A Phase I Trial of an IV-Administered Vascular Endothelial Growth Factor Trap for Treatment in Patients with Choroidal Neovascularization due to Age-Related Macular Degeneration

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Objectives: To assess the safety, pharmacokinetics, and biological activity of IV administration of vascular endothelial growth factor trap (VEGF Trap), a recombinant protein containing the binding domains of VEGF receptors 1 and 2, in patients with neovascular age-related macular degeneration (AMD).

Design: Randomized, multicenter, placebo-controlled clinical trial.

Participants: Twenty-five patients were enrolled (11 male, 14 female); 19 received VEGF Trap (0.3 [n = 7], 1.0 [n = 7], or 3.0 mg/kg [n = 5]), and 6 received a placebo.

Methods: Patients were randomized to receive a placebo or 0.3-, 1.0-, or 3.0-mg/kg VEGF Trap—a single IV dose followed by a 4-week observation period and then 3 doses 2 weeks apart.

Main Outcome Measures: Safety and biological activity, including change in excess retinal thickness and volume assessed by optical coherence tomography and visual acuity (VA) measured by the Early Treatment Diabetic Retinopathy Study protocol.

Results: The majority of adverse events attributable to VEGF Trap were mild to moderate in severity, but 2 of 5 patients treated with 3.0 mg/kg experienced dose-limiting toxicity (1 with grade 4 hypertension and 1 with grade 2 proteinuria); therefore, all patients in the 3.0 mg/kg–dose group were withdrawn from the study. The mean percent changes in excess retinal thickness were −12%, −10%, −66%, and −60%, respectively, for the placebo and 0.3-, 1.0-, and 3.0-mg/kg groups at day 15 ($P<0.02$ by analysis of covariance [ANCOVA]) and −5.6%, +47.1%, and −63.3% for the placebo and 0.3- and 1.0-mg/kg groups at day 71 ($P<0.02$, ANCOVA). A significant change in VA was not noted in this small study.

Conclusions: The maximum tolerated dose of IV VEGF Trap in this study population was 1.0 mg/kg. This dose resulted in elimination of about 60% of excess retinal thickness after either single or multiple administrations. Alternative routes of delivery to increase the therapeutic window are being explored. *Ophthalmology 2006; 113:1522–1532 © 2006 by the American Academy of Ophthalmology.*

Age-related macular degeneration (AMD) is the most common cause of severe vision loss in patients over the age of 60 years in developed countries.[1] It is recognized by the presence of drusen, yellow deposits beneath the retina, and pigmentary changes due to atrophy and proliferation of retinal pigment epithelium (RPE) cells. These changes are accompanied by gradual death of photoreceptors and moderate decreases in visual acuity (VA); this constellation of

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signs is referred to as atrophic or nonneovascular AMD. Patients with nonneovascular AMD are at risk for development of choroidal neovascularization and thereby converting to neovascular AMD. Patients with neovascular AMD account for only about 10% of patients with AMD, but account for the majority of those with severe vision loss.[2]

The pathogenic events underlying conversion from nonneovascular to neovascular AMD are uncertain, but studies in animal models suggest that increased expression of vascular endothelial growth factor (VEGF) is likely to play a critical role. Inhibition of VEGF receptor signaling by systemic administration of kinase inhibitors[3] or a blockade of VEGF by intraocular injection of an anti-VEGF antibody fragment[4] significantly suppresses choroidal neovascularization in animal models. These data suggest that VEGF is an important therapeutic target for treatment of choroidal neovascularization.

Several VEGF antagonists have been developed and tested in patients with neovascular AMD. Pegaptanib (Macugen, [OSI] Eyetech Pharmaceuticals, Inc., New York, New York) is an RNA molecule that binds $VEGF_{165}$ but not other isoforms of VEGF-A. Intraocular injection of pegaptanib every 6 weeks for 1 year reduced the percentage of patients with classic choroidal neovascularization due to AMD who experienced severe loss of vision (loss of $\geq$15 letters) from 45% in the sham injection group to 30%.[5] Six percent of patients treated with pegaptanib, compared with 2% in the sham injection group, had a substantial improvement in vision (gain of $\geq$15 letters). Relative to sham treatment, the increase in size of choroidal neovascularization lesions was slowed but not stopped. These benefits are modest, but they confirmed that VEGF is a therapeutic target in neovascular AMD.

Ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) is another VEGF antagonist; it is a Fab fragment of an antibody that binds all isoforms of VEGF-A. Monthly intraocular injections of ranibizumab in AMD patients with occult or minimally classic subfoveal choroidal neovascularization reduced the percentage of patients with severe loss of vision over the course of a year from 38% in the sham injection group to 5%, and the percentage of patients who experienced substantial improvement in vision increased from 4.6% to 34% (reported at the meeting of the American Society of Retina Specialists, July 2005, Montreal, Canada). These data suggest that antagonism of all isoforms of VEGF-A in AMD patients with choroidal neovascularization can result in stabilization of vision in the majority of patients and substantial improvement in vision in about a third of patients. Preliminary reports using ranibizumab in patients with classic subfoveal choroidal neovascularization have been equally impressive and confirm that VEGF-A is a very important target in the treatment of neovascular AMD, but suggest several questions. Are the superior results with intravitreous injection of ranibizumab compared with those with pegaptanib due to the inhibition of all VEGF-A isoforms, compared with inhibition of only $VEGF_{165}$; superior pharmacokinetics; a combination of both; or some other reason?

If the superiority of ranibizumab over pegatanib is due to its ability to neutralize all of the VEGF-A isoforms as opposed to just $VEGF_{165}$, then perhaps neutralizing other VEGF family members in addition to VEGF-A would provide an even greater benefit. Placental growth factor is a VEGF family member that contributes to ocular neovascularization and excessive vascular permeability, providing a rationale for targeting multiple family members and not just VEGF-A.[6] Vascular endothelial growth factor receptors bind multiple members of the VEGF family; VEGF receptor 1 binds VEGF-A and placental growth factor, and VEGF receptor 2 binds VEGF-A, VEGF-B, and VEGF-C. A soluble form of VEGF receptor 1 consisting of just the extracellular domain—the receptor without the transmembrane or intracellular portions of the molecule—is normally produced in the body and seems to be a component of the endogenous system that modulates new vessel growth. Gene therapy resulting in elevated levels of soluble VEGF receptor 1 inhibits ocular neovascularization in animal models and has antiangiogenic activity.[7–15]

The VEGF Trap is a recombinant soluble VEGF receptor protein in which the binding domains of VEGF receptors 1 and 2 are combined with the Fc portion of immunoglobulin G. The receptor portion of the molecule has a very high affinity for all VEGF-A isoforms ($K_d < 1$ pmol/l), placental growth factor 1 and 2, and VEGF-B, VEGF-C, and VEGF-D. So VEGF Trap is distinguished from ranibizumab by its higher potency for neutralization of all VEGF-A isoforms and its ability to inhibit other related proangiogenic and pro-permeability VEGF family members. The Fc portion slows clearance by conferring the long circulating half-life of an antibody to the molecule.[16] Either systemic or intravitreous administration of VEGF Trap strongly suppressed laser-induced choroidal neovascularization in mice[17] and in primates (Association for Research in Vision and Ophthalmology abstract no. 3258, 2005). The broader activity and the higher affinity of VEGF Trap are theoretical advantages over ranibizumab, but whether theoretical advantages translate into practical advantages can be determined only by clinical trials.

Although intravitreous injection of a VEGF antagonist has the benefit of limiting systemic exposure, it has the disadvantage of producing large fluctuations in intraocular levels, which cannot be easily measured, making it impossible to determine effective tissue levels. It is possible to measure plasma levels after intravascular administration, and because there is no barrier between the systemic circulation and the choroid, in this setting plasma levels approximate tissue levels, making pharmacodynamic analyses possible. Correlating plasma levels with toxicity is also extremely useful because it provides knowledge regarding plasma levels that should be avoided. This allows the rational design of alternative modes of delivery by measuring plasma levels that occur after local administration and making sure they fall below toxic levels. For this reason, probing the safety of an agent after systemic administration provides important information regardless of the ultimate mode of delivery. Systemic administration of bevacizumab (Avastin, Genentech) in combination with antimetabolites has been shown to cause hypertension and proteinuria and is associated with an increased risk of thromboembolic events.[18] In an oncology trial in which patients receive

multiple subcutaneous injections of VEGF Trap, only hypertension and proteinuria have been identified as definite drug-related side effects. Based in part on this reasonable safety profile, we performed a dose-ranging, placebo-controlled, randomized trial investigating the safety, pharmacokinetics, and biological activity of IV-administered VEGF Trap in patients with neovascular AMD.

