NEW ANTIANGIOGENIC THERAPIES FOR AGE-RELATED MACULAR DEGENERATION
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ABSTRACT

New targeted pharmacologic approaches for the management of age-related macular degeneration (AMD) are based on inhibiting pathologic angiogenesis, which underlies choroidal neovascularization. These new therapies improved results obtained with photodynamic therapy alone. Two antivascular endothelial growth factor (anti-VEGF) drugs have been approved for the treatment of neovascular AMD, and several others are in development. VEGF continues to be the target of many antiangiogenic substances based on extensive scientific data demonstrating the integral role of VEGF in pathologic angiogenesis.

Strategies for preventing vision loss in age-related macular degeneration (AMD) have progressively improved over the past decade. Earlier treatment approaches—laser photocoagulation and photodynamic therapy—are based on destroying choroidal neovascularization in AMD. Photodynamic therapy, which has largely displaced thermal laser photocoagulation, can prevent vision loss in patients with predominantly classic lesions and possibly in selected lesions with other compositions but does not usually improve vision in patients with AMD. Increased understanding of the pathophysiology of choroidal neovascularization in AMD, particularly the factors involved in pathologic angiogenesis, has led to development of targeted pharmacologic approaches that improve upon results with photodynamic therapy alone. Among the angiogenic factors implicated in neovascular AMD, vascular endothelial growth factor (VEGF) appears to be the most important contributor to pathologic angiogenesis. Several anti-VEGF drugs for AMD have been introduced or are being developed. Pegaptanib (Macugen, Eyetech Pharmaceuticals, Inc and Pfizer Inc, New York, New York), the first anti-VEGF drug to be introduced, targets 1 of several isoforms of VEGF. Clinical efficacy and tolerability of pegaptanib are reviewed elsewhere in this monograph. This article discusses data on the newer anti-VEGF drugs ranibizumab (Lucentis, Genentech, Inc, San Francisco, California), which was licensed in June 2006 for the treatment of neovascular AMD in the United States, and bevacizumab (Avastin, Genentech, Inc, San Francisco, California), which has been used off-label for the treatment of neovascular AMD. Both ranibizumab and bevacizumab differ from pegaptanib in targeting multiple VEGF isoforms. In addition to these anti-VEGF drugs, other angiogenesis-targeted investigational therapies that offer promise in the treatment of neovascular AMD are discussed.

RANIBIZUMAB

Ranibizumab is a humanized therapeutic antibody fragment that was designed to inhibit VEGF. In June 2006, ranibizumab was licensed in the United States for the treatment of neovascular AMD. Whereas pegaptanib is an aptamer—an oligonucleotide that binds to VEGF with high affinity—ranibizumab is an antibody fragment. Ranibizumab was designed for
optimal retinal penetration following intravitreal injection (better than that of a full-length antibody). Additionally, whereas pegaptanib inhibits only the pathologic VEGF isoform 165, ranibizumab has a broader spectrum of anti-VEGF activity with inhibition of VEGF isoforms 110, 121, and 165. Ranibizumab has been studied in an extensive program of clinical trials, some of which are ongoing.

**PHASE III PIVOTAL TRIALS: MARINA AND ANCHOR**

After the safety and tolerability of multiple intravitreal ranibizumab doses were established in phase I/II clinical trials, the ranibizumab pivotal phase III clinical trials, MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) and ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD), were conducted. MARINA was a randomized, multicenter, double-blind, parallel-group, placebo-controlled study of ranibizumab 0.3 mg, ranibizumab 0.5 mg, and placebo in 716 patients with minimally classic or occult neovascular AMD with recent disease progression. One-year results have been previously reviewed. The percentage of patients who maintained vision (ie, lost <15 letters in visual acuity) or improved vision (ie, gained at least 15 letters in visual acuity) was approximately 95% in each ranibizumab group compared to 62% in the placebo group. The percentage of patients who improved vision by at least 15 letters was 25% with ranibizumab 0.3 mg and 34% with ranibizumab 0.5 mg compared to approximately 5% with placebo. Approximately 40% of patients treated with either dose of ranibizumab achieved a visual acuity score of at least 20/40 compared to 11% of patients treated with placebo. The benefits of ranibizumab over placebo were maintained during the second year of treatment. At the end of 2 years of treatment, the mean letter difference between the group treated with ranibizumab 0.5 mg and the placebo group was 21.5 (Figure).

