COMPOSITIONS COMPRISING 15-HEPE FOR TREATING OR PREVENTING HEMATOLOGIC DISORDERS, AND/OR RELATED DISEASES

TECHNICAL FIELD

[0001] The present application relates generally to compositions comprising 15-HEPE, and to methods of using the same.

SEQUENCE LISTING

[0002] This disclosure includes a sequence listing, which was submitted in ASCII format via EFS-Web, and is hereby incorporated by reference in its entirety. The ASCII copy, created on April 1, 2020, is named Sequence Listing 124318-8014.US00_ST25.txt and is 3 kilobytes in size.

BACKGROUND

[0003] Hematologic disorders include red blood cell disorders and thrombophilia. Red blood cell disorders are a class of conditions that affect the production, life-span, and shape of red blood cells (RBCs) and its oxygen transport molecule, hemoglobin. These conditions inhibit the transport of oxygen from the lungs to the rest of the body. Thrombophilia is a class of disorders that increase a subject's risk of developing blood clots in veins and arteries. These clots can break loose from the blood vessel and travel through the blood stream to an organ thereby preventing blood flow to that organ resulting in ischemia. These conditions lead to an increased risk of stroke and/or pulmonary embolism.

SUMMARY

[0004] The application relates to compositions comprising 15-hydroxyeicosapentaenoic acid (15-HEPE) and to methods of using such compositions in the treatment of a variety of diseases and disorders.

[0005] ~~In some aspects, t~~The present disclosure provides methods of treating and/or preventing a hematologic disorder in a subject in need thereof, the method comprising administering to the subject 15-HEPE or a composition comprising 15-HEPE.

[0005a] In one aspect, the present disclosure provides use of 15-hydroxyeicosapentaenoic acid (15-HEPE) in free acid form, esterified form, conjugate form, or salt form in the manufacture of a medicament for treating and/or preventing a hematologic disorder, a hemoglobin disorder, a red blood cell disorder, and/or hemolytic anemia in a subject in need thereof, wherein the medicament is to be administered to the subject to provide up to 8 g of the 15-HEPE.

[0006] ~~In some aspects, t~~The present disclosure also provides methods of treating and/or preventing a hematologic disorder in a subject in need thereof, the method comprising administering to the subject up to about 8g of a composition comprising 15-HEPE, wherein the 15-HEPE represents at least about 90% by weight, of all fatty acids in the composition.

[0007] ~~In yet another aspect, t~~The present disclosure also provides methods of treating and/or preventing a hematologic disorder in a subject in need thereof, the method comprising administering to the subject up to about 8g of a composition comprising 15-HEPE, wherein the 15-HEPE represents at least about 90% by weight, of all fatty acids in the composition, and the subject exhibits one or more of: (a) an increase in red blood cell count; (b) a decrease in red cell distribution width; and/or (c) a decrease in reticulocyte count.

[0008] In various ~~embodiment~~examples, the hematologic disorder is selected from the group consisting of inherited hemolytic anemia, acquired hemolytic anemia, Fanconi anemia, iron deficiency anemia, folate deficiency, B12 deficiency, and myelodysplastic syndrome.

[0009] ~~In some aspects, t~~The present disclosure also provides methods of treating and/or preventing a hemoglobin disorder in a subject in need thereof, the method comprising administering to the subject 15-HEPE or a composition comprising 15-HEPE.

[0010] ~~In other aspects, t~~The present disclosure also provides methods of treating and/or preventing a red blood cell disorder in a subject in need thereof, the method comprising administering to the subject 15-HEPE or a composition comprising 15-HEPE.

[0011] ~~In another aspect, t~~The present disclosure also provides methods of treating and/or preventing a hemoglobin disorder and/or a red blood cell disorder in a subject in need thereof, the method comprising administering to the subject up to about 8g of a composition comprising 15-HEPE, wherein the 15-HEPE represents at least about 90% by weight, of all fatty acids in the composition.

[0012] ~~In yet another aspect, t~~The present disclosure also provides methods of treating and/or preventing a hemoglobin disorder and/or a red blood cell disorder in a subject in need thereof, the method comprising administering to the subject up to about 8g of

a composition comprising 15-HEPE, wherein the 15-HEPE represents at least about 90% by weight, of all fatty acids in the composition, and the subject exhibits one or more of: (a) an increase in red blood cell count; (b) a decrease in red cell distribution width; and/or (c) a decrease in reticulocyte count.

[0013] In various ~~embodiment~~examples, the hematologic disorder, the hemoglobin disorder, and/or the red blood cell disorder are selected from the group consisting of inherited hemolytic anemia, acquired hemolytic anemia, Fanconi anemia, iron deficiency anemia, folate deficiency, B12 deficiency, and myelodysplastic syndrome.

