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In this Issue...

1

DRUG THERAPY OF AGE
RELATED MACULAR
DEGENERATION

6

NEW MOLECULAR
ENTITIES &
BIOLOGICALS

11

CE ASSESSMENT
QUESTIONS

12

2006 EXHIBIT
SCHEDULE

Drug Therapy of Age Related Macular Degeneration

Goal: Increase the awareness of age related macular degeneration as a common cause of vision loss and understanding of the potential benefits and risks associated with medications used for treatment.

Learning Objectives

1. Describe the epidemiology, pathophysiology, and health consequences of age related macular degeneration.
2. Identify the administration method and dosing schedule for medications used in the treatment of age related macular degeneration.
3. Explain the mechanism of action of the vascular endothelial growth factor antagonist drugs in the treatment of age-related macular degeneration.
4. Characterize the evidence available for drug therapies which have been studied for the treatment of age-related macular degeneration.
5. Describe the quantitative measures of benefit, and risks associated with drug therapies for age related macular degeneration.

Introduction

Age-related macular degeneration (ARMD) is the leading cause of blindness in people over 55 years old in developed countries.¹ ARMD is a degenerative disorder of the retina causing a loss of central vision, which can severely limit the ability to perform daily tasks such as reading, walking, driving and recognizing faces.² The vision loss and subsequent limitations in daily activities causes depression in one-third of patients with ARMD.³ The prevalence of ARMD is 30% in patients 75 years and older, and 7% have the advanced form.⁴ It is estimated that 8 million people in the United States are at risk for developing ARMD in the next 5 years and 1.75 million currently have the advanced form of ARMD.^{4,6}

Pathogenesis

The inside of the eye consists of three primary layers of tissue that are crucial to normal vision. The innermost layer, the neurosensory retina, receives light that enters the eye. The retinal pigment epithelium (RPE), which lies beneath the photoreceptor cells of the retina, provides metabolic support and removes cellular debris. The third layer is the choroidal, which is a network of blood vessels that supplies oxygen and nutrients to the RPE and photoreceptor cells.⁵

The central part of the retina, the macula, has the greatest concentration of photoreceptor cells, which provide high-resolution visual acuity, color vision and central vision. During the early stages of ARMD, acellular debris, or drusen, accumulate within the basement membrane of the RPE and appear as yellow spots on the macula. Small drusen often appear on the macula as part of the normal aging process, but, if the drusen are intermediate in size or numerous, it is indicative of early ARMD.⁷ Patients with early ARMD may also have RPE abnormalities such as hypopigmentation or hyperpigmentation. Patients with the intermediate form of ARMD have at least one large drusen (≥ 125 microns), multiple intermediate drusen or geographic atrophy of sections of RPE not involving the center of the fovea (middle of the macula).² The geographic atrophy causes the macula to lose function; this most commonly presents as blurred central vision that worsens slowly and is called dry ARMD.⁸ Ten percent of cases continue to the advanced form. The most common cause of advanced ARMD is choroidal neovascularization (CNV), or wet ARMD.⁸ The CNV cause more damage by leaking blood and/or serum which can lead to localized retinal detachment and scarring underneath the retina.⁹ Although the wet form is not as common the

dry form, it accounts for the majority of vision loss in patients with ARMD.¹⁰ The visual prognosis for patients with dry ARMD is often slow and insidious¹¹ and is responsible for 20% of legal blindness (visual acuity < 20/200 uncorrected).¹² Wet ARMD may result in rapid loss of central vision and progression to visual acuity of < 20/200.⁸

Evaluation and Classification

The Amsler grid is used to detect subtle visual changes and for patient self-monitoring with early and intermediate forms of ARMD. The Amsler grid consists of graph paper with a dot in the middle. The patient focuses on the dot with one eye at a time, and, if any lines appear wavy or missing, the patient should see a physician as soon as possible for further testing.² Increased problems reading in low lighting may also indicate progression of ARMD.² Other symptoms which indicate worsening of ARMD include blurring of faces, difficulty seeing colors, dark or empty spaces in the center of vision, difficulty reading road signs, and difficulty seeing at a distance or during twilight hours. Any of these effects require prompt evaluation by an ophthalmologist, preferably a retina specialist.

Fluorescein angiography is indicated in ARMD patients when the patient complains of unexplained blurred vision and/or clinical examination shows elevation of the RPE or retina, subretinal blood, hard exudates or subretinal fibrosis.⁸ Fundus photographs are typically obtained when angiography is performed to detect and evaluate serous detachments of the retina or RPE, determining the etiology of blocked fluorescence or late leakage of undetermined source.⁸ Stereo biomicroscopic examination of the macula and visual acuity measurement are also part of the standard evaluation.

Age-related macular degeneration with CNV may be subcategorized based upon the appearance of the lesions on fluorescein angiography. The lesions are considered to be either classic or occult. In classic lesions, the membranes are clearly delineated, well demarcated and leak fluorescein uniformly. Occult lesions are indistinct, hidden, poorly demarcated, and the fluorescein leakage is patchy. Patients may also have lesions with characteristics of both classic and occult CNV. Individual patients may be described as having classic with no occult CNV, predominately classic (the area of classic CNV makes up at least 50% of the entire lesion), minimally classic (the area of classic is less than 50% but greater than 0%), and occult with no classic CNV.⁸ The location of CNV is also important and is categorized as extrafoveal (≥ 200 microns from the foveal center), juxtafoveal (between 1 and 199 microns from the foveal center) and subfoveal (under the foveal center). The angiographic subtypes of wet ARMD may be used in therapy selection decisions.