Materials and Methods

Ethical Considerations

The study was conducted in compliance with the Declaration of Helsinki, US Code 21 of Federal Regulations, and the Harmonized Tripartite Guidelines for Good Clinical Practice (1996). The study was reviewed and approved by the Western Institutional Review Board for some centers and by local institutional review boards for others. There were 3 participating centers: MacPherson Retina Center at Baylor College of Medicine, Houston, Texas; New York Eye and Ear Infirmary, New York, New York; and Wilmer Eye Institute of the Johns Hopkins University School of Medicine, Baltimore, Maryland. Each study subject had comprehensive discussions with one of the investigators and gave written informed consent before study entry.

Study Design

The study was a randomized, placebo-controlled, dose escalation trial in subjects with subfoveal choroidal neovascularization due to neovascular AMD. Three dose levels of VEGF Trap were investigated (0.3, 1.0, and 3.0 mg/kg). In each cohort, subjects were randomized in a 3:1 ratio (drug:placebo). After enrollment in the 0.3-mg/kg cohort was completed, there was a 2-week waiting period before the 1.0-mg/kg cohort was begun. There was also a 2-week waiting period after the 1.0-mg/kg cohort was enrolled before enrollment of the 3.0-mg/kg cohort was begun.

Study Population

The main inclusion criteria for the study were (1) male or female (any ethnicity), 50 years or older; (2) diagnosis of neovascular AMD in the study eye with leaking subfoveal choroidal neovascularization $\leq$ 12 optic disc areas (measured according to the protocol of the Macular Photocoagulation Study[1]); (3) best-corrected VA (BCVA) score of 20/40 or worse; (4) clear ocular media and adequate pupillary dilation (able to dilate pupils to $\geq$4 mm using standard mydriatics) to permit good stereoscopic fundus photography; and (5) retinal thickness $\geq$ 250 μm in the macular region as measured by optical coherence tomography (OCT).

Subjects were excluded from the study if they (1) had another disease besides neovascular AMD in the study eye that could affect vision or safety evaluation, (2) had previous laser photocoagulation to the center of the fovea in the study eye, (3) were eligible for photodynamic therapy in the study eye unless they refused it, or (4) had intraocular surgery or another treatment in the study eye within 3 months of screening. Nor were subjects eligible for the study if they had (1) symptomatic or unstable coronary artery disease, angina, congestive heart failure, or an arrhythmia requiring active medical management within the last 30 days; (2) myocardial infarction or treatment for acute congestive heart failure within the past 6 months; (3) malignancy other than basal cell carcinoma of the skin diagnosed and treated within the last 5 years; (4) a history of peripheral vascular disease; (5) blood pressure (BP), treated or untreated, $>$ 140/90 mmHg on at least 3 repeated determinations on separate days during the 6 weeks before study entry; or (6) abnormal renal function, as defined by creatinine $>$ upper limit of normal, proteinuria 1+ or greater on 2 repeat determinations, urine protein:creatinine ratio $\geq$ 1, or 24-hour urinary protein excretion of $\geq$300 mg. During the treatment period of this study, the only approved treatment for subfoveal choroidal neovascularization in patients with AMD was photodynamic therapy. Because photodynamic therapy was the standard of care, all patients who were eligible for photodynamic therapy were encouraged to have photodynamic therapy and not enter the trial. Several of the patients had prior photodynamic therapy (5 subjects had multiple prior photodynamic therapy treatments, and 8 had at least 1 prior photodynamic therapy) and still showed evidence of leakage. All of these patients were eligible for photodynamic therapy and it was recommended, but they refused because they felt it was not benefiting them and they preferred to enter a trial rather than have additional photodynamic therapy. There were more of these patients (4/7 with prior photodynamic therapy) in the 0.3-mg/kg group than in the 1.0-mg/kg (2/7) and 3.0 mg/kg (2/5) groups due to random variation in a small study.

Infusions of VEGF Trap or Placebo

Patients were randomized 3:1 to receive VEGF Trap or an inactive saline infusion at each dose level. Masking of treatment assignment was the responsibility of the investigational pharmacist at each participating center. Individual patient doses were prepared by diluting the appropriate volume of VEGF Trap (25 mg/ml) with 0.9% sodium chloride to yield a final concentration of 4 mg/ml. The volume of solution to be prepared was 25 to 150 ml, depending on the patient's dose and body weight. Patients randomized to receive placebo infusions received an infusion of a volume of normal saline (0.9% sodium chloride) equivalent to the volume of active drug solution that would be administered for the patient's weight and dose level. The drug or placebo was infused over a period of no less than 1 hour by a registered nurse or physician's assistant under the guidance of one of the investigators. In addition, internists or anesthesiologists were also coinvestigators at all sites and helped to oversee the administration of the study drug and aid in the management of adverse events.