ANCHOR is an ongoing randomized, multicenter, double-blind, active-control, parallel-group study of ranibizumab 0.3 mg, ranibizumab 0.5 mg, and verteporfin (Visudyne, Novartis Pharma AG, Basel, Switzerland) photodynamic therapy in 423 patients with predominantly classic neovascular AMD. One-
year results are available. The percentage of patients who maintained vision (ie, lost <15 letters in visual acuity) or improved vision (ie, gained at least 15 letters in visual acuity) was 94% in the ranibizumab 0.3-mg group and 96% in the ranibizumab 0.5-mg group compared to 64% of patients treated with verteporfin photodynamic therapy (P <.0001). Data on mean change in visual acuity from baseline to month 12 show that patients treated with ranibizumab improved, on average, whereas those treated with verteporfin declined (Figure). In recently presented subgroup analyses from ANCHOR, ranibizumab was superior to verteporfin photodynamic therapy regardless of patients’ age, visual acuity quartile or lesion size at baseline, and whether occult choroidal neovascular membrane was present. On the basis of better results with ranibizumab, patients in the verteporfin group were given access to ranibizumab for the remainder of the study.

THE FOCUS STUDY

The FOCUS (RhuFab V2 Ocular Treatment Combining the Use of Visudyne to Evaluate Safety) study is an ongoing randomized, single-blind, parallel-group clinical trial involving 162 patients with predominantly classic subfoveal neovascular AMD. Patients were treated with ranibizumab plus verteporfin photodynamic therapy or verteporfin alone. At 1 year, stable or improved vision was observed in approximately 90% of patients in the group receiving ranibizumab plus verteporfin compared to approximately 68% in the group receiving verteporfin alone. The percentage of patients with vision gain of 15 or more letters was 24% in the group receiving combination therapy compared to 5% of patients in the group receiving verteporfin alone.

PIER STUDY

The PIER study is an ongoing randomized, double-blind, parallel-group, phase IIIB trial involving 184 patients with predominantly classic, or recent disease progression with minimally classic or occult with no classic choroidal neovascularization AMD. Patients are being treated with ranibizumab (0.3 mg or 0.5 mg) or placebo once every 3 months for up to 24 months. Data from the first year of treatment were released in June 2006. The primary efficacy endpoint was mean change in visual acuity, measured as number of letters, from baseline to month 12. At month 12, the mean number of letters lost was significantly lower with either dose of ranibizumab (1.6 letters for 0.3 mg and 0.2 letters for 0.5 mg) compared to placebo (16.3 letters; P ≤.0001; Figure). Earlier in the treatment period, at month 3, patients treated with ranibizumab gained visual acuity compared to baseline. On average, patients treated with ranibizumab gained 2.9 letters (0.3-mg group) and 4.3 letters (0.5-mg group) from baseline to month 3 compared to a loss of 8.7 letters in the placebo group. A similar pattern of results was observed for secondary endpoints at 1 year. The percentage of patients who lost fewer than 15 letters in visual acuity from baseline was higher with ranibizumab (83% for 0.3 mg, 90% for 0.5 mg) than placebo (49%). The percentage of patients who improved vision by at least 15 letters was slightly higher with ranibizumab (12% for 0.3 mg, 13% for 0.5 mg) than placebo (10%). The percentage of patients who achieved 20/40 vision at 12 months was higher with ranibizumab (30% for 0.3 mg, 28% for 0.5 mg) than placebo (11%).

Although ranibizumab was associated with significant benefit versus placebo in visual acuity at both 3-month and 12-month assessments, the efficacy results at 12 months were less robust than those observed in the pivotal phase III studies, MARINA and ANCHOR. The PIER study differed from MARINA and ANCHOR in that PIER employed a quarterly dosing regimen, whereas MARINA and ANCHOR employed monthly dosing regimens. Most likely, the quarterly dosing regimen is less effective than monthly dosing, although no definitive conclusions can be made in the absence of studies directly comparing dosing regimens. The optimal dosing regimen for ranibizumab is currently being explored in ongoing clinical trials. One of these trials, SAILOR, is a 1-year trial initiated in November 2005. In SAILOR, patients will be administered ranibizumab 0.3 mg or 0.5 mg once monthly for 3 months and thereafter on an as-needed basis. Planned enrollment is up to 5000 patients.

SAFETY

ADVERSE EVENTS

With ranibizumab, as with other injected intraocular medications, there is a small risk (<0.1% per injection) of endophthalmitis and retinal detachments. Proper aseptic injection technique should always be
used. In addition, patients should be monitored during the week following the injection to permit early treatment should an infection occur. Less serious adverse events reported more often with ranibizumab than placebo in phase III clinical studies included conjunctival hemorrhage, eye pain, and increased intraocular pressure.

**Thromboembolic Events**

The incidence of arterial thromboembolic events in the first year of phase III clinical trials was 2.1% (18 of 874 patients) among those treated with ranibizumab 0.3 mg or 0.5 mg compared to 1.1% (5 of 441 patients) in the control arms.

**Immunoreactivity**

The pretreatment incidence of immunoreactivity to ranibizumab was 0% to 3% across treatment groups. After monthly dosing for 12 to 24 months, low titers of antibodies were detected in approximately 1% to 6% of patients. The clinical significance of immunoreactivity to ranibizumab is unclear at this time, although some patients with the highest levels of immunoreactivity were noted to have iritis or vitritis.

**Bevacizumab**

The anti-VEGF drug bevacizumab is a full-length humanized monoclonal anti–VEGF-A antibody. In this respect, bevacizumab differs from ranibizumab, which is the Fab fragment of the whole-length humanized antibody designed to better penetrate the retina due to its smaller size. Similar to ranibizumab, bevacizumab binds all isoforms of VEGF. Bevacizumab was developed and licensed for the treatment of metastatic colorectal cancer. It is not licensed for the treatment of neovascular AMD and is being used for it off-label. There have been no large, controlled clinical trials of bevacizumab for neovascular AMD, but data from small, open-label studies with relatively short treatment periods have been promising.

Bevacizumab was initially administered systemically and most recently intravitreally for the treatment of neovascular AMD. Systemic therapy was tried with the rationale that bevacizumab administered in this manner could leak from the choroidal neovascularization and inhibit extracellular VEGF. In an open-label, single-center study, 9 patients were treated with an intravenous infusion of bevacizumab (5 mg/kg) followed by 1 or 2 additional doses at 2-week intervals. In affected eyes at 12 weeks, mean and median letter scores increased from baseline by 8 letters and 12 letters, respectively. Mean and median central retinal thickness measured by ocular coherence tomography (OCT) decreased by 157 µM and 177 µM, respectively. Mildly elevated blood pressure was observed by week 6 of treatment. Elevations in blood pressure were controlled by starting or changing antihypertensive medication. No serious ocular or other systemic adverse events were reported.

A retrospective study of 266 patients with neovascular AMD treated with intravitreal injection of bevacizumab 1.25 mg over a 3-month period was recently reported. More than two-thirds of patients (69.7%) had not responded to other treatments including pegaptanib and photodynamic therapy with or without concomitant triamcinolone. At baseline, patients’ mean visual acuity was 20/184. At the 1-month follow-up (n = 244), mean visual acuity had improved from baseline to 20/137 (P < .001 vs baseline), and approximately one-third of patients (30.3%) had improved visual acuity (ie, at least a halving of the visual angle). At the 2-month follow-up (n = 222), mean visual acuity was 20/122 (P < .001 vs baseline), and improved visual acuity was present in 31.1% of patients. At the 3-month follow-up (n = 141), mean visual acuity was 20/109 (P < .001 vs baseline), and improved visual acuity was present in 39.3% of patients. Mean central macular thickness measured by OCT progressively decreased over the 3-month treatment period. The authors characterized the results as favorable but cautioned that the duration of follow-up was not long enough to draw conclusions.

In another retrospective study, the short-term safety and efficacy of intravitreal bevacizumab were assessed in 50 patients who received at least 1 administration of bevacizumab with additional monthly injections given over 3 months at the discretion of the investigator. Mean visual acuity improved from 20/160 at baseline to 20/120 at month 3. Mean central retinal thickness measured by OCT decreased from baseline by 99.6 microns. No drug-related serious ocular or systemic adverse events were reported. Although these results are promising, randomized clinical trials are needed to further evaluate the efficacy and safety of systemic bevacizumab for neovascular AMD.
OTHER THERAPIES

Several other therapies are being developed for neovascular AMD, and early results have been encouraging. All of these new therapies are designed to inhibit angiogenesis through various mechanisms.

- VEGF-Trap is a composite soluble decoy receptor fusion protein that contains portions of the extracellular domains of 2 VEGF receptors: VEGFR-1 (flt-1) and VEGFR-2 (KDR). The VEGF-Trap (R1R2) has a high affinity for VEGF and can be administered systemically or intravitreally. Results of a phase I clinical study of intravitreally administered VEGF-Trap have recently been presented. VEGF-Trap (0.05, 0.15, 0.5, 1, 2, or 4 mg) was administered as a single intravitreal injection to 21 patients in an open-label, parallel-group study. Patients were followed for 6 weeks. Nearly all of the 20 patients evaluable for efficacy (95%) had stable or improved visual acuity (defined as loss of <15 letters) at 6 weeks. The best corrected visual acuity for all patients increased by a mean of 4.8 letters at 6 weeks. Mean improvement in best corrected visual acuity in the 2-mg and 4-mg dosing groups was 13.5 letters. These changes were associated with a decrease in retinal thickness. Median retinal thickness decreased by 134 microns at 6 weeks when measured by OCT. No systemic adverse events or serious ocular adverse events were reported. A phase II trial has been initiated on the basis of these preliminary results.

- Anecortave acetate is an angiostatic cortisone that inhibits angiogenesis. Angiostatic cortisones were chemically modified from corticosteroids with the aim of reducing unwanted side effects, such as cataracts and elevated intraocular pressure, while maintaining the antiangiogenic potency of corticosteroids. Unlike anti-VEGF drugs, which solely affect VEGF, angiostatic cortisones inhibit multiple growth factors thought to be important in angiogenesis. In a randomized, placebo-controlled, parallel-group assessment of 128 patients with subfoveal choroidal neovascularization, patients were treated with anecortave acetate 3 mg, 15 mg, or 30 mg or placebo via posterior juxtascleral depot with retreatment at 6-month intervals at the investigator's discretion. At month 12, the 15-mg dose was significantly better than placebo for mean change from baseline vision, stabilization of vision, and prevention of severe vision loss, but not for inhibition of total lesion growth. No major safety concerns were identified. In a subsequent prospective, masked, randomized, multicenter, parallel group, noninferiority clinical trial comparing anecortave acetate with photodynamic therapy for neovascular AMD, it failed to prove noninferiority, which means the treatment could be the same or worse than verteporfin therapy. In a subgroup analysis, the clinical outcome for anecortave acetate was numerically, but not statistically significantly, better in patients for whom reflux of the drug during posterior juxtascleral delivery was controlled and who were treated within a 6-month treatment window (57% vs 49% with photodynamic therapy; 95% confidence interval, -4.3% favoring photodynamic therapy to +21.7% favoring anecortave acetate).

- Squalamine lactate, a synthetic molecule that is administered systemically, inhibits multiple aspects of angiogenesis including growth factor signaling, integrin expression, and cytoskeletal formation. In an open-label, parallel-group, phase II clinical trial, squalamine lactate 10 mg, 20 mg, or 40 mg was administered intravenously once weekly for 4 weeks. Patients were followed through month 4. In the 20-mg group, improvement in visual acuity of at least 3 lines was observed for 17% of eyes, and 83% of patients avoided 15 or more letter loss. In the 40-mg group, improvement in visual acuity of at least 3 lines was observed for 17% of eyes, and 100% of patients avoided 15 or more letter loss. No serious drug-related adverse events were reported. Phase III clinical trials are ongoing.

- Sirna-027, a short interfering ribonucleic acid (RNA), targets the VEGF-1 receptor. Short interfering RNAs work by initiating processes that turn off specific genes. A phase I dose-escalation trial with 6 Sirna-027 dose cohorts enrolled 26 patients. At 8 weeks after a single injection of Sirna-027, less than 3 lines of vision loss was observed in 96% of patients. Approximately one-quarter (23%) of patients experienced improvement of more than 3 lines in visual acuity. These changes were associated with a decrease in central foveal thickness measured by OCT. It is anticipated that phase II studies will be initiated in 2006.
CONCLUSIONS

Enhanced understanding of the factors involved in pathologic angiogenesis in AMD has led to development of targeted pharmacologic therapies that inhibit choroidal neovascularization and prevent or slow deterioration of visual acuity. The 2006 introduction of ranibizumab, a growth factor-targeted therapy, constitutes a significant advance in the management of AMD. Clinically significant improvement in visual acuity was observed in more patients than with previously published studies with other treatments. Ranibizumab has also been demonstrated to be superior to photodynamic therapy, which was a mainstay of treatment for AMD before the introduction of anti-VEGF drugs. Several other agents in the development pipeline for AMD inhibit various aspects of pathologic angiogenesis and appear promising based on early clinical studies.

REFERENCES