Risk Factors

The pathophysiology of ARMD remains poorly understood; however the main risk factor is increasing age. Other known risk factors are white race, heredity and cigarette smoking.^{13,14} Numerous studies have found cigarette smoking consistently is a major risk factor. Smoking doubles the risk of ARMD; this risk appears to be dose related.¹⁵ A number of case-controlled and population controlled studies have shown mixed findings regarding an association between ARMD development and hypertension, atherosclerosis and other cardiovascular diseases.¹⁶⁻¹⁸ Other risk factors that have been studied are low levels of antioxidants, dietary fat, hormonal status, female gender, sunlight exposure and alcohol use, but results have been inconsistent.⁸

Although the mechanisms for development of ARMD are only partially understood, there is good evidence that vascular endothelial growth factor (VEGF) plays a role in the development of neovascularization and in causing these vessels to be more permeable or leaky. In addition, recent evidence suggests that gene activity that is associated with ARMD and that the complement cascade and inflammation play a significant role in disease development.¹⁹ Research is underway to develop gene-based and other therapies to treat ARMD. This article will focus on the current drug therapy options for the treatment of wet ARMD.

Current Treatment Options for Neovascular ARMD

The current treatment of ARMD presents many challenges. Current therapy can slow the progression of ARMD, but it cannot cure it. Photocoagulation with thermal laser has been used in the treatment of neovascular macular degeneration; however, less than 15% of patients are considered candidates for this form of treatment. Photocoagulation has been shown to reduce risk of severe visual loss in patients with extrafoveal classic CNV. However, recurrence rates of lesions are about 50% over the subsequent three years.⁸ Juxtafoveal or subfoveal lesions are currently not generally recommended for treatment with photocoagulation because of a small overall treatment benefit, the immediate loss of vision associated with this procedure, and higher rates of persistence or recurrence of lesions.⁸ Laser photocoagulation damages the retina over the treated CNV.

Photodynamic Therapy (PDT)

Verteporfin (Visudyne[®], Novartis) was approved by the FDA in 2000. It is used in photodynamic therapy, which involves intravenous administration of verteporfin followed by application of a nonthermal laser to the area of the CNV lesion. Light activation of verteporfin results in local damage of the neovascular endothelium and vessel occlusion with little to no damage to the overlying retinal pigmented epithelium or photoreceptor cells. In the United States, Visudyne[®] is FDA indicated for the treatment of predominately classic subfoveal CNV due to age-related macular degeneration. According to the product labeling, there is insufficient evidence to indicate Visudyne for the treatment of predominantly occult subfoveal CNV.²⁰ However, in Europe, Japan, and Australia, the approved labeling includes authorization for treatment of patients with CNV that is entirely of the occult form.²¹ In addition, the American Academy of Ophthalmology guidelines mention that photodynamic therapy with verteporfin may be considered for patients with occult CNV with vision < 20/50 or if the CNV is < 4 disc areas in size when the vision is > 20/50.⁸ This difference in recommendations is based on differing interpretations of the findings of the clinical trials with verteporfin. The description of the clinical trial results will provide further explanation for these recommendations.

The pivotal studies submitted with the new drug application for verteporfin are the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) studies. The results of the first year of follow-up of two identical randomized clinical trials were published in 1999.²² Eligible subjects in these two trials had ARMD and subfoveal CNV with at least some of the lesion being classic, the greatest dimension of the lesion was ≤ 5400 micrometers, their best corrected visual acuity was between 20/40 and 20/200, and they were ≥ 50 years of age. Subjects were randomized (2:1) to treatment with photodynamic therapy using verteporfin ($n = 402$) or placebo ($n = 207$). A follow-up exam was performed every 3 months and the subjects were retreated if angiography demonstrated fluorescein leakage.

The primary outcome of the study was the proportion of subjects who experienced fewer than 15 letters lost on the visual acuity examination. A loss of 15 letters, which is equivalent to three lines on the chart, is considered a moderate visual acuity loss. In each group, 94% of subjects completed the examination at month 12. The verteporfin group received an average of 3.4 treatments compared to 3.7 treatments in the placebo group. At the 12-month examination, 61.2% of the verteporfin treated group had lost fewer than 15 letters on the visual acuity exam compared to 46.4% of placebo treated subjects ($p < 0.001$). In the active treatment group, 85% of subjects avoided severe vision loss (≥ 30 letters) compared to 76% in the control group. Other vision outcomes measured also favored the active treatment, including the proportion of subjects with improvement in vision and change in contrast sensitivity. There was less progression of the CNV lesions with active treatment and fewer subjects with fluorescein leakage at

12 months compared to placebo. The advantages of photodynamic therapy were evident at the 3-month examination and continued throughout the study.²²

The differing recommendations for use of verteporfin in selected types of patients are based on a subgroup analysis of the study. In subjects with predominately classic CNV less than 15 letters of vision loss was experienced by 67% of the 159 verteporfin treated subjects, compared to 39% of 84 subjects in the control group ($p < 0.001$). However, in the subgroup of subjects with minimally classic CNV, there was no significant difference in the proportion with less than 15 letters of vision loss (55.9% vs. 55.3% in the verteporfin and placebo groups, respectively). There was also no benefit found in treatment of subjects with evidence of occult CNV. The greatest difference in response between active treatment and control was found in subjects with predominately classic CNV and no occult CNV.²²

