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(54) METHOD FOR TREATING INTRAOCULAR NEOVASCULAR DISEASES

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(57) **ABSTRACT**

A method is provided for administering to a mammal suffering from, or at risk for, an intraocular neovascular disorder with regular dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist.

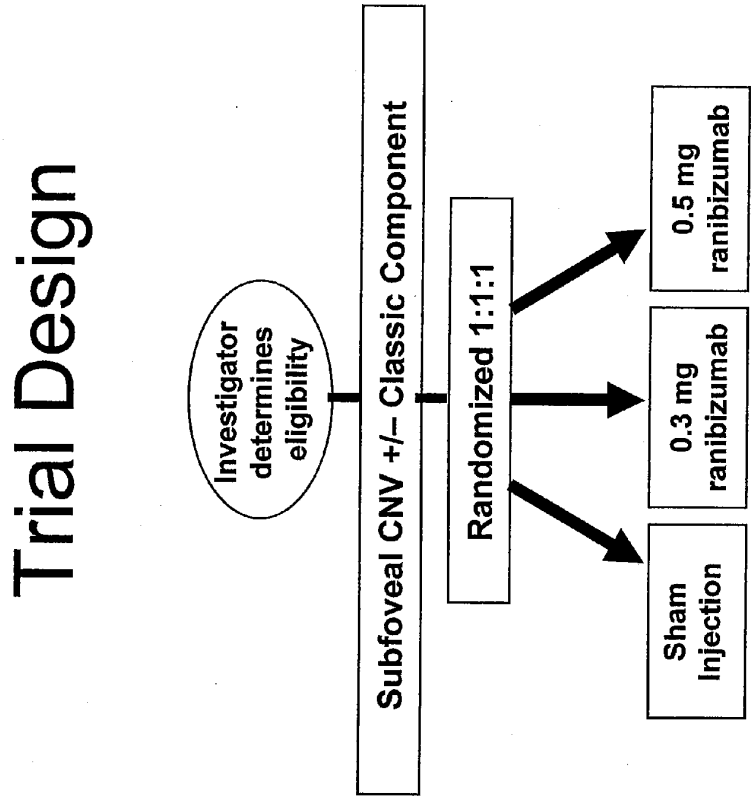

Figure 1

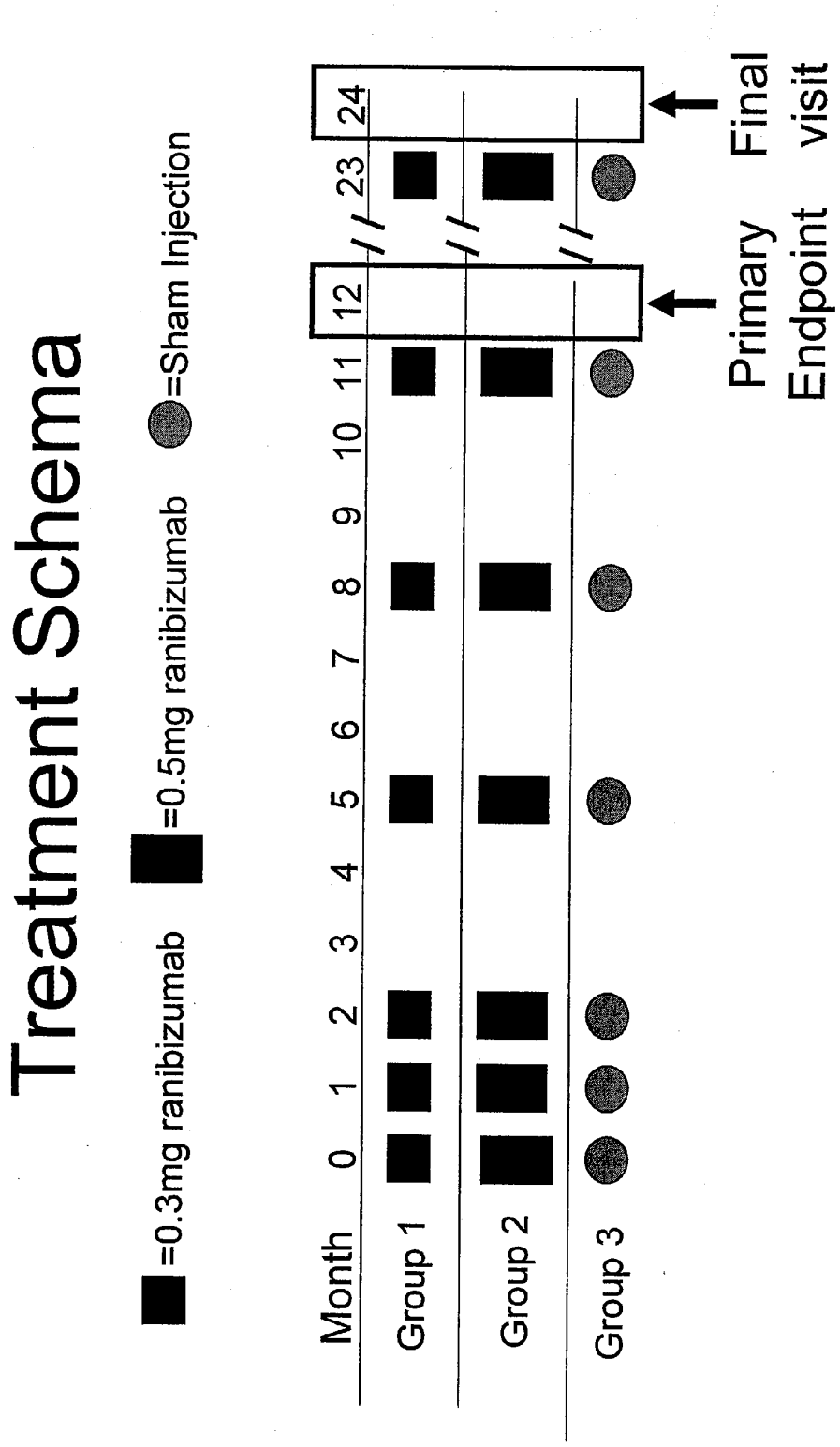

Figure 2

METHOD FOR TREATING INTRAOCULAR NEOVASCULAR DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of PCT/US2005/038006 filed 21 Oct. 2005 which claims priority to U.S. Provisional Application No. 60/621,209, filed 21 Oct. 2004, the contents of which applications are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] This invention relates to methods for treating an intraocular neovascular disorder with a VEGF antagonist. Methods for administering to a mammal suffering from, or at risk for, an intraocular neovascular disorder include monthly dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist.

BACKGROUND OF THE INVENTION

[0003] Angiogenesis is implicated in the pathogenesis of intraocular neovascular diseases, e.g., proliferative retinopathies, age-related macular degeneration (AMD), etc., as well as a variety of other disorders. These include solid tumors, rheumatoid arthritis, and psoriasis (Folkman et al. *J. Biol. Chem.* 267:10931-10934 (1992); Klagsbrun et al. *Annu. Rev. Physiol.* 53:217-239 (1991); and Garner A, *Vascular diseases. In: Pathobiology of ocular disease. A dynamic approach*. Garner A, Klintworth G K, Eds. 2nd Edition Marcel Dekker, NY, pp 1625-1710 (1994)).

[0004] The search for positive regulators of angiogenesis has yielded many candidates, including aFGF, bFGF, TGF-α, TGF-β HGF, TNF-α, angiogenin, IL-8, etc. (Folkman et al. and Klagsbrun et al). The negative regulators so far identified include thrombospondin (Good et al. *Proc. Natl. Acad. Sci. USA*. 87:6624-6628 (1990)), the 16-kilodalton N-terminal fragment of prolactin (Clapp et al. *Endocrinology,* 133:1292-1299 (1993)), angiostatin (O'Reilly et al. Cell, 79:315-328 (1994)) and endostatin (O'Reilly et al. Cell, 88:277-285 (1996)).

[0005] Work done over the last several years has established the key role of vascular endothelial growth factor (VEGF) in the regulation of normal and abnormal angiogenesis (Ferrara et al. *Endocr. Rev.* 18:4-25 (1997)). The finding that the loss of even a single VEGF allele results in embryonic lethality points to an irreplaceable role played by this factor in the development and differentiation of the vascular system (Ferrara et al.).

[0006] Human VEGF exists as at least six isoforms ($VEGF_{121}$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{183}$, $VEGF_{189}$, and $VEGF_{206}$) that arise from alternative splicing of mRNA of a single gene (Ferrara N, Davis Smyth T. *Endocr Rev* 18:1-22 (1997)). $VEGF_{165}$, the most abundant isoform, is a basic, heparin binding, dimeric glycoprotein with a molecular mass of ~45,000 daltons (Id). Two VEGF receptor tyrosine kinases, VEGFR1 and VEGFR2, have been identified (Shibuya et al. *Oncogene* 5:519-24 (1990); Matthews et al., *Proc Natl Acad Sci USA* 88:9026-30 (1991); Terman et al., *Oncogene* 6:1677-83 (1991); Terman et al. *Biochem Biophys Res Commun* 187:1579-86 (1992); de Vries et al., *Science* 255:989-91 (1992); Millauer et al. *Cell* 72:835-46 (1993); and, Quinn et al. *Proc Natl Acad Sci USA* 90:7533-7 (1993)). VEGFR1 has the highest affinity for VEGF, with a Kd of ~10-20 pM (de Vries et al., *Science* 255:989-91 (1992)), and VEGFR2 has a somewhat lower affinity for VEGF, with a Kd of 75-125 pM (Terman et al., *Oncogene* 6:1677-83 (1991); Millauer et al. *Cell* 72:835-46 (1993); and, Quinn et al. *Proc Natl Acad Sci USA* 90:7533-7 (1993)).

[0007] VEGF has several biologic functions, including regulation of VEGF gene expression under hypoxic conditions (Ferrara N, Davis Smyth T. *Endocr Rev* 18:1-22 (1997)), mitogenic activity for micro and macrovascular endothelial cells (Ferrara N, Henzel W J. *Biochem Biophys Res Commun* 161:851-8 (1989); Leung et al., *Science* 246:1306-9 (1989); Connolly et al. *J Clin Invest* 84:1470-8 (1989a); Keck et al. *Science* 246:1309-12 (1989); Plouet et al., *EMBO J* 8:3801-6 (1989); Conn et al. *Proc Natl Acad Sci USA* 87:2628-32 (1990); and, Pepper et al., *Exp Cell Res* 210:298-305 (1994)), and induction of expression of plasminogen activators and collagenase (Pepper et al., *Biochem Biophys Res Commun* 181:902-6 (1991)).

[0008] Furthermore, VEGF has been shown to be a key mediator of neovascularization associated with tumors and intraocular disorders (Ferrara et al.). The VEGF mRNA is overexpressed by the majority of human tumors examined. Berkman et al. *J Clin Invest* 91:153-159 (1993); Brown et al. *Human Pathol* 26:86-91 (1995); Brown et al. *Cancer Res* 53:4727-4735 (1993); Mattern et al. *Brit J Cancer.* 73:931-934 (1996); and Dvorak et al *Am J Pathol* 146:1029-1039(1995). Also, the concentration of VEGF in eye fluids are highly correlated to the presence of active proliferation of blood vessels in patients with diabetic and other ischemia-related retinopathies. Aiello et al., *N. Engl. J. Med.* 331:1480-1487 (1994). Furthermore, recent studies have demonstrated the localization of VEGF in choroidal neovascular membranes in patients affected by AMD. Lopez et al., *Invest. Ophtalmo. Vis. Sci.* 37:855-868 (1996); Kvanta et al., *Invest Ophthalmol Vis Sci* 37:1929-34 (1996).

[0009] Age related macular degeneration (AMD) is a leading cause of severe, irreversible vision loss among the elderly. Bressler, *JAMA* 291:1900-1 (2004). It is characterized by a broad spectrum of clinical and pathologic findings, such as pale yellow spots known as drusen, disruption of the retinal pigment epithelium (RPE), choroidal neovascularization (CNV), and disciform macular degeneration. The manifestations of the disease are classified into two forms: non exudative (dry) and exudative (wet or neovascular). Drusen are the characteristic lesions of the dry form, and neovascularization characterizes the wet form. Disciform AMD is the fibrotic stage of the neovascular lesion.

[0010] There is a dramatic increase in the prevalence of AMD with advancing age. See, e.g., Leibowitz et al., *Surv Ophthalmol* 24(Suppl):335-610 (1980) and Klein et al., *Ophthalmology* 99:933-43 (1992). Although the wet form of AMD is much less common, it is responsible for 80%-90% of the severe visual loss associated with AMD (Ferris et al., *Arch Ophthamol* 102:1640-2 (1984)). There is an estimated 1-1.2 million prevalent cases of wet AMD. The cause of AMD is unknown; however, it is clear that the risk of developing AMD increases with advancing age. Other known risk factors include family history and cigarette smoking. Postulated risk factors also include oxidative

stress, diabetes, alcohol intake, and sunlight exposure. D'Amico, *N Engl J Med* 331:95-106 (1994) and Christen et al., *JAMA* 276:1147-51 (1996).

[0011] Dry AMD is characterized by changes in the RPE and Bruch's membrane. It is thought that the RPE, compromised by age and other risk factors, deposits lipofuscin and cellular debris on Bruch's membrane. These changes may be seen ophthalmoscopically as drusen, which are scattered throughout the macula and posterior retinal pole. There are also variable degrees of atrophy and pigmentation of the RPE. Dry AMD may be asymptomatic or accompanied by variable and usually minimal visual loss and is considered to be a prelude to development of wet AMD.