[0014] ~~In yet another aspect, T~~the present disclosure also provides methods of treating and/or preventing hemolytic anemia in a subject in need thereof, the method comprising administering to the subject up to about 8g of a composition comprising 15-HEPE, wherein the 15-HEPE represents at least about 90% by weight, of all fatty acids in the composition.

[0015] In some ~~embodiment~~examples, the hemolytic anemia is inherited hemolytic anemia or acquired hemolytic anemia. In another ~~embodiment~~example, the acquired hemolytic anemia is acquired as secondary to infection, from a medication, from a hematological malignancy, from autoimmune disease, from hypersplenism, following placement of a mechanical heart valve, a blood transfusion, or a combination thereof. In yet another ~~embodiment~~example, the sickle cell disease and sickle cell anemia are associated with sickle cell crisis, a vaso-occlusive crisis, a splenic sequestration, or a combination thereof.

[0016] In some ~~embodiment~~examples, the subject exhibits an increase in red blood cell count, a decrease in red blood cell distribution width, and a decrease in reticulocyte count. In some aspects, the present disclosure provides methods of treating and/or preventing thrombophilia disorders in a subject in need thereof, the method comprising administering to the subject 15-HEPE or a composition comprising 15-HEPE.

[0016a] In another aspect, the present disclosure provides use of 15-hydroxyeicosapentaenoic acid (15-HEPE) in free acid form, esterified form, conjugate form, or salt form in the manufacture of a medicament for treating and/or preventing a thrombophilia disorder, thrombophilia, a venous thromboembolism, an arterial

thrombosis, and/or an embolism in a subject in need thereof, wherein the medicament is to be administered to the subject to provide up to 8 g of the 15-HEPE.

[0017] ~~In other aspects, t~~The present disclosure also provides methods of treating and/or preventing thrombophilia in a subject in need thereof, the method comprising administering to the subject up to about 8g of a composition comprising 15-HEPE, wherein the 15-HEPE represents at least about 90% by weight, of all fatty acids in the composition.

[0018] ~~In another aspect, t~~The present disclosure also provides method of treating and/or preventing thrombophilia in a subject in need thereof, the method comprising

administering to the subject up to about 8g of a composition comprising 15-HEPE, wherein the 15-HEPE represents at least about 90% by weight, of all fatty acids in the composition, and the subject exhibits one or more of: (a) an increase in prothrombin time; (b) an increase in activated partial thromboplastin time; and/or (c) a decrease in fibrinogen concentration.

[0019] ~~In yet another aspect, t~~The present disclosure also provides methods of treating and/or preventing a venous thromboembolism in a subject in need thereof, the method comprising administering to the subject up to about 8g of a composition comprising 15-HEPE, wherein the 15-HEPE represents at least about 90% by weight, of all fatty acids in the composition.

[0020] ~~In one aspect, t~~The present disclosure provides methods of treating and/or preventing an arterial thrombosis in a subject in need thereof, the method comprising administering to the subject up to about 8g of a composition comprising 15-HEPE, wherein the 15-HEPE represents at least about 90% by weight, of all fatty acids in the composition.

[0021] ~~In another aspect, t~~The present disclosure also provides methods of preventing an embolism in a subject in need thereof, the method comprising administering to the subject up to about 8g of a composition comprising 15-HEPE, wherein the 15-HEPE represents at least about 90% by weight, of all fatty acids in the composition.

[0022] In some ~~embodiment~~examples, the subject exhibits an increase in prothrombin time, an increase in activated partial thromboplastin time, and a decrease in fibrinogen concentration.

[0023] In another ~~embodiment~~example, the 15-HEPE is in a free acid form, esterified form, or salt form. In yet another ~~embodiment~~example, the esterified form is an alkyl ester form or a triglyceride form. In some ~~embodiment~~examples, the 15-HEPE comprises 15(S)-HEPE, 15(R)-HEPE, or combinations thereof.

[0024] In some ~~embodiment~~examples, the 15-HEPE is in the form of an ethyl ester (15-HEPE EE) or the 15-HEPE is in the form of an optically active ester (15(S)-HEPE EE).

[0025] In some ~~embodiment~~example**s**, the composition comprises about 10 mg to about 10,000 mg of 15-HEPE. In another ~~embodiment~~example, the composition comprises about 1 g to about 2 g of 15-HEPE. In another ~~embodiment~~example, the composition comprises about 2 g or more of 15-HEPE. In yet another ~~embodiment~~example, the composition is formulated

to provide about 5 mg 15-HEPE per kg of bodyweight (mg/kg), about 50 mg/kg, about 250 mg/kg, or about 500 mg/kg to the subject. In various ~~embodiment~~examples, the 15-HEPE represents at least about 90%, by weight, of all fatty acids present in the composition.