Adverse events occurring more frequently with verteporfin included visual disturbances, injection site events, infusion-related back pain and photosensitivity reactions.²²

The 24-month follow-up data from TAP were reported in 2001.²³ Blinded treatment as described in the first TAP report was continued for an additional year. The 24-month examination was completed by 87% of the verteporfin treated subjects and 86% of the control group. During the second year of the study, the verteporfin treated subjects received an average of 2.2 more treatments, for a total of 5.6 over the 2 years, and control subjects received an average of 2.8 more treatments, for a total of 6.5. The primary outcome measurement of less than 15 letters of vision loss was obtained in 53% of the verteporfin treated subjects at 24 months compared to 38% in the placebo treated group ($p < 0.001$). This is a reduction of 8% in both groups compared to the 12-month results. The percentage of subjects avoiding severe vision loss (30 letters) at the 24-month visit was 82% vs. 70% for the verteporfin compared to the control group ($p < 0.001$). This represents 3% and 6% fewer than the 12-month results for the verteporfin and placebo groups, respectively. Subgroup analysis again showed a treatment benefit in the proportion of subjects with less than 15 letters of vision loss in those with predominantly classic CNV (59% vs. 31% in the verteporfin and control group, respectively ($p < 0.001$)). In the minimally classic subgroup, these results were 47.5% compared to 44.2% for the verteporfin and placebo groups, respectively ($p = 0.58$). As was observed in the 12-month results, the subjects with no evidence of occult CNV showed benefit of treatment, whereas those with some occult CNV did not. Curiously, the small subgroup of subjects with occult but no classic CNV showed a trend for benefit from verteporfin.²⁴

The subgroup of subjects with occult with no classic CNV was further studied in the Verteporfin in Photodynamic Therapy (VIP) trial.²⁴ The protocol in this study was very similar to TAP except that the subjects had 1) occult with no classic CNV presumed to have recent disease progression (visual or anatomic deterioration in the last 3 months or evidence of hemorrhage from CNV) or 2) presumed early onset classic CNV based on a visual acuity of 20/40 or better. Subjects were randomized to verteporfin ($n = 225$) or placebo ($n = 114$). Occult with no classic CNV was present in 74% of the verteporfin group and 81% of the control. At the 12-month examination 51% of the verteporfin treated subjects had lost at least 15 letters of visual acuity compared to 54% of placebo treated subjects ($p = 0.52$). The VIP authors reported the result of visual acuity as the percentage of subjects who lost at least 15 letters as opposed to the percentage who lost less than 15 letters, which was reported in TAP. However, after the 12-month examination, the verteporfin treated subjects were less likely to deteriorate. At the 24-month examination, 54% of verteporfin compared to 67% of placebo treated subjects had lost more than 15 letters on visual acuity examination ($p = 0.023$). For severe vision loss (at least 30 letters) at 24 months, the results were 30% compared to 47% for verteporfin and placebo treated

subjects, respectively ($p = 0.001$). Other outcomes measured, contrast sensitivity and fluorescein angiographic changes, favored verteporfin treated subjects at both the 12-month and 24-month assessments. Considering that the size of the treatment benefit in these subjects with occult and no classic CNV is rather modest, additional subgroup analyses were performed to find characteristics more predictive of responsiveness to treatment. These analyses identified more favorable response to verteporfin treatment in subjects with smaller lesions at presentation, and those with lower visual acuity at presentation.²⁴ The results of this study partially explain the recommendations from the American Academy of Ophthalmology and the product labeling in Europe and other countries outside of the United States as mentioned earlier.

Overall adverse events in the VIP study were similar to the results in TAP. However, a potentially serious adverse event occurred in 10 subjects treated with verteporfin in this study; severe visual acuity decrease, which was defined as loss of 20 letters or more occurring within 7 days after treatment. It is currently thought that the incidence of this reaction is between 1% and 4%. In many cases, visual acuity improves within the next 3 months, and some patients return to a level of visual acuity that would be considered a therapeutic success by the 12- or 24-month follow-up.²⁴

Additional follow-up exploratory subgroup analyses have been published by the TAP study group that also suggest subjects with minimally classic CNV are more responsive to treatment with verteporfin when they have smaller lesions or worse visual acuity at presentation.²⁵ Further study is necessary to determine if these are reliable criteria for selection of patients for treatment with verteporfin.

The Visudyne in Minimally Classic CNV (VIM) trial evaluated the efficacy of verteporfin in subjects with ARMD and minimally classic CNV.²⁶ Subjects in this study had minimally classic subfoveal CNV. If they had relatively small lesions (defined as ≤ 4 MPS disc areas), the visual acuity was 20/250 or better, and if they had larger lesions (> 4 but ≤ 6 MPS disc areas), the visual acuity was required to be between 20/50 and 20/250. Other protocol characteristics were similar to TAP and VIP except that half of the subjects in each group were given a reduced fluence (RF) rate of light resulting in half the usual total light dose from standard light fluence (SF). Subjects were randomized to treatment with verteporfin ($n = 77$) or placebo ($n = 77$). Of note, at some point in the course of the study, 17 of the 40 subjects assigned to placebo received at least one treatment with verteporfin and light as open-label therapy because of development of predominantly classic CNV in the study eye or fellow eye. At the 12-month examination, 47% of the placebo treated subjects had lost at least 15 letters of visual acuity compared to 14% treated with verteporfin and RF ($p = 0.002$ compared to placebo) and 28% treated with verteporfin and SF ($p = 0.08$ compared to placebo). At the 24-month examination, the results were 62% for placebo, 26% for verteporfin and RF ($p = 0.003$ compared to placebo) and 53% for verteporfin and SF ($p = 0.45$ compared to placebo). When the RF and SF groups treated with verteporfin were pooled, the combined results were better for verteporfin treated subjects than placebo subjects at both the 12-month ($p = 0.004$) and 24-month ($p = 0.03$) examinations. Comparing the RF and SF groups treated with verteporfin resulted in a significant difference favoring RF in some, but not all, outcome measurements at 12 or 24 months. Adverse events reported in this study were similar to previous studies. The results of this study provide additional evidence that photodynamic therapy with verteporfin reduces the risk of moderate loss of visual acuity in patients with ARMD and minimally classic CNV. The authors also recommend additional study of the reduced fluence light dose.

