TREATMENT OF AMD USING AAV2 VARIANT WITH AFLIBERCEPT

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/351,234, filed June 16, 2016, the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE DISCLOSURE

[0002] Aflibercept is a recombinant fusion protein that acts as a decoy receptor for vascular endothelial growth factor subtypes A and B (VEGF-A and VEGF-B) and placental growth factor (PIGF). By binding to these ligands, aflibercept is able to prevent these ligands from binding to vascular endothelial growth factor receptors (VEGFR), VEGFR-1 and VEGFR-2, to suppress neovascularization and decrease vascular permeability. Aflibercept consists of domain 2 of VEGFR-1 and domain 3 of VEGFR-2 fused with the Fc fragment of IgG1. Aflibercept is commercially marketed under the trade name EYLEA® (aflibercept), which is an ophthalmic intravitreal aflibercept fusion protein injection.

SUMMARY

[0003] While EYLEA® (aflibercept) is the current standard of care for treating wet AMD in patients, a gene therapy method of delivering aflibercept into an eye can provide an improved treatment option for patients because gene therapy can provide prolonged or sustained release of aflibercept in vivo without requiring repeated injections, which can increase the risks of inflammation, infection, and other adverse effects in some patients. Additionally, by not requiring repeated injections, gene therapy addresses the patient compliance and adherence challenge associated with therapies that require repeated injections, as non-compliance can result in vision loss and deterioration of the eye disease or condition. The rate of non-compliance and non-adherence to treatment regimens that require repeated or frequent trips to medical offices for administration is higher among elderly patients, who are most impacted by AMD. Delivering aflibercept into an eye of a patient via gene therapy can thus provide a safer, potentially more cost-effective, and more convenient treatment option for patients, and improve patient outcomes by addressing the non-compliance and non-adherence problem.

[0004] The present disclosure relates to pharmaceutical compositions and methods for the prevention or treatment of neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy (DR) in patients with DME, retinal vein occlusion, and related eye diseases or conditions, in a primate or human subject by administering intravitreally or subretinally a

pharmaceutical composition comprising a pharmaceutically effective amount of a vector or viral particles (e.g., rAAV) comprising a nucleic acid encoding aflibercept, a functional fragment, or a variant thereof.

[0005] Disclosed herein is a method of treating an eye condition or disease, the method comprising administering a unit dose of a pharmaceutical composition by intravitreal injection to an eye of a primate subject in need thereof, wherein the pharmaceutical composition comprises: (a) a rAAV2 variant comprising an amino acid sequence LGETTRP inserted between positions 587 and 588 of capsid protein VP1, and a nucleic acid sequence encoding a polypeptide having at least 80% homology to aflibercept, a functional fragment, or variant thereof, and (b) a pharmaceutically acceptable excipient. In some cases, the eye condition or disease is neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion, diabetic macular edema (DME), or diabetic retinopathy associated with DME. In some cases, the eye condition or disease is choroidal neovascularization or wet AMD. In some cases, the unit dose comprises between 1E12 to 1E13 vector genomes. In some cases, the unit dose comprises between 2E12 to 6E12 vector genomes. In some cases, the unit dose comprises a volume that is not more than 100 μL. In some cases, the unit dose comprises a volume that is not more than 50 μL. In some cases, the subject is a non-human primate. In some cases, the subject is a human. In some cases, the subject is responsive to aflibercept. In some cases, the subject has been pre-treated with aflibercept. In some cases, the administering by intravitreal injection occurs not more than once in at least 2 years. In some cases, the administering by intravitreal injection occurs not more than once in at least 5 years. In some cases, the administering by intravitreal injection is a one-time administration. In some cases, the pharmaceutical composition is a suspension or a refrigerated suspension. In some cases, the method further comprises agitating the suspension to ensure even distribution of the suspension prior to the administering step. In some cases, the method further comprises warming the pharmaceutical composition to room temperature prior to the administering step.

[0005a] In one aspect, there is provided use of a unit dose of a pharmaceutical composition in the manufacture of a medicament for treating an eye condition or disease, wherein the medicament is to be administered by intravitreal injection to an eye of a primate subject in need thereof, and wherein the pharmaceutical composition comprises:
(a) a rAAV2 variant comprising an amino acid sequence LGETTRP inserted between positions 587 and 588 of capsid protein VP1, and a nucleic acid sequence encoding a polypeptide comprising a sequence having at least 95% homology to aflibercept, and
(b) a pharmaceutically acceptable excipient.