Study Activities and Assessments

Subjects were monitored closely for safety and tolerability using the following assessments and procedures: slit-lamp biomicroscopy, indirect ophthalmoscopy, tonometry, BCVA measurement, adverse event reporting, vital signs, physical examinations, serum electrolytes, creatinine, quantitative protein determination in 24-hour urine specimens, and measurement of serum neutralizing antibodies directed against VEGF Trap. Hypertension was graded based on the Common Terminology Criteria for Adverse Events. Grade 2 hypertension is defined as a recurrent or persistent ($\geq$24 hours), or symptomatic increase in BP by $>$20 mmHg (diastolic) or to $>$150/100 if previously within normal limits; monotherapy may be indicated. Grade 3 hypertension is defined as a recurrent or persistent or symptomatic increase in BP by $>$20 mmHg (diastolic) or to $>$150/100 if previously within normal limits that requires treatment with more than one drug or more intensive therapy than previously. However, for purposes of this study, grade 3 hypertension that could be easily controlled with a commonly used combination of 2 agents (e.g., a diuretic, an angiotensin converting enzyme inhibitor, and/or a β-blocker) was not considered a dose-limiting toxicity (DLT). This modification of the criteria was made to reflect current standard clinical practice in the management of hypertension. Hypertension that met the criteria for a grade 3 increase and could not be controlled with a combi-

nation of commonly used antihypertensives was considered grade 3. Grade 4 or malignant hypertension is hypertension with life-threatening consequences (e.g., hypertensive crisis). A DLT was defined as any Common Terminology Criteria for Adverse Events grade 3 or 4 toxicity or grade 2 or 3 ocular toxicity. Any grade 1 or 2 toxicity that resulted in dose reduction or discontinuation of study drug was considered a potential DLT to be reviewed by the Investigator and Study Director. Other DLTs were urinary protein excretion of >2 g/24 hours or Common Terminology Criteria for Adverse Events grade 2 or greater potential immunotoxicity, including but not limited to allergic reaction/hypersensitivity (including drug fever), autoimmune reaction, vasculitis, erythema mutliforme, rash/desquamation, urticaria, and/or asymptomtic bronchospasm. This includes infusion-related hypersensitivity reactions, symptoms of which may include flushing, dyspnea, tachycardia, bronchospasm (symptomatic or asymptomatic), hypotension, anxiety, myalgias, edema, and nausea.

Stereoscopic color fundus photography and fluorescein angiography (FA) were performed at baseline and days 29, 71, and 99. Optical coherence tomography was performed at each study visit. Figure 1 (available at http://aaojournal.org) shows a flowchart of study activities. Patients in the first and second cohorts received all 4 infusions and were monitored through all study visits. All of the patients in the 3.0-mg/kg dose group were withdrawn from study after the DLT was identified. The first enrolled patient received all 4 infusions; the second patient received 2 infusions; and the third, fourth, and fifth patients each received 1 infusion.

Reading Center

The Retinal Imaging Research and Reading Center (RIRRC) at the Wilmer Eye Institute served as the reading center for fluorescein angiographic and OCT analyses. All images were evaluated by a grader who was masked with respect to treatment group. Interpretation of optical coherence tomograms is more difficult in patients with choroidal neovascularization than in patients with diabetic macular edema. In patients with choroidal neovascularization, the computer often misinterprets borders, and therefore, the computer-generated foveal thickness, on which eligibility is based, may be misleading. In some instances, baseline scans that had computer-generated values that were >250 μm, thereby allowing patients to be entered, had lower values when read later by the reading center in masked fashion. The values obtained in the reading center are more accurate because the borders selected by the computer for measurements were scrutinized and, when incorrect, were reset manually to get a more accurate reading.