The TAP study group has reported 3-year²⁷, 4-year²⁸, and 5-year²⁹ results of open-label follow-up of subjects who agreed to continue to participate in that study. Subjects who completed the 24-month examination could receive open-label verteporfin therapy for an ad-

ditional three years, regardless of which group they were originally assigned. Follow-up visits occurred every three months through 48 months and then a final visit at 60 months. Between months 48 and 60 any examination or treatment was at the discretion of the investigator. Patients could be treated as often as every three months up to month 48 if there was evidence of leakage from the CNV detected on fluorescein angiography. Of the 402 patients who had originally been assigned to treatment with verteporfin, 320 participated in the follow-up. The average number of treatments received by this group was 1.3 in the third year, 0.4 in the fourth year and 0.1 in the final year. The 36-month follow-up was completed by 271 subjects, 237 subjects completed the 48-month visit, and 193 subjects completed the 60-month follow-up. These follow-up reports indicate that, in patients with predominately classic lesions as well as the entire treated group as a whole, vision outcomes remain stable for 24 to 60 months. Additional treatments did not result in new or increased incidence of adverse events, and treatment of both eyes in one visit did not pose additional risk. All the previous studies restricted treatment to one eye at a time. The long-term results need to be viewed with some caution because the subjects who did not participate in the follow-up study were older, had a poorer level of visual acuity, and were more likely to have evidence of fluorescein leakage from classic CNV or evidence of progression of CNV at the 24 month visit.

Patients who receive verteporfin should avoid direct sunlight or bright indoor light for 5 days after treatment. Sunscreens are not effective for prevention of photosensitivity reactions in patients who have received verteporfin, and protective clothing is required if they must go outdoors in daylight during the 5-day post-treatment period. After photodynamic therapy with verteporfin, follow-up by telephone is recommended after 2 to 3 days to determine if there has been any acute visual loss and to ascertain if any other adverse events have occurred. Repeat examinations, including fluorescein angiograms, should be considered every three months for two years or more. Retreatment may be given at those same intervals as indicated, as demonstrated in the long-term follow-up reports from TAP.

Vascular Endothelial Growth Factor (VEGF) Inhibitors

Pegaptanib

Pegaptanib sodium (Macugen[®]) was approved in 2004 for the treatment of ARMD.³⁰ Pegaptanib is an oligonucleotide aptamer that binds with high affinity and specificity to VEGF 165 (vascular endothelial growth factor isoform 165).³¹ Research indicates that VEGF 165 is the main ocular stimulus for the development of CNV in the macula.³² The recommended dosage of pegaptanib is 0.3 mg given by intravitreal injection every 6 weeks.³³ The most common adverse events associated with pegaptanib are blurred vision due to vitreous floaters and opacities, anterior chamber inflammation, eye pain, punctate keratitis, corneal edema and eye discharge.³⁴ Serious injection-related adverse events include endophthalmitis, retinal detachment, cataracts and traumatic injury to the eye.³¹

The FDA's approval of pegaptanib for the treatment of ARMD was based on two pivotal studies later published by Gragoudas and associates.³⁵ The results of a 54-week pooled analysis of the pivotal studies demonstrated the short term efficacy and safety of pegaptanib in ARMD.³⁶ The VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N) consisted of two concurrent, randomized, double-blind, multi-center dose ranging controlled clinical trials in 1208 patients with subfoveal sites of CNV with a range of visual acuity of 20/40 to 20/320 in the study eye and 20/800 or better in the other eye. Patients with all angiographic subtypes were included. Patients were excluded if they had prior subfoveal thermal laser therapy, non age-related CNV, more than one prior PDT treatment or evidence of severe cardiac disease within the past 6 months.

Patients were randomly assigned to receive pegaptanib 0.3 mg (n

=294), pegaptanib 1.0 mg (n = 300), pegaptanib 3.0 mg (n = 296) or sham (n = 296) administered by intravitreal injection into one eye every 6 weeks over 48 weeks. All patients with classic lesions were allowed PDT therapy at the discretion of the ophthalmologist, who was masked to randomization. The primary efficacy endpoint was the percent of patients losing less than 15 letters of visual acuity defined as 3 lines on the ETDRS eye charts at 2 meters from baseline to week 54. Secondary outcomes included the percentage of patients maintaining visual acuity or gaining 5, 10 or 15 letters of visual acuity from baseline to 54 weeks, mean change in visual acuity at 6, 12 and 54 weeks, the percent of patients who lost more than 30 letters, and the percent who maintained visual acuity of better than 20/200. The results of the combined analysis after 54 weeks showed a statistically significant benefit of losing fewer than 15 letters of visual acuity for patients assigned 0.3 mg pegaptanib (70%, $p < 0.001$), 1.0 mg pegaptanib (71%, $p < 0.001$), 3 mg pegaptanib (65%, $p = 0.03$) all compared to sham injection (55%). None of the analyses showed that either 1.0 mg or 3.0 mg of pegaptanib was more effective than 0.3 mg. The secondary efficacy endpoints also all favored each dose of pegaptanib compared to placebo. For the currently recommended dose of pegaptanib (0.3 mg) 33% of subjects maintained vision, 22% gained ≥ 5 letters, 11% gained ≥ 10 letters and 6% gained ≥ 15 letters of visual acuity. The results for all doses were similar. The mean change in visual acuity was better for all doses of pegaptanib compared to the sham injection for all time points beginning at 6 weeks; however, the trend was still a steady decline throughout the study for all groups.

Pegaptanib showed efficacy at 6 weeks and increased until week 54. There was no evidence that angiographic lesion subtype impacted the study results. Photodynamic therapy was given to 22% of patients during the study and did not appear to alter the results of the efficacy of pegaptanib. The majority of adverse events associated with drug therapy were generally mild and transient, and the investigators attributed them to the injection procedure and not the drug. In both the pegaptanib and sham groups, 1% discontinued due to adverse events.

The long-term efficacy data for pegaptanib have not been published at this time. The manufacturer's in-house information for the 2-year efficacy study is briefly mentioned in the current product labeling with slightly more information available on their website.³⁷ At week 54, approximately 1050 of the original subjects from the V.I.S.I.O.N. study were re-randomized (1:1) to continue their original pegaptanib dose every 6 weeks, or to discontinue treatment but continue follow-up. Subjects who had been in the placebo group were randomized in equal proportions to one of 5 groups: continue placebo treatment, stop treatment, or receive 0.3 mg, 1 mg or 3 mg pegaptanib intravitreal injection every 6 weeks. The primary endpoint at 102 weeks was a loss of < 15 letters on visual acuity. Data are reported only for the 0.3 mg pegaptanib dose and usual care. By week 102, 59% of subjects receiving pegaptanib lost < 15 letters compared to 45% receiving usual care ($p < 0.05$). These results indicate that pegaptanib was less effective during the second year compared to the first year. Patients who continued pegaptanib during the second year had less vision loss than those who discontinued treatment.³⁷ These data have not undergone a peer review publication process.

D'Amico and associates³⁸ published the two-year safety data from the V.I.S.I.O.N. group. During the second year, subjects originally assigned to pegaptanib were re-randomized (1:1) to continue their original treatment or discontinue therapy. Subjects who had been in the placebo group were randomized in equal proportions to one of 5 groups: continue placebo treatment (n= 51), stop treatment, or receive 0.3 mg (n = 128), 1mg (n = 126) or 3 mg (n = 120) pegaptanib intravitreal injection every 6 weeks. During the first year of study, 7545 injections were given, and, during the second year, 2663 were given. The most common side effects were generally mild to moderate, transient and did not appear to be dose dependent. After 54 weeks, the adverse effects occurring more frequently in the pegaptanib 0.3 mg

group compared to the sham group were eye pain (33% vs. 28%), vitreous floaters (30% vs. 8%), punctate keratitis (33% vs. 27%), vitreous opacities (18% vs. 10%), and increased intraocular pressure (14% vs. 3%). The increase in intraocular pressure was temporary. At 54 weeks, the serious complications were 12 cases of endophthalmitis (0.16% per injection), six cases of retinal detachment (0.08% per injection), and five cases of traumatic cataract (0.07% per injection). No evidence of systemic toxicity was reported, and cardiac disorders occurred in 5% of the sham injection subjects compared to 3% in the active treatment groups. There was no difference in the rate of hypertension, thromboembolic events or serious hemorrhagic events between active treatment and control. After 104 weeks, there was no change in the safety profile. There were four cases of endophthalmitis (0.10% per injection), one case of traumatic cataract, and seven cases of retinal detachment (0.17% per injection). The investigators attributed the most serious adverse events to the intravitreal injection preparation and procedure and not the study drug. Many of the cases of endophthalmitis were attributed to improper procedures.

Ranibizumab

On June 30, 2006, the FDA approved ranibizumab (Lucentis®, Genentech) 0.5 mg intravitreal injection once a month for treatment of patients with ARMD.³⁹ Ranibizumab is a recombinant humanized monoclonal antibody Fab fragment which binds to VEGF and inhibits its biologic activity.³² The recommended dosage is 0.5 mg by intravitreal injection every 4 weeks.³⁹ The most common adverse events associated with ranibizumab are conjunctival hemorrhage, iris and uveal tract inflammation, iridocyclitis, iritis, eye pain, blurred vision due to vitreous floaters, retinal hemorrhage, increased intraocular pressure, and vitreous detachment.⁴⁰ Injection-related serious adverse events that have occurred are endophthalmitis, retinal detachment, and cataract.⁴⁰

The approval of ranibizumab was based on three pivotal studies.³⁹ These pivotal trials were all two-year phase III, multi-center, randomized, double blind studies that compared the efficacy and safety of monthly intravitreal injections of ranibizumab 0.3 mg or 0.5 mg to sham injection or PDT. At press time, these studies were not available in a peer-reviewed publication, and the results for the 0.3 mg dose have not been provided.