[0006] Disclosed is a pharmaceutical composition comprising a suspension that further comprises a rAAV2 variant comprising an amino acid sequence LGETTRP inserted between positions 587 and 588 of a capsid protein VP1, and a nucleic acid sequence encoding a polypeptide having at least 80% homology to aflibercept, a functional fragment, or variant thereof. In some cases, the nucleic acid sequence comprises a sequence of SEQ ID NO: 2. In some cases, a unit dose of the composition comprises between 1E12 to 1E13 vector genomes. In some cases, a unit dose of the pharmaceutical composition comprises 2E12 to 6E12 vector genomes. In some cases, a kit comprises the suspension pharmaceutical composition and a solution for diluting the pharmaceutical composition. In some cases, the pharmaceutical

composition comprises not more than 1 mL. In some cases, the pharmaceutical composition comprises not more than 0.5-1.0 mL. In some cases, the pharmaceutical composition comprises less than or equal to 0.5 mL. In some cases, the solution in the kit comprises a buffer, salt, alcohol, a surfactant, or any combination thereof. In some cases, the kit comprises a syringe.

[0007] Disclosed is a method of treating an eye condition or disease comprising: agitating a refrigerated suspension, the suspension comprising: a rAAV2 variant comprising an amino acid sequence LGETTRP inserted between positions 587 and 588 of a capsid protein VP1, and a nucleic acid sequence encoding a polypeptide having at least 80% homology to aflibercept, a functional fragment, or variant thereof; and administering a volume of the refrigerated suspension to an eye of a human subject via intravitreal injection. In some cases, the subject is characterized as having been pre-treated with aflibercept. In some cases, the subject is responsive to aflibercept. In some cases, the refrigerated suspension comprises no more than 1 mL of the solution. In some cases, the refrigerated suspension comprises no more than 0.5 mL. In some cases, the volume administered to the subject is not more than 50 μL. In some cases, the volume administered to the subject is not more than 100 μL. In some cases, the volume comprises a unit dose of between 1E12 to 1E13 vector genomes. In some cases, the volume comprises a unit dose of between 2E12 to 6E12 vector genomes. In some cases, the administering step occurs not more than once in at least 2 years. In some cases, the administering step is a one-time injection. In some cases, the method further comprises assaying the subject for responsiveness to aflibercept before administering the composition. In some cases, the suspension comprises a pharmaceutically acceptable excipient. In some cases, the excipient comprises a surfactant or a stabilizer. In some cases, the surfactant is selected from polysorbates, sodium dodecyl sulfate, sodium lauryl sulfate, lauryl dimethyl amine oxide, polyethoxylated alcohols, polyoxyethylene sorbitan, octoxynol, Brij, pluronic, and polyoxyl castor oil. In some cases, the pharmaceutically acceptable excipient comprises phenol, mannitol, sorbitol, or sodium chloride. In some cases, the eye condition or disease is neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion, diabetic macular edema (DME), or diabetic retinopathy associated with DME. In some cases, the eye condition or disease is choroidal neovascularization or wet AMD. In some cases, the method further comprises warming the suspension to room temperature before administration.

INCORPORATION BY REFERENCE

[0008] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a unit dose of a pharmaceutical composition in the manufacture of a medicament for treating an eye condition or disease, wherein the medicament is to be administered by intravitreal injection to an eye of a primate subject in need thereof, and wherein the pharmaceutical composition comprises:

    (a) a rAAV2 variant comprising an amino acid sequence LGETTRP inserted between positions 587 and 588 of capsid protein VP1, and a nucleic acid sequence encoding a polypeptide comprising a sequence having at least 95% homology to aflibercept, and

    (b) a pharmaceutically acceptable excipient.

2. The use of claim 1, wherein the eye condition or disease is neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion, diabetic macular edema (DME), or diabetic retinopathy associated with DME.
3. The use of claim 1, wherein the eye condition or disease is choroidal neovascularization or wet AMD.
4. The use of any one of claims 1-3, wherein the polypeptide encoded by the nucleic acid comprises a sequence having 100% homology to alibercept.
5. The use of any one of claims 1-4, wherein the unit dose is between 1E12 to 1E13 vector genomes.
6. The use of any one of claims 1-4, wherein the unit dose is between 2E12 to 6E12 vector genomes.
7. The use of any one of claims 1-6, wherein the unit dose is in a volume that is not more than 100 μL.
8. The use of claim 7, wherein the unit dose is in a volume that is not more than 50 μL.
9. The use of any one of claims 1-8, wherein the subject is a human.
10. The use of any one of claims 1-9, wherein the subject is responsive to aflibercept.
11. The use of any one of claims 1-10, wherein the subject has been pre-treated with aflibercept.
12. The use of any one of claims 1-11, wherein the intravitreal injection occurs not more than once in at least 2 years.
13. The use of claim 12, wherein the intravitreal injection occurs not more than once in at least 5 years.
14. The use of any one of claims 1-11, wherein the intravitreal injection is a one-time administration.

15. The use of any one of claims 1-14, wherein the pharmaceutical composition is a suspension.
16. The use of claim 15, further comprising agitating the suspension to ensure even distribution of the suspension prior to the injection.
17. The use of any one of claims 1-16, further comprising warming the pharmaceutical composition to room temperature prior to the injection.