[0012] Wet AMD is typically characterized by CNV of the macular region. The choroidal capillaries proliferate and penetrate Bruch's membrane to reach the RPE and may extend into the subretinal space. The increased permeability of the newly formed capillaries leads to accumulation of serous fluid or blood under the RPE and/or the neurosensory retina or within the neurosensory retina. When the fovea becomes swollen or detached, decreases in vision occur. Fibrous metaplasia and organization may ensue, resulting in an elevated subretinal mass called a disciform scar that constitutes end-stage AMD and is associated with permanent vision loss (D'Amico D J. *N Engl J Med* 331:95-106 (1994)).

[0013] The neovascularization in AMD can be classified into different patterns based on fluorescein angiography of subfoveal chorodial neovascular lesions. TAP and VIP Study Groups, *Arch Ophthalmol* 121:1253-68 (2003). The major angiographic patterns are termed classic and occult and are associated with different degrees of aggressiveness, vision losses, and response to different treatment options.

[0014] The diffusible nature of VEGF and its specificity of action for endothelial cells support a key role in the process of abnormal blood vessel growth and vascular leakage. Increased expression of VEGF in retinal photoreceptors or RPE of transgenic mice stimulates neovascularization within the retina, and VEGF antagonists partially inhibit retinal neovascularization in animal models (Okamoto et al. *Am J Pathol* 151:281-91 (1997); Schwesinger et al., *AM J. Pathol*. Mar; 158(3):1161-72 (2001)). Anti-VEGF neutralizing antibodies inhibit intraocular angiogenesis in models of ischemic retinal disorders (Adamis et al. *Arch. Ophthalmol.* 114:66-71 (1996)), and also suppress the growth of a variety of human tumor cell lines in nude mice (Kim et al. *Nature* 362:841-844 (1993); Warren et al. *J. Clin. Invest.* 95:1789-1797 (1995); Borgström et al. *Cancer Res.* 56:4032-4039 (1996); and Melnyk et al. *Cancer Res.* 56:921-924 (1996)). Therefore, anti-VEGF monoclonal antibodies or other VEGF antagonists are promising candidates for use in treatments of intraocular neovascular disorders, and new methods of administering therapeutic compounds, which increases the effectiveness of the therapeutic compound, are needed.

SUMMARY OF THE INVENTION

[0015] One object of the present invention is to provide an improved method of administering a therapeutic compound. This and other objects will become apparent from the following description.

[0016] Methods for treating intraocular neovascular disease are provided. For example, methods include administering to a mammal a number of first individual doses of a VEGF antagonist, followed by administering to the mammal a number of second individual doses of the antagonist, wherein the second individual doses are administered less frequently than the first individual doses.

[0017] In one embodiment of the invention, a method for treating wet form age-related macular degeneration is provided, which comprises administering to a mammal a number of first individual doses of an VEGF antagonist, followed by administering to the mammal a number of second individual doses of the antagonist, wherein the second individual doses are administered less frequently than the first individual doses.

[0018] In one embodiment, the mammal is in need of treatment. Typically, the mammal is a human.

[0019] In one embodiment, the administration of the VEGF antagonist is ocular. In one aspect, the administration is intraocular. In another aspect, the administration is intravitreal.

[0020] A VEGF antagonist is administered in the methods of the invention. In one aspect, the VEGF antagonist is an anti-VEGF antibody, e.g., a full length anti-VEGF antibody or an antibody fragment. In one embodiment, the anti-VEGF antibody is a Fab antibody fragment. In one embodiment, the antibody fragment is Y0317.

[0021] In one embodiment of the invention, the first individual doses are administered at one month intervals (e.g., about 3 individual doses). Typically, there is more than one first individual dose. In another embodiment, the second individual doses are administered at three month intervals (e.g., about 6 individual doses). In one aspect of the invention, the second individual doses are administered beginning three months after the number of first individual doses. In one embodiment, a number of second individual doses are administered to the mammal during a period of at least 22 months following the number of first individual doses.

[0022] In one embodiment of the invention, the number of first individual doses and the number of second individual doses are administered over a time period of about 2 years. In one aspect, the first individual dose is administered at month 0, 1 and 2. In another aspect, the second individual dose is administered at month 5, 8, 11, 14, 17, 20 and 23. For example, the first individual dose is administered at month 0, 1, and 2 and the second individual dose is administered at month 5, 8, 11, 14, 17, 20 and 23. In one embodiment, the VEGF antagonist is administered over less than 2 years, or optionally, administered over greater than 2 years.

[0023] Other aspects of the invention will become apparent from the following description of the embodiments which are not intended to be limiting of the invention.

BRIEF DESCRIPTION OF THE FIGURES

[0024] FIG. **1** schematically illustrates the study in Example 1.

[0025] FIG. **2** schematically illustrates a dosing regimen for treating, e.g., age-related macular degeneration (AMD) with a VEGF antagonist.

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