MARINA⁴¹ (Minimally classic/occult trial of the Antivascular Ranibizumab In treatment of Neovascular ARMD) compared the efficacy and safety of monthly intravitreal injections of ranibizumab 0.3 mg (n = 240) or 0.5 mg (n = 240) compared to sham injection (n = 238). The primary efficacy endpoint was the loss of < 15 letters on the visual acuity test. At 12 months, this was achieved by 95% of subjects treated with ranibizumab 0.5mg and by 62% in the sham injection group. The results at 24 months were 90% and 53%, respectively. Both of these results were statistically significant. The results for the 0.3 mg dose were not provided. A remarkable result of this trial was that at month 12, 34% of the ranibizumab treated subjects had achieved a gain of at least 15 letters, and by 24 months this gain was achieved by 33%. In the sham injection subgroup, the gain of 15 letters was achieved in 5% and 4% at 12 and 24 months (p < 0.0001). In addition there was a mean positive change of 7.2 letters at 12 months and 6.6 letters at 24 months in the ranibizumab 0.5 mg treated group. The sham group lost a mean of 10.5 letters and 14.9 letters at 12 and 24 months (p < 0.001). The improvement in vision with ranibizumab occurred within the first month and was maintained for the 24-month period. Severe visual loss (30 letters or more) at 24 months was also less frequent with ranibizumab; (3% compared to 23% with sham injection, p < 0.0001). The most common adverse events in the ranibizumab group were conjunctival hemorrhage, vitreous floaters, and increased intraocular pressure. The rate of serious adverse events at 24 months was < 2%.

The ANCHOR³⁹ study was the second pivotal study including 423 patients with predominantly classic ARMD and compared

monthly 0.3 mg (n = 140), or 0.5 mg (n = 140) intravitreal injections of ranibizumab with verteporfin PDT (n = 143). The primary outcome at 12 months showed a loss of < 15 letters in visual acuity in 64% of subjects treated with PDT compared to 96% for ranibizumab 0.5 mg (p < 0.0001). The secondary outcome for gain of ≥ 15 letters in visual acuity was 6% and 40% for the PDT and ranibizumab groups, respectively (p < 0.0001). Once again, the mean change in visual acuity with ranibizumab was positive with a gain of 11.3 letters compared to a loss of 9.5 letters for PDT (p < 0.0001). Both groups had similar adverse events; the most frequently occurring were conjunctival hemorrhage, eye pain, increased IOP and vitreous floaters. The overall rate of reported intraocular inflammation adverse events was 15% in 0.5 mg group compared to 2.8% in the PDT group. This study is ongoing with subjects in the PDT group being offered ranibizumab for the remainder of the trial.

The final pivotal trial was the PIER³⁹ trial in 184 patients with neovascular ARMD with or without a classic component in the CNV. Subjects were randomized to intravitreal injections of ranibizumab 0.3 mg (n = 60), ranibizumab 0.5 mg (n = 61) or sham (n = 63) once a month for 3 months and then once every 3 months for 24 months. The 2-year data are not yet available. After 1 year, 90% of ranibizumab patients had lost fewer than 15 letters in visual acuity compared with 49% in the sham group (p ≤ 0.0001). With the less frequent dosing, after 3 months, the secondary outcomes of this trial were not as favorable as the previous studies mentioned. At 12 months, only 13% of ranibizumab treated subjects gained at least 15 letters of visual acuity compared to 10% in the sham group (not statistically significant). The change in mean visual acuity was -0.2 letters in the ranibizumab treated group compared to -16.3 in sham treated subjects (p < 0.0001). The adverse events were similar to the other studies. There were no reported cases of endophthalmitis or serious intraocular inflammation related to the study drug. In all three pivotal trials for ranibizumab, the data looks promising, but these are relatively short-term efficacy and safety data in a limited sample population. Furthermore, in each study, those randomized to sham injection or PDT also showed some improvement in the primary and secondary outcomes.

Bevacizumab

A third VEGF inhibitor, bevacizumab (Avastin®, Genentech), has also been used in the treatment of neovascular ARMD. Bevacizumab

(continued on page 8)



ACCREDITATION INFORMATION



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New Molecular Entities & Biologicals

FDA Approvals
May 2006 – July 2006

An *IDIS* search retrieved articles relevant to the new drugs and their approved uses. These articles provide a selection of key critical studies and reviews. Additional information on these newly approved drugs will be available in the FDA Approval Package (an official United States Food and Drug Administration [FDA] document) that is compiled for new drugs following approval. The FDA Approval Package includes reviews of the pivotal and supportive clinical studies conducted during the approval process. These studies are often not published elsewhere. FDA Approval Packages are selectively indexed and included as part of the *IDIS* database as they become available. Use the descriptor *155 FDA APPROVAL PACKAGE* in combination with the valid drug term to retrieve these documents from the *IDIS* database.

