In one embodiment, there is provided a combination for use in increasing the bioavailability of subcutaneously administered immune globulin (IG) for the treatment of an IG-treatable disease or condition in a subject, comprising:

a first composition comprising IG formulated for subcutaneous single dosage administration of 0.5 grams (g) to 70 g, wherein:

the concentration of IG is 5 to 15% w/v

the IG is formulated in a volume of liquid that is 50 mL to 700 mL; and

a second composition, comprising a soluble hyaluronidase, formulated for direct subcutaneous single dosage administration in an amount that is at a ratio of 10-500 Units (U) hyaluronidase per gram (g) of the IG, wherein:

the soluble hyaluronidase is formulated in a volume of liquid that is 5 to 30 mL;

the hyaluronidase is formulated separately from the IG for administration prior to administration of the IG and at the same site as the IG;

the IG and hyaluronidase are formulated for administration every 3-4 weeks or monthly; and

the amount of hyaluronidase effects increased bioavailability of the IG when administered in combination with the IG to at least 90% of the bioavailability of the same single dosage of IG administered via intravenous administration for treatment of the same IG-treatable disease or condition.

In one embodiment, there is provided the use of a combination for formulation of a medicament for increasing the bioavailability of subcutaneously administered immune globulin (IG) to at least 90% of the bioavailability of the same single dosage of IG administered via intravenous administration for treating an IG-treatable disease or condition in a subject, wherein the combination comprises:

a first composition comprising IG formulated for subcutaneous single dosage administration of 0.5 grams (g) to 70 g every 3-4 weeks or monthly, wherein the concentration of IG is 5 to 15% w/v; and

a second composition comprising a soluble hyaluronidase formulated for subcutaneous single dosage administration every 3-4 weeks or monthly prior to administration of, and at the same site as, the IG in a volume that is 5 to 30 mL and in an amount that is a ratio of 10-500 Units (U) hyaluronidase per gram (g) of the IG; wherein:

the soluble hyaluronidase is formulated separately from the IG for administration prior to administration of the IG and at the same site as the IG; and

the hyaluronidase effects increased bioavailability of the IG when administered in combination with the IG to at least 90% of the bioavailability of the same single dosage of IG administered via intravenous administration for treatment of the same IG-treatable disease or condition.

Claims:

1. A combination for use in increasing the bioavailability of subcutaneously administered immune globulin (IG) for the treatment of an IG-treatable disease or condition in a subject, comprising:

a first composition comprising IG formulated for subcutaneous single dosage administration of 0.5 grams (g) to 70 g, wherein:

the concentration of IG is 5 to 15% w/v

the IG is formulated in a volume of liquid that is 50 mL to 700 mL; and

a second composition, comprising a soluble hyaluronidase, formulated for direct subcutaneous single dosage administration in an amount that is at a ratio of 10-500 Units (U) hyaluronidase per gram (g) of the IG, wherein:

the soluble hyaluronidase is formulated in a volume of liquid that is 5 to 30 mL;

the hyaluronidase is formulated separately from the IG for administration prior to administration of the IG and at the same site as the IG; and

the amount of hyaluronidase effects increased bioavailability of the IG when administered in combination with the IG to at least 90% of the bioavailability of the same single dosage of IG administered via intravenous administration for treatment of the same IG-treatable disease or condition.

2. Use of a combination for formulation of a medicament for increasing the bioavailability of subcutaneously administered immune globulin (IG) to at least 90% of the bioavailability of the same single dosage of IG administered via intravenous administration for treating an IG-treatable disease or condition in a subject, wherein the combination comprises:

a first composition comprising IG formulated for subcutaneous single dosage administration of 0.5 grams (g) to 70 g, wherein the concentration of IG is 5 to 15% w/v; and

a second composition comprising a soluble hyaluronidase formulated for subcutaneous single dosage administration prior to administration of, and at the same site

as, the IG in a volume that is 5 to 30 mL and in an amount that is a ratio of 10-500 Units (U) hyaluronidase per gram (g) of the IG; wherein:

the soluble hyaluronidase is formulated separately from the IG for administration prior to administration of the IG and at the same site as the IG; and

the hyaluronidase effects increased bioavailability of the IG when administered in combination with the IG to at least 90% of the bioavailability of the same single dosage of IG administered via intravenous administration for treatment of the same IG-treatable disease or condition.

3. The composition or use of claim 1 or claim 2, wherein the IG in the composition is between 20 to 30 grams (g), 21 g to 42 g, 27 g to 61 g or 25.5 g to 61.2 g of IG.

4. The composition or use of any of claims 1-3, wherein the amount of hyaluronidase in the formulation is between 1000 Units to 10,000 Units or 5000 Units to 7500 Units.

5. The composition or use of any of claims 1-4, wherein the soluble hyaluronidase is a PH20, or a PH20 lacking all or a portion of the GPI anchor attachment signal sequence, such that upon expression, the hyaluronidase is soluble.

6. The composition or use of claim 5, wherein the PH20 is selected from an ovine PH20, bovine PH20 or human PH20, wherein the human PH20 lacks all or a portion of the GPI anchor attachment signal sequence, such that upon expression, the hyaluronidase is soluble.

7. The composition or use of claim 6, wherein the PH20 is a human PH20 selected from among polypeptides having the sequence of amino acids set forth in any of SEQ ID NOS:4-9, or a sequence of amino acids that exhibits at least 91% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOS:4-9.

8. The composition or use of any of claims 5-7, wherein the soluble hyaluronidase is designated rHuPH20.

9. The combination or use of any of claims 1-8, wherein the IG has a protein concentration that is 6 to 15% w/v, or 8 to 12% w/v of IG composition.

10. The combination or use of any of claims 1-9, wherein the soluble hyaluronidase is designated rHuPH20.

11. The combination of any of claims 1-10, wherein the IG-treatable disease or condition is selected from among immunodeficiency; acquired hypogammaglobulinemia secondary to hematological malignancies; Kawasaki's disease; chronic inflammatory demyelinating polyneuropathy (CIDP); Guillain-Barre Syndrome; Idiopathic thrombocytopenic purpura; inflammatory myopathies; Lambert-Eaton myasthenic syndