corrected visual acuity score. Important secondary endpoints included the mean change in vision from baseline, the proportion of patients who gained 15 letters or more at month 12, and the mean area of leakage. Exploratory endpoints included the proportion of patients whose vision was 20/40 or better at month 12, the proportion of patients gaining zero or any letters, the proportion of patients gaining 30 or more letters, and the proportion of patients with severe vision loss (losing more than 30 letters).

Patients were randomized in a 1:1:1 fashion among three arms: sham, ranibizumab 0.3 mg, and ranibizumab 0.5 mg. Beginning at month 0, and once a month thereafter, patients received either an injection of active medication or a sham injection through the 12-month timeframe for the primary endpoint, and continued up to 2 years. Approximately 80–90 percent of the patients remained in the study for the full 24 months. At the discretion of the investigator, patients could receive PDT if there was a conversion to predominantly classic CNV or if there was a loss of >20 letters on two consecutive visits, and small lesions <2 DAs in size. Patients in the sham group were allowed to cross over to the ranibizumab 0.5 mg group at unmasking in October 2005, and 12 patients in the sham group chose to do so in the final 2 months of the study.

At month 12, 95 percent of patients in both ranibizumab arms maintained or improved vision, defined as the loss of <15 letters, compared with 62 percent of patients in the sham group. By month 24, 92 percent of patients in the ranibizumab 0.3 mg group and 90 percent of patients in the 0.5 mg group had lost <15 letters from baseline, while 53 percent of patients in the sham group met this endpoint (Table 4). By the end of the study, between 26 and 33 percent of patients treated with ranibizumab had gained ≥15 letters, compared with 4 percent or fewer of the sham-treated patients.

At baseline, between 11 and 15 percent of all study patients had 20/40 vision or better. After 2 years, 42 percent and 35 percent of patients in the ranibizumab 0.5 mg and 0.3 mg groups, respectively, had 20/40 vision or better. The percentage of patients who had 20/200 vision or worse increased from 13 to 48 percent in the sham group by the end of the study, but decreased by month 12 for both ranibizumab groups. The percentage of patients with 20/200 vision or worse at 24 months was the same as at baseline for the ranibizumab 0.3 mg group and increased about 2 percentage points for the ranibizumab 0.5 mg group (Table 4).

Patients in both ranibizumab groups gained about seven letters from baseline by month 12, for an overall difference of 17 letters between sham and ranibizumab-treated groups halfway through the study; by month 24, the difference between the ranibizumab groups and the sham group had grown to 20–21 letters (Figure 1). The mean area of leakage due to CNV increased in the sham group, but decreased in both the 0.3 mg and 0.5 mg groups.

Ranibizumab vs. PDT in ANCHOR

Like MARINA, ANCHOR was a randomized, multicenter, double-masked study. It was designed to compare the efficacy and safety of ranibizumab with verteporfin PDT in subjects with predominantly classic subfoveal CNV. The primary endpoint was the same as in MARINA: the proportion of subjects losing <15 letters. Key secondary endpoints were the proportion of subjects who gained ≥15 letters and the mean change in visual acuity from baseline to month 12 (Brown 2006).

The principal eligibility criteria included age ≥50 years, visual acuity between 20/40 and 20/320, with primary or recurrent subfoveal CNV due to AMD. The lesion had to meet the criteria for PDT treatment. Exclusion criteria included prior subfoveal laser treatment, PDT, or experimental treatments for wet AMD. Following fluorescein angiography to confirm the lesion subtype, patients

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**TABLE 3** Demographics and baseline characteristics of subjects in MARINA

<table>
<thead>
<tr>
<th></th>
<th>Sham (n=238)</th>
<th>Ranibizumab 0.3 mg (n=238)</th>
<th>Ranibizumab 0.5 mg (n=240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>66.8</td>
<td>64.3</td>
<td>63.3</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>97.1</td>
<td>96.2</td>
<td>96.7</td>
</tr>
<tr>
<td>Age, mean (years)</td>
<td>77.0</td>
<td>77.4</td>
<td>76.8</td>
</tr>
<tr>
<td>Mean VA (ETDRS letter score)</td>
<td>53.6</td>
<td>53.1</td>
<td>53.7</td>
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<tr>
<td>Mean lesion size (DA)</td>
<td>4.4</td>
<td>4.3</td>
<td>4.5</td>
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<tr>
<td>CNV classification (% of subjects)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Occult with no classic</td>
<td>63.4</td>
<td>63.4</td>
<td>62.1</td>
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<tr>
<td>Minimally classic</td>
<td>36.6</td>
<td>36.1</td>
<td>37.9</td>
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<tr>
<td>Predominantly classic</td>
<td>0</td>
<td>0.4</td>
<td>0</td>
</tr>
</tbody>
</table>

CNV=choroidal neovascularization, DA=optic-disk area (equal to 2.54 mm²), ETDRS=Early Treatment of Diabetic Retinopathy Study, VA=visual acuity.

SOURCE: ROSENFELD 2006
### TABLE 4  Selected endpoints in MARINA at months 12 and 24

<table>
<thead>
<tr>
<th></th>
<th>Month 12</th>
<th></th>
<th>Month 24</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (n=238)</td>
<td>Ranibizumab 0.3 mg (n=238)</td>
<td>Ranibizumab 0.5 mg (n=240)</td>
<td>Sham</td>
</tr>
<tr>
<td><strong>Primary endpoint (% of subjects)</strong></td>
<td>Losing &lt;15 letters from baseline (%)</td>
<td>62.2</td>
<td>94.5</td>
<td>94.6</td>
</tr>
<tr>
<td><strong>Secondary endpoints (% of subjects)</strong></td>
<td>Letter gain or loss from baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gain ≥15 letters</td>
<td>5.0</td>
<td>24.8*</td>
<td>33.8*</td>
</tr>
<tr>
<td></td>
<td>Loss ≥30 letters (severe loss)</td>
<td>14.3</td>
<td>0.8*</td>
<td>1.2*</td>
</tr>
<tr>
<td></td>
<td>Visual acuity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>VA ≥20/40 (baseline)</td>
<td>10.9</td>
<td>38.7*</td>
<td>40.0*</td>
</tr>
<tr>
<td></td>
<td>(15.1)</td>
<td></td>
<td>(11.3)</td>
<td>(15.0)</td>
</tr>
<tr>
<td></td>
<td>VA ≥20/200 (baseline)</td>
<td>42.9</td>
<td>12.2*</td>
<td>11.7*</td>
</tr>
<tr>
<td></td>
<td>(13.4)</td>
<td></td>
<td>(14.7)</td>
<td>(12.9)</td>
</tr>
<tr>
<td></td>
<td><strong>VA=visual acuity.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>*P &lt;.001 vs. sham.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>SOURCE: ROSENFELD 2006</strong></td>
<td></td>
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</tbody>
</table>

### FIGURE 1  Number of letters gained or lost, MARINA

*Mean change from baseline at month 24 (secondary endpoint)*

- **Baseline (Day 7)**
  - Ranibizumab 0.5 mg (n=240)
    - 6.5
  - Ranibizumab 0.3 mg (n=238)
    - 6.5
  - Sham (n=238)
    - 6.1

- **Month**
  - 6
  - 12
  - 18
  - 24

**Source:** ROSENFELD 2006
were randomized to PDT with sham ranibizumab injection, or sham PDT with ranibizumab 0.3 mg, or sham PDT with ranibizumab 0.5 mg. The arms were well-matched with respect to demographics and baseline ocular characteristics (Table 5).

Subjects who were randomized to the ranibizumab 0.3 or 0.5 mg groups received monthly intravitreal injections starting at month 0, while the subjects randomized to receive verteporfin PDT received monthly sham injections. All subjects received either active verteporfin PDT or sham PDT on the first visit. On subsequent visits, the necessity for repeat verteporfin versus sham PDT was determined based on angiographic evidence of retinal leakage. Thus, all subjects had the potential to have PDT or sham PDT every 3 months, and all subjects received either an actual ranibizumab injection or a sham injection monthly.

Consistent with the results achieved in the previously mentioned trials of PDT, 64 percent of the PDT group in ANCHOR met the primary endpoint, compared with 94 and 96 percent of the ranibizumab 0.3 and 0.5 mg groups, respectively (Table 6). At month 12, a gain of 8.5 and 11.3 letters was observed in the ranibizumab 0.3 and 0.5 mg groups, respectively, which equals differences of 18 and 21 letters, respectively, compared with PDT (Figure 2).

A gain of ≥15 letters was observed in 36 and 40 percent in the ranibizumab-treated subjects, as opposed to only in 5.6 percent in the PDT arm. While none of the ranibizumab-treated patients experienced severe loss in visual acuity (losing ≥30 letters from baseline to month 12), 13 percent of the PDT group experienced such a loss. In addition, marked differences in visual acuity (20/40 or better and 20/200 or worse) were observed at month 12 between the ranibizumab groups and PDT-treated patients (Table 6).

### Safety analysis of ranibizumab

In analyzing the combined safety data from MARINA and ANCHOR, ocular and systemic serious adverse events that have been observed in previous anti-VEGF studies were considered. The ocular events include endophthalmitis, uveitis, retinal detachment, retinal tear, vitreous hemorrhage, and lens damage.

Generally, ocular adverse events were minimal (Table 7). Rates of endophthalmitis were low, with no positive cultures in MARINA and one in ANCHOR. The incidence of inflammatory, non-infectious uveitis amounted...
TABLE 7 Combined safety data for 2 years of MARINA and 1 of ANCHOR: key ocular serious AEs

<table>
<thead>
<tr>
<th></th>
<th>MARINA 24 months</th>
<th>ANCHOR 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (n=236)</td>
<td>Ranibizumab 0.3 mg (n=238)</td>
</tr>
<tr>
<td>Number of events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presumed endophthalmitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture positive</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Culture negative</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Culture not done</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Uveitis</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Rhegmatogenous</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal tear</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Lens damage</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AE=adverse event.
*One case reported as uveitis by investigator.
†Same subject had 2 episodes each reported as uveitis, received systemic antibiotics once.
‡Same subject had 2 episodes.

SOURCES: BROWN 2006, ROSENFIELD 2006
to six in MARINA and one in ANCHOR. Only one case of retinal detachment occurred in MARINA, in the sham group, and two in ANCHOR, including one in the sham group. Incidences of retinal tearing and vitreous hemorrhage were low. Only one patient from MARINA experienced lens damage.

While some systemic adverse events might be expected to arise from anti-VEGF therapy, the apparent systemic safety risks are minimal. The incidence of hypertension was similar across populations in each study, with very little change in blood pressure (Table 8). Key arterial thromboembolic events occurred in similar rates across all groups in both studies. Greater immunoreactivity to ranibizumab was found in MARINA, but patients with more immunoreactivity did not differ from those with less immunoreactivity in terms of outcomes. Immunoreactivity to antigen-binding fragment is found in healthy patients. Slightly more nonocular hemorrhages occurred in the ranibizumab groups (21–22 percent in the ranibizumab groups versus 13 percent in the sham group) in the second year of MARINA, but the study was not powered to determine if this was due to chance or ranibizumab.

Because of the relatively small number of patients enrolled in MARINA and ANCHOR, a larger study (N=5,000) began enrolling patients in November 2005 in a phase 3b study to assess further the safety and tolerability of ranibizumab. This study is known as SAILOR. Patients with all subtypes of new or recurrent active subfoveal neovascular AMD are being enrolled in this 1-year study to evaluate the safety of ranibizumab 0.3 mg and 0.5 mg administered once monthly for 3 months and thereafter on an as-needed basis.

Conclusion
The FDA granted a biologics license application for ranibizumab on June 30, 2006. Approval of ranibizumab means that, for the first time, patients with neovascular AMD can be treated with a biologic therapy that has demonstrated the ability to maintain vision in 95 percent of patients, regardless of lesion subtype, and to improve visual acuity in a substantial number of patients.

References

3 Safety Assessment of Intravitreal Lucentis for AMD.


MPS (Macular Photocoagulation Study) Group. Subfoveal neovascular lesions in age-related macular degeneration.


PANEL DISCUSSION

Ranibizumab Therapy In the Managed Care Market

PANELISTS

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SUMMARY

After Pravin Dugel, MD’s presentations on macular degeneration and its treatment, medical and pharmacy decision makers from third-party payers discussed the implications of the data he presented. Lee Termi, of MediMedia USA, moderated the discussion, which focused largely on how payers would approach ranibizumab (Lucentis).

LEE TERMINI: What are your initial impressions of what Dr. Dugel presented today?

SHERMAN PODOLSKY, MD: Dr. Dugel, when patients come to you, what are their two or three most important concerns with respect to their daily lives?

PRAVIN U. DUGEL, MD: Their most important concern, bar none, is their ability to live independently. As soon as patients hear “macular degeneration,” they think they are going to go blind. The first thing I tell them is that they will never go blind — they will be able to live independently. The next thing that concerns them is driving, which is related to their independence. After that is paying bills. That is the order of business: blindness, driving, paying bills.

ALBERT J. RIZZOLI, MD: What do you actually tell the patient?

DUGEL: You can’t set expectations that are too high. I would tell them we have a drug that I think works better than anything we have had before. I would tell them that the chances of being able to maintain their vision are excellent, perhaps as high as 90 percent. There is also a chance that they might gain some vision.

GARY L. JOHNSON, MD, MBA: Could you explain the physiology of how vision improves after treatment?

DUGEL: It is believed to be similar to what happens when you have a cut in your skin: first you get bright red blood, and then a clot, eventually followed by a scar. Around that scar, the skin is stretched because the scar contracts. The same thing happens under the retina, and it happens fairly quickly. When it contracts, photoreceptors are sheared away; they die and never come back. Clearly, as soon as there is blood, some photoreceptor cells will never regain function. But there is less and less damage as you go out. It ap-
serves that photoreceptors that are slightly peripheral can be rescued to a certain extent, and that is the basis for visual-acuity improvement.

**BRET S. YARCZOWER, MD:** Does the velocity of macular degeneration, the change over time, play any role in the choice of therapy?

**DUGEL:** The sooner we detect it, the more vision we can save. But you’re touching on the issue of use: Where do you draw the line? If you see a patient whose artificial vision is 20/200, do you tell that patient there is nothing more we can do, or do you tell them we can continue injecting you for 6 months or a year, and is there a chance we might improve your vision?

We can do an optical coherence tomography, or OCT, which essentially shows a cross-section of the layers of the retina. It’s a simple test with no side effects; no dye is involved. It’s a fairly accurate measure of the thickness and fluid consistency of the retina. If the clot has already set and produced a scar, the damage is done. It would not be a good idea to have this patient go through a series of injections. On the other hand, if OCT shows thickening because of fluid, you can tell the patient that if we can get rid of that fluid, perhaps some cells will be recovered.

**CHARLES A. STEMPLÉ, DO, MBA:** Will vessels hyperproliferate if you stop treatment?

**DUGEL:** The crux of your question is, “When do you stop?” I don’t know. I would treat for a year and then use OCT to guide me from that point on. If OCT showed fluid, I would continue treating. If the fluid were gone, I might watch it a little more closely, and if the fluid recurred I would treat. We will adjust our protocol according to the differences among patients **[Editor’s note: See “How much is enough?” at left].**

**YARCZOWER:** The measure we’re seeing in these trials seems like kind of a crude measure of improvement — letters that you can or can’t see. I would like a better perspective of what a loss of 15 or 30 letters means in terms of vision.

**GLENDA S. OWENS, RPh, MHA:** Yes. I was fascinated by the research, but this is new lingo for us — the letters and lines. I still don’t know how I can explain to somebody from a managed care perspective what kind of outcome this really is. It would be more intuitive to say, “Now these patients can drive when, before treatment, they couldn’t,” or “They have improved their vision from 20/125 to 20/40” **[Editor’s note: see “Translating lines to quality of life,” page 18].**

**ROBERT LoNIGRO, MD, MS:** This is a revolution in the treatment of macular degeneration. Things will not be the same from now on. I suspect that, as with other biologics, this will be a fairly expensive intervention; pegaptanib (Macugen) is already on the market, but the potential population for ranibizumab is much larger. Potential other uses for this agent or agents like it make me very concerned that the financial floodgate is opening. I have yet to understand what the real benefit is, in terms of vision improvement, and that is what will persuade my health plan to invest. How do we figure out whether we are going to cover it for everybody or whether we are going to require prior authorization for it? I don’t know.