[0026] In some ~~embodiment~~examples, the 15-HEPE is orally administered. In various ~~embodiment~~examples, the composition is administered in 1 to 8 capsules per day.

BRIEF DESCRIPTION OF THE FIGURES

[0027] FIG. 1 is a schematic diagram of the study described in Example 1 and its duration.

[0028] FIG. 2 shows the body weight changes of the animals according to the study described in Example 1.

[0029] FIG. 3 shows the body weight on the day of sacrifice of the animals according to the study described in Example 1.

[0030] FIGs. 4A-4D show the kidney weight and kidney-to-body weight ratio of the animals on the day of sacrifice according to the study described in Example 1.

[0031] FIG. 5 shows the kidney hydroxyproline content for the animals according to the study described in Example 1.

[0032] FIGs. 6A-6G show the Sirius red staining of the animals according to the study described in Example 1.

[0033] FIG. 7 shows a plot depicting the Sirius red-positive area (%) of the animals according to the study described in Example 1.

[0034] FIGs. 8A-8D show the gene expression analyses for α-SMA, TIMP-1, TGF-β, and Collagen Type 1 of the animals according to the study described in Example 1, respectively.

[0035] FIG. 9 is a schematic diagram of the study described in Example 2 and its duration.

[0036] FIG. 10 shows the body weight changes of the animals according to the study described in Example 2.

[0037] FIG. 11 shows the body weight on the day of sacrifice of the animals according to the study described in Example 2.

CLAIMS

We claim:

1. Use of 15-hydroxyeicosapentaenoic acid (15-HEPE) in free acid form, esterified form, conjugate form, or salt form in the manufacture of a medicament for ~~A method of~~ treating and/or preventing a hematologic disorder, a hemoglobin disorder, a red blood cell disorder, and/or hemolytic anemia in a subject in need thereof, wherein the medicament is to be administered to the subject to provide up to 8 g of the 15-HEPE~~the method comprising administering to the subject 15-hydroxyeicosapentaenoic acid (15-HEPE) or a composition comprising 15-HEPE~~.

~~2. A method of treating and/or preventing a hemoglobin disorder in a subject in need thereof, the method comprising administering to the subject 15-HEPE or a composition comprising 15-HEPE.~~

~~3. A method of treating and/or preventing a red blood cell disorder in a subject in need thereof, the method comprising administering to the subject 15-HEPE or a composition comprising 15-HEPE.~~

~~4. A method of treating and/or preventing hemolytic anemia in a subject in need thereof, the method comprising administering to the subject up to about 8g of a composition comprising 15-HEPE.~~

~~5.~~2. The use~~method~~ of claim 1, wherein the hematologic disorder is selected from the group consisting of anemia, a blood cancer, and a coagulation defect.

~~6.~~3. The use~~method~~ of claim ~~5~~2, wherein the anemia is a nutritional anemia, a non-nutritional anemia, or a combination thereof.

~~7.~~4. The use~~method~~ of claim ~~5~~2, wherein the blood cancer is selected from the group consisting of lymphoma, leukemia, and myeloma.

~~8.~~5. The use~~method~~ of claim ~~5~~2, wherein the coagulation defect is selected from the group consisting of thrombophilia, hemophilia, Von Willebrand disease, and thrombocytopenia.

~~9.~~6. The use~~method~~ of any one of the preceding claims, wherein the subject has an increase in red blood cell count, a decrease in red blood cell distribution width, and/or a decrease in reticulocyte count compared to a control subject not receiving ~~the 15-HEPE or~~ the ~~composition~~ medicament.

~~10.~~7. The use~~method~~ of any one of the preceding claims, wherein the subject has an increase in red blood cell count of at least 10%, at least 15%, at least 20%, at least 25%, or at least 30% compared to a control subject not receiving ~~the 15-HEPE or~~ the ~~composition~~medicament.

~~11.~~8. The use~~method~~ of any one of the preceding claims, wherein the subject has a decrease in red blood cell distribution width of from ~~about~~ 15% to ~~about~~ 20%, from ~~about~~ 20% to ~~about~~ 25%, from ~~about~~ 25% to ~~about~~ 30%, from ~~about~~ 30% to ~~about~~ 35%, or from ~~about~~ 35% to ~~about~~ 40% compared to a control subject not receiving ~~the 15-HEPE or~~ the ~~composition~~medicament.

~~12.~~9. The use~~method~~ of any one of claims ~~9~~6 to ~~11~~8, wherein the control subject has a red blood cell distribution width greater than 15%.