Optical Coherence Tomography

Optical coherence tomography was performed using StratusOCT (Carl Zeiss Meditec, Dublin, CA). The RIRRC provided detailed instruction in the protocol for image acquisition, and a representative from the RIRRC visited each study site to certify competence and compliance. Two standard protocols (6-mm fast macular thickness map and 6×6-mm crosshair) and 1 modified acquisition protocol (3-line 8-mm papillomacular axis scan) were used. The 3-line 8-mm papillomacular axis scans utilized the disc as a landmark to ensure reproducible placement of scan lines at each visit; 1 line was at the superior margin, 1 was at the inferior margin, and 1 passed through the center of the disc. The 6×6-mm crosshair was a high-resolution scan used to follow morphological changes in the macula. The fast macular thickness map performed 6 linear scans 6 mm in length centered on the patient fixation at equally spaced angular orientations in 1.96 seconds. Retinal thickness at any point was defined as the distance between outer and inner reflectivity bands of the OCT cross section. Foveal thickness (in micrometers; defined as the mean height of the neurosensory retina in a central 1-mm-diameter area) and total macular volume (in cubic millimeters) were computed automatically by the StratusOCT software (version 4.0). Due to the advanced nature of the disease and extensive change in the RPE morphology, manual scan profiling was used to correct any artifacts produced by the automated analysis algorithm.

Fluorescein Angiography

High-resolution digital FA was performed using an FF4 fundus camera (Carl Zeiss Meditec, Oberkochen, Germany) attached to an MRP (Boston, MA) capture station. A modified FA acquisition protocol was used for image acquisition, and compliance was monitored by a site visit. Digital mages were sent to the RIRRC and analyzed using EyeRoute Proview software (version 6.1, Anka Systems Inc., McLean, VA). Two independent investigators graded each FA for markers of disease activity (progression/regression), including blood and pigment epithelial detachment. Each fluorescein angiogram was analyzed further using advanced image segmentation techniques for edge detection to determine the lesion size and maximum area and extent of leakage.

Statistical Methods

All statistical analyses were performed in SAS (version 9.0, SAS Institute, Cary, NC). Changes in continuous measures were assessed using analysis of covariance with a main effects model that included baseline excess foveal thickness as a covariate and treatment effects. Due to the small numbers of patients in this study, the assumptions of the parametric model of homoscedasticity and normality were examined, and if the parametric assumptions were unwarranted, rank analogs were to be advanced. A rank analysis of covariance was then to be performed. In fact, due to the small number of subjects in this study, parametric assumptions were not met; therefore, the primary analysis method was the rank analysis of covariance with a main effects model.

Results

Patient Population

Nine patients were enrolled in the first cohort (0.3-mg/kg VEGF Trap and placebo), 9 in the second (1.0-mg/kg and placebo), and 8 in the third (3.0-mg/kg and placebo). Figure 1 (available at http://aaojournal.org) shows the patient disposition in the study. One patient in the second cohort who was thought initially to have occult choroidal neovascularization was determined by the reading center not to have it. Although safety data could have been obtained from this patient, because there was no possibility for the patient to receive any benefit, it was judged inappropriate to expose the patient to any possible risk; therefore, the patient was withdrawn from the study. In addition, when DLT was observed in a patient in the 3-mg/kg cohort, dosing was stopped for all patients in that cohort, and the study was terminated.

Table 1 shows the demographics of the study subjects. The age and gender distributions were similar across all 4 groups. By chance, subjects who were randomized to receive placebo treatment had worse VA at baseline than patients randomized to receive VEGF Trap. Lesion sizes were similar across all groups, except for the 0.3 mg/kg, which had a smaller average lesion size. Each group had a combination of predominantly classic, occult, and minimally classic choroidal neovascularization lesions.

Table 1. Demographics and Disease History

	Placebo (n = 6)	0.3 mg/kg (n = 7)	1 mg/kg (n = 7)	3 mg/kg (n = 5)
Age (yrs) [mean (range)]	76.7 (64–86)	76.3 (58–81)	79.6 (68–88)	73.8 (69–81)
Gender (male:female)	3:3	3:4	2:5	3:2
ETDRS letters read [mean (range)]	27.8 (12–50)	47.9 (24–69)	49.9 (16–64)	47.8 (8–72)
Lesion size (DAs) (mean)	6	3	6.5	7
Lesion type (Occult:classic:minimally classic)	2:3:1	4:2:1	1:1:3	1:2:2
Foveal thickness (μm) [mean (range)]	384.4 (300–483)	299.6 (238–340)	348.8 (221–680)	414.4 (289–563)

DA = disc area; ETDRS = Early Treatment Diabetic Retinopathy Study.