**TERMINI:** If you start out by saying ranibizumab is revolutionary, how could you not make it available?

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**How much is enough?**

Shortly after the U.S. Food and Drug Administration approved ranibizumab (Lucentis), questions arose as to how often patients who are considered appropriate for the therapy should receive it. Although patients could receive up to 12 injections over the course of a year, the manufacturer, Genentech, has estimated that “The average patient will be treated approximately 5 to 7 times per year” (MCW 2006).

During the panel discussion last March captured within this section, Pravin Dugel, MD, was asked about frequency of use and whether ranibizumab would be administered by retinal specialists or ophthalmologists.

“In the short-term, only retinal specialists [would administer the treatment],” Dugel replied. “In the long-term, I don’t know. If I were in [the managed care medical or pharmacy director’s] situation, I would make every attempt to make sure ranibizumab is used only by retinal specialists, because they will use this medication appropriately. I think you will find less abuse there.”

Dugel recommended that payers identify specialists they trust to guide them on appropriate use of ranibizumab.

“I think the way to do this is to distinguish providers in your community with a track record, whom you know are involved in clinical trials like these and are able to do more than just glean information from the Internet,” he told the panel. “Anything can be abused, but if a request comes to you for a person to get ranibizumab after 6 months, then you might say, ‘Well, what did the OCT [optimal coherence tomography] show?’ Then you would know [whether the request is appropriate] after speaking with someone you trust.”

Several managed care medical and pharmacy directors who participated in the discussion felt that the denial rate for ranibizumab would be extraordinarily low, in light of the manufacturer’s strategy of building a sales force for retinal specialists only. “You have to look at it in terms of what the cost per review is,” said one medical director. “The denial rate is going to be low, and considering the incidence of the use of this drug will be low, there are far bigger fish to fry.”

**References**


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**TREATMENT OF MACULAR DEGENERATION**

17
LoNIGRO: It’s an interesting conundrum. Ranibizumab sounds like it is better than current treatment, so we probably will pay for it. At the same time, we have a lot of data in front of us, and I’m still trying to internalize it to figure out what we’re really going to be paying for. This may be the best treatment we have for this disorder, but what is the marginal benefit versus the marginal cost? We’re facing the people who are paying for health care, there are 800 different biologic agents coming to the market, and all of a sudden the cost of health care is doubling. That is part of the picture.

STEMPLE: If ranibizumab is priced premium to pegaptanib and verteporfin (Visudyne), the question is whether there is a population subset that should use verteporfin or pegaptanib first in step therapy. So, first off, you have to show across the entire patient population that ranibizumab is clearly superior — that there is no subset that health plans could designate for verteporfin or pegaptanib first — because that’s what health plans are going to look for.

The products on the marketplace today have defined populations for which they may be effective, but even if you take those subsets, ranibizumab is clearly superior for all patients and all disease states. There isn’t any subset for which ranibizumab would not be a preferred agent. From what we have seen today, ranibizumab totally displaces the other two agents. There is no reason to keep the other two in any preferred positioning.

[Editor’s note: At this point, several participants discussed the importance of the manufacturer’s effort to identify populations for which ranibizumab is appropriate. Some likened it to a similar effort with omalizumab [Xolair]. “Genentech was successful because it established specific criteria for the use of omalizumab,” said one medical director. “It didn’t break the bank. For the most part, I’ve stopped reviewing omalizumab because it is not worth reviewing anymore. I have not seen anybody use it inappropriately.”]

RIZZOLI: What we didn’t hear is when to start this. Dr. Dugel, you said everybody starting at age 50 begins to develop macular degeneration, so there’s your group. Are you going to treat all of those patients?

DUGEL: No. Only a minority of that group — 10 percent of people who have macular degeneration — have wet, or exudative, macular degeneration. Of those patients, the majority already have subfoveal neovascularization when they come to see me, and that’s the group that I would treat.

PODOLSKY: Realistically, how many patients would be
treated? Many plans do preauthorization, but if the therapy in question is an accepted therapy, then preauthorization is a waste of time and money. I wonder if the number of people who will be treated is such that the dollar average would be too low to even come close to the radar screen.

[Editor’s note: Here, a Genentech representative presented an estimate that about 1.3 people per 1,000 in the Medicare population would be appropriate candidates for ranibizumab.]

PODOLSKY [to LoNigro]: Bob, you have 10,000 Medicare patients in your membership?

LoNIGRO: Right.

PODOLSKY: Out of 710,000 people. So for him, it’s going to end up being 10 people who need this. My point is, in a major plan, 10 people will get it [a few] times a year for 1 year, maybe 2. In terms of preauthorization, that’s a lot of work — and for what? If the retinal specialists want to do it, they should just go ahead and do it.

TERMINI: Anyone else?

BALAKRISHNA R. PAI, MD: The complication and side-effect profiles are very impressive. I feel very comfortable using this medication.

JOHNSON: It sounds like a revolutionary, efficacious product that may supplant other forms of therapy, but the key is patient selection. What are the alternatives, how long do you monitor patients, and how long do you keep them on therapy?

DUGEL: It is my firm belief that once this goes on the market, every other therapy I’ve talked about today is going to be of historic significance only. This is far superior to everything across the board. There is no comparison.

So, all the money that is spent now on PDT, on pegaptanib, and on thermal laser photocoagulation are going to go out the door, except for the 5 percent or so of patients who may show up with an extrafoveal, well-defined neovascular membrane. Those people will still need thermal laser photocoagulation.
Points To Ponder

On the basis of the clinical trial data presented in this supplement, the arrival of ranibizumab (Lucentis) promises to change the way MCOs think about treatment for their members with neovascular age-related macular degeneration (AMD). Data from the pivotal phase 3 MARINA and ANCHOR trials show that ranibizumab is more efficacious than sham or photodynamic therapy (PDT) with verteporfin (Visudyne) in maintaining visual acuity. In upwards of 90 percent of patients, ranibizumab has been shown to maintain visual acuity, and in a substantial proportion, to even improve visual acuity.

The benefits of ranibizumab have been observed in patients with each of the three subtypes of choroidal neovascular lesion (occult, minimally classic, and predominantly classic). Additionally, in MARINA, ranibizumab was more efficacious than sham in improving patients’ vision-related quality of life.

Discussions by the managed care medical and pharmacy directors who attended this advisory board meeting suggested that ranibizumab raises numerous important questions for MCOs, such as:

Patient population. What criteria make patients eligible or ineligible for therapy?

Age. Can a patient be too old for ranibizumab therapy?

Comorbidities. Do certain comorbidities preclude ranibizumab therapy? Or would ranibizumab therapy be especially desirable in the context of some comorbidities as a means of preserving some quality of life even as the patient’s overall health declines?

Length of therapy. How long should ranibizumab treatment be used? One year? Two years? Indefinitely? How to know when to stop therapy? How to know when to resume therapy, assuming there is a benefit from resumption of therapy?

Monitoring therapy. By what means, and how often, should response to ranibizumab therapy be monitored? What is the best outcome for assessing response to therapy? Change in visual acuity? Change in quality of life? Some combination of both?

Safety of therapy. Clinical trial data are reassuring but ultimately inconclusive because of the small numbers of subjects. What will postmarketing data show?

Prior authorization. Should prior authorization be required for ranibizumab? If so, what are the criteria for approving or denying the treatment?

Step therapy. Is step therapy ever appropriate for treatment of age-related macular degeneration? If so, how should ranibizumab be used? As the first step? Last step?

Preferred therapy. Are the benefits of ranibizumab such that it should be regarded as the preferred therapy for neovascular AMD?

Current products. What does the availability of ranibizumab mean for the use of other treatments for neovascular AMD? How should ranibizumab be used with respect to pegaptanib and verteporfin?

Formulary placement. In a tiered formulary, where should ranibizumab be placed? What kind of copayment should be required for ranibizumab? A fixed amount or a percentage?

Cost-effectiveness. Is ranibizumab cost-effective? If so, by what measures?

Cost savings. Does ranibizumab therapy result in cost savings for a health plan, such as by reducing treatment for AMD-related depression or hospitalization for fractures owing to vision-related falls, or are the benefits of ranibizumab therapy expressed primarily in terms of maintained or improved quality of life?