~~13.~~10. The use~~method~~ of any one of the preceding claims, wherein the subject has a decrease in reticulocyte count of at least ~~about~~ 5%, at least ~~about~~ 10%, at least ~~about~~ 15%, or at least ~~about~~ 20% compared to a control subject not receiving ~~the 15-HEPE or~~ the ~~composition~~medicament.

~~14.~~11. The use~~method~~ of any one of claims ~~9~~6 to ~~13~~10, where the control subject has a reticulocyte count greater than 5% of the total number of red blood cells.

~~15.~~12. The use~~method~~ of any one of the preceding claims ~~2 to 14~~, wherein the hemoglobin disorder and/or the red blood cell disorder is selected from the group consisting of inherited hemolytic anemia, acquired hemolytic anemia, Fanconi anemia, iron deficiency anemia, folate deficiency, B12 deficiency, and myelodysplastic syndrome.

~~16.~~13. The use~~method~~ of claim ~~15~~12, wherein the inherited hemolytic anemia is selected from the group consisting of sickle cell disease, sickle cell anemia, β-thalassemia, and hereditary spherocytosis.

~~17.~~14. The use~~method~~ of claim ~~15~~12, wherein the acquired hemolytic anemia is acquired from a disorder or condition selected from the group consisting of a condition secondary to a primary infection, a medication, a hematological malignancy, an autoimmune disease, hypersplenism, positioning of a mechanical heart valve, and a blood transfusion.

~~18.~~15. The use~~method~~ of claim ~~16~~13, wherein the sickle cell disease and sickle cell anemia are associated with sickle cell crisis, a vaso-occlusive crisis, and/or splenic sequestration.

~~19.~~16. Use of 15-hydroxyeicosapentaenoic acid (15-HEPE) in free acid form, esterified form, conjugate form, or salt form in the manufacture of a medicament for ~~A method of~~ treating and/or preventing a thrombophilia disorder, thrombophilia, a venous thromboembolism, an arterial thrombosis, and/or an embolism in a subject in need thereof, wherein the medicament is to be administered to the subject to provide up to 8 g of the 15-HEPE~~the method comprising administering to the subject 15-HEPE or a composition comprising 15-HEPE~~.

~~20. A method of treating and/or preventing thrombophilia in a subject in need thereof, the method comprising administering to the subject 15-HEPE or up to about 8g of a composition comprising 15-HEPE.~~

~~21. A method of treating and/or preventing a venous thromboembolism in a subject in need thereof, the method comprising administering to the subject 15-HEPE or up to about 8g of a composition comprising 15-HEPE.~~

~~22. A method of treating and/or preventing an arterial thrombosis in a subject in need thereof, the method comprising administering to the subject 15-HEPE or up to about 8g of a composition comprising 15-HEPE.~~

~~23. A method of preventing an embolism in a subject in need thereof, the method comprising administering to the subject 15-HEPE or up to about 8g of a composition comprising 15-HEPE.~~

~~24.~~17. The use~~method~~ of ~~any one claims 19 to 23~~claim 16, wherein the subject has an increase in prothrombin time, an increase in activated partial thromboplastin

time, and/or a decrease in fibrinogen concentration compared to a control subject not receiving the ~~composition~~medicament.

~~25. The method as in any one of the preceding claims, wherein the 15-HEPE is in free acid form, esterified form, conjugate form, or salt form.~~

~~26.~~18. The use~~method~~ of any one of the preceding claims, wherein the 15-HEPE represents at least ~~about~~ 90%, by weight, of all fatty acids in the ~~composition~~medicament.

~~27.~~19. The use~~method~~ of any one of the preceding claims, wherein the ~~composition~~medicament comprises up to ~~about~~ 2 g of the 15-HEPE.

~~28.~~20. The use~~method~~ of any one of the preceding claims, wherein the ~~composition~~medicament is to be administered in 1 to 8 capsules per day.

~~29. The method of any one of the preceding claims, wherein the composition comprises at least 2 g of 15-HEPE.~~

~~30. The method of any one of the preceding claims, wherein the composition is formulated to provide about 5 mg of 15-HEPE per kg of bodyweight (mg/kg), about 50 mg/kg, about 250 mg/kg, or about 500 mg/kg to the subject.~~

~~31.~~21. The use~~method~~ of any one of the preceding claims, wherein ~~the 15-HEPE or~~ the ~~composition comprising 15-HEPE is orally administered~~ medicament is formulated for oral administration.

~~32. The method of any one of the preceding claims, wherein the 15-HEPE is in free acid form, esterified form, conjugate form, or salt form.~~

~~33.~~22. The use~~method~~ as in any one of the preceding claims, wherein the esterified form of 15-HEPE is a methyl ester, an ethyl ester, or a combination thereof.