Preliminary Safety Assessment

The most common adverse events were headache, hypertension, proteinuria, and hoarseness (Table 2). Hypertension, proteinuria, and hoarseness were expected adverse events, because they are class effects of systemic VEGF antagonists and had been seen in prior studies of VEGF Trap in patients with advanced malignancies (Proc ASCO abstract 3009, 2004). Adverse events were dose related and were most common in the 1.0- and 3.0-mg/kg cohorts (Table 2), but they were mild and easily managed in the 1.0-mg/kg group.

VEGF Trap administration was associated with a dose-dependent increase in mean BP. The highest readings generally were recorded 2 weeks after the first dose. Table 3 shows the change from baseline to day 15 (2 weeks after dose) in mean systolic and diastolic BPs. The increase in diastolic pressure was statistically significant at all dose levels studied. By 4 weeks after the first dose, BP generally returned to baseline (data not shown), except in one patient whose clinical course is described below. All patients with BP elevations were treated successfully for their hypertension during the repeated-dosing portion of the study. Increases in mean BP were not noted past day 29.

Severe hypertension and proteinuria occurred only in patients who received 3 mg/kg (Table 4). In one patient in the 3-mg/kg cohort, proteinuria reached a level predefined as dose limiting, and in another patient, hypertension was dose limiting (Table 5 [available at http://aaojournal.org]). The patient with severe hypertension was slow to respond to a change in antihypertensive regimen and developed congestive heart failure with pulmonary edema requiring hospitalization. This resolved with diuresis and more aggressive management of hypertension. Due to these DLTs, no additional VEGF Trap was administered to patients in the 3.0-mg/kg cohort, but follow-up was continued to monitor safety. All adverse events resolved after VEGF Trap was discontinued. As a result of the safety analysis, 1.0 mg/kg was determined to be the maximum tolerated intravascular dose of VEGF Trap in this patient population.

Foveal Thickness by Optical Coherence Tomography

The prespecified primary measure of bioactivity was the effect on excess foveal thickness assessed by OCT. Normal foveal thickness is 179±17 μm[19]; therefore, excess foveal thickness is measured as foveal thickness − 179 μm. Figure 2A presents sequential foveal thickness values for each patient in the 1.0-mg/kg cohort. The normal range of 145 to 213 μm, 2 standard deviations (SDs) above and below 179 μm, is shaded. Three of 5 patients who received 1.0-mg/kg VEGF Trap had reduction of foveal thickness into the normal range, and the other 2 were close to the normal range, whereas the 2 patients treated with the placebo had little or no reduction in foveal thickness. It is notable that every patient treated with 1.0-mg/kg VEGF Trap had reduction in foveal thickness 2 weeks after the first infusion and an increase over the next 2 weeks, and then most had reduction after the second, third, and fourth infusions.

Figure 2B illustrates the median percentage change in excess foveal thickness. Drug infusions are shown by arrows located at the top of the figure (days 1, 29, 43, and 57). Eight days after the initial infusion, all 3 cohorts treated with VEGF Trap showed a decrease in excess foveal thickness, but the effect with 0.3 mg/kg was marginal and lost at subsequent time points. In patients treated with 1.0-mg/kg VEGF Trap, there was a persistent effect at 2 weeks with elimination of 70% of excess foveal thickness, but by 1 month, the effect was reduced; there was a 40% decrease in excess foveal thickness. After subsequent infusions of 1.0-mg/kg VEGF Trap, there was again reduction in excess foveal thickness, and at day 71, 2 weeks after the fourth infusion, excess foveal thickness was almost eliminated (80% reduction). Although only a

Table 2. Adverse Events

	Placebo (n = 6)	0.3 mg/kg (n = 7)	1.0 mg/kg (n = 7)	3.0 mg/kg (n = 5)	All Doses (n = 19)
Headache		1 (14.3)	3 (42.9)	4 (80.0)	8 (42.1)
Hypertension			3 (42.9)	3 (60.0)	6 (31.6)
Proteinuria			3 (42.9)	3 (60.0)	6 (31.6)
Hoarseness	1 (16.7)		1 (14.3)	3 (60.0)	5 (26.3)
Arthralgia	1 (16.7)	1 (14.3)	1 (14.3)	1 (20.0)	3 (15.8)
Cough	1 (16.7)	1 (20.0)	2 (28.6)		3 (15.8)
Aggravation of arthritis pain				3 (60)	3 (15.8)

n (% of subjects at dose level).

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