Generic Name Trade Name (FDA Therapeutic Classification)	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)	Indication/Use Dosage Form	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Darunavir <i>Prezista</i> (AA)	Tibotec, Inc. (June 23, 2006)	DARUNAVIR 8180853 (4 citations)	Human immunodeficiency virus (HIV) Oral Tablet	SYN-ACQ IMMUNE DEFICIENCY 042.
Dasatinib <i>Sprycel</i> (OAA)	Bristol Myers Squibb (June 28, 2006)	DASATINIB 10120854 (1 citation)	Chronic myeloid leukemia Oral	LEUKEMIA, MYELOID, CHRONIC 205.1
Idursulfase <i>Elaprase</i> (FT)	Human Genetics Thera. (July 24, 2006)	IDURSULFASE 44000028 (0 citations) No published human studies have been found for entry into the <i>IDIS</i> database.	Hunter syndrome Injection	MUCOPOLYSACCHARIDOSIS 277.5
Ranibizumab <i>Lucentis</i> (BIOL)	Genentech (June 30, 2006)	RANIBIZUMAB 14000508 (6 citations)	Wet age-related macular degeneration Injection	DEGENERATION, MACULA/POLE 362.5
Varenicline Tartrate <i>Chantix</i> (S)	Pfizer (May 10, 2006)	VARENICLINE 92000239 (3 citations)	Smoking cessation Oral Tablet	DEPEND/ABUSE, TOBACCO 305.1

Therapeutic Potentials:

S = Standard Review, the drug appears to have therapeutic qualities similar to those of one or more already marketed drugs

AA= Accelerated Approval

FT=Fast Track

P = Priority Review, significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease

BIOL= Biological

O = Orphan drug



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Selected Bibliography

Darunavir

Young B, Markowitz M. Do new protease inhibitors offer improved clinical effectiveness? Issues of PI potency and efficacy. *JAIDS J Acquir Immune Defic Sy.* 2004; 35:S3-S12. (IDIS Article Number 517441)

*This is one of 4 review articles in a supplement devoted to the new protease inhibitors. This review discusses the efficacy of each the new protease inhibitors, including **darunavir**, which is listed under its laboratory name, TMC-114. The authors present information from a Phase II randomized study of 50 HIV patients who were experiencing PI (protease inhibitor) treatment failure. Darunavir, at 3 different dosages, plus ritonavir was substituted for the failing PI, and the result was that 97% of patients had a minimum of 0.5 log₁₀ reduction in viral RNA from base line.*

Dasatinib

Haslam S. Dasatinib: The emerging evidence of its potential in the treatment of chronic myeloid leukemia. *Core Evidence.* 2005;1:1-12. (IDIS Article Number 554151)

*Safety, tolerability and response data from Phase I clinical trials are presented in this review. These trials found that **dasatinib** (Sprycel) was well tolerated and was frequently able to overcome imatinib resistance in patients with chronic myeloid leukemia.*

Ranibizumab

Heier JS, Antoszyk AN, Pavan PR, Leff SR, et al. Ranibizumab for treatment of neovascular age-related macular degeneration: A Phase I/II multicenter, controlled, multidose trial. *Ophthalmology.* 2006; 113:633-642. (IDIS Article Number 553629)

From a total of 64 patients, 53 were randomized to 3 months of intravitreal injections of ranibizumab at doses of 4 injections of 0.3 mg or 1 injection of 0.3 mg and then 3 injections of 0.5 mg, and 11 patients were randomized to usual care. After 4 injections of the study drug, visual acuity (VA) increased 9.4 +/- 13.3 (p=0.0048) and 9.1 +/- 17.2 (p=0.0024) letters in the 0.3 mg and 0.5 mg groups respectively, while VA in the usual care group decreased 5.1 +/- 9.6 letters. Investigators concluded that ranibizumab was safe and effective, resulting in improved visual acuity as compared with usual care, and also decreased leakage from choroidal neovascularization.

Varenicline

Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: Varenicline. *Int J Clin Pract.* 2006; 60: 571-576. (IDIS Article Number 555045)

*This review includes information on the neurobiology of nicotine dependence and presents several drug therapies for smoking cessation, including **varenicline**. The mechanism of action for varenicline is explained, and data from Phase II and Phase III randomized trials gives information on dosing, safety and efficacy, as well as some pharmacokinetics.*

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zumab intravitreal injection has been approved for use in the treatment of metastatic carcinoma of the colon or rectum. It is currently in phase III trials for several other types of cancer, but there is not a formal manufacturer sponsored trial for this drug in the treatment of ARMD. In fact, Genentech has actively recommended against this use of their product. Genentech specifically developed ranibizumab for this indication instead of bevacizumab. Bevacizumab is a full-sized monoclonal IgG antibody, and ranibizumab is an antibody fragment engineered to have a high affinity for VEGF and to penetrate the retina better. However, during the time that ranibizumab was still in clinical trials, bevacizumab was already on the market. Even though it was not marketed in a dosage form intended for intravitreal injection, ophthalmologists began to use it. Anecdotal experience with bevacizumab by intravitreal injection for ARMD has been very positive initially.

Four short-term retrospective case series have been published. The largest one included 266 consecutive patients.⁴² Patients with ARMD and CNV were treated with intravitreal injection of bevacizumab 1.25 mg during a 3-month period. The baseline mean visual acuity was 20/184, and that improved to 20/137 at one month, to 20/122 at two months, and to 20/109 at three months. The mean central macular thickness also decreased during the three months of follow-up. Two patients had mild vitritis at one month, and an additional patient had mild vitritis at two months. There were no cases of endophthalmitis, retinal tear or retinal detachment.⁴²

Another retrospective case series reported the results of treatment of ARMD and CNV with intravitreal bevacizumab 1.25 mg in 81 eyes of 79 patients.⁴³ In this series, patients could receive monthly injections until macular edema, subretinal fluid and/or retinal pigment epithelial detachment resolved. Follow-up ranged from four to 15 weeks. By week eight, approximately half of the patients had complete resolution of retinal thickening, subretinal fluid and retinal pigment epithelial detachment. Median visual acuity improved from 20/200 to 20/80 at eight weeks. No cases of uveitis, endophthalmitis, ocular toxicity or thromboembolic events occurred. Three-fourths of the subjects in this series had received previous therapy with photodynamic therapy and/or pegaptanib.⁴³

The third published case series involved 53 eyes in 50 patients,⁴⁴ and a fourth included 17 patients.⁴⁵ Both reports followed patients for three months, the anatomic and visual improvements in these reports were essentially the same as the first two. Rosenfeld⁴⁶ has published a thoughtful editorial of issues to address when considering the use of intravitreal bevacizumab.

Conclusion

Before the approval of verteporfin, there was little to offer patients with advanced ARMD. Photocoagulation therapy is useful for a small percentage of patients and even then offers only modest therapeutic benefits compared to the risks. Photodynamic therapy with verteporfin expands the eligible population that may benefit from treatment compared to photocoagulation. However, even though photodynamic therapy can reduce the risk of progression of disease, improvement in vision is infrequent. Much is yet to be learned about the use of VEGF inhibiting drugs for the optimal treatment of ARMD including the optimal interval for follow-up examinations and repeated treatments, the total number of treatments to be used over time, and the potential long-term risks. In the absence of direct comparative trials, it is difficult to positively conclude that one of these drugs is more effective or safer than another. Differences in response to therapy may depend on the type of lesion the patient has, how far the disease has progressed before treatment is initiated, or additional factors which will be discovered with further research. Early results indicate that improvement in vision in some patients can be achieved with VEGF inhibiting drugs. Combinations of therapy are also being investigated. For now, careful examination of the results of the randomized trials

which have been completed can be used to guide treatment. The advances in treatment also call for an emphasis on public as well as health professional education to recognize early signs or symptoms of macular degeneration. Rapid referral for further evaluation and selection of the best treatment as soon as possible presents a significant opportunity for clinically meaningful benefits. Additional research with new treatments, as well as research on genetic factors involved with ARMD, hold great promise to ultimately decrease the substantial loss of vision that currently occurs with this disease.

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Volume: 17 Issue: 3 SEPTEMBER 2006

Title of Educational Activity (Article)

DRUG THERAPY OF AGE RELATED MACULAR DEGENERATION

Name _____

Address _____

City _____ State _____ Zip _____

Social Security Number (optional) _____

Pharmacy License Number(s) _____

I hereby certify that I have taken this test:

Signature/Date

(circle the correct answer)

1. ARMD is a degenerative disorder of the :
 - a. iris
 - b. retina
 - c. cornea
 - d. optic nerve
2. The prevalence of ARMD in patients 75 years or older is:
 - a. 10%
 - b. 20%
 - c. 30%
 - d. 40%
3. Pegaptanib acts by binding to:
 - a. VEGF 165
 - b. retinal pigment epithelium
 - c. drusen < 250 microns
 - d. all isoforms
4. The recommended dose of Ranibizumab is:
 - a. 0.3 mg by intravitreal injection once a month
 - b. 0.5 mg by intravenous injection once every 6 weeks
 - c. 0.5 mg by intravitreal injection once a month
 - d. 0.3 mg by intravenous injection once every 6 weeks
5. Which of the following is NOT a side effect seen with pegaptanib therapy:
 - a. vitreous floaters
 - b. vitreous opacities
 - c. anterior chamber inflammation
 - d. corneal abrasion
6. The primary outcome of the TA study was:
 - a. loss of more than 30 letters on the visual acuity exam
 - b. loss of less than 15 letters on the visual acuity exam
 - c. gain of more than 15 letters on the visual acuity exam
 - d. gain of more than 30 letters on the visual acuity exam
7. Which of the following is true?
 - a. bevacizumab is a monoclonal IgG antibody and ranibizumab is an antibody fragment
 - b. bevacizumab was approved in June 2006 for the treatment of ARMD
 - c. bevacizumab showed a visual acuity gain of 15 letters in the MARINA trial
 - d. bevacizumab is used with photodynamic therapy in the VIM study

8. In the MARINA study the secondary outcome of ranibizumab showed:
 - a. severe visual loss at 24 months was more frequent with ranibizumab compared to sham
 - b. visual acuity loss of <15 letters at 24 months was 5% for sham and 95% for ranibizumab
 - c. ranibizumab had an improvement compared to sham injection in the gain of \geq 15 letters in visual acuity at 24 months
 - d. ranibizumab was superior to photodynamic therapy with pegaptanib
9. The TAP study group has published follow-up efficacy results for verteporfin for how many years?
 - a. 5 years
 - b. 10 years
 - c. 15 years
 - d. 20 years
10. Patients treated with verteporfin should be counseled to do all the following EXCEPT:
 - a. avoid direct sunlight for 5 days after treatment
 - b. wear protective clothing if they must go outdoors during daylight during the 5 days after treatment
 - c. avoid bright indoor light for 5 days after treatment
 - d. protect themselves from sunlight with

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PROGRAM EVALUATION

	Excellent	4	3	2	Poor	1
Overall quality	5	4	3	2	1	
Relevance to practice	5	4	3	2	1	
Value of content	5	4	3	2	1	
	Agree	Disagree				
Important to pharmacists	5	4	3	2	1	
Increased my knowledge	5	4	3	2	1	
Achieved stated objectives	5	4	3	2	1	
Was educational and not promotional	5	4	3	2	1	
It took me _____ hours and _____ minutes to read this article and complete the assessment questions.						

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December 3-7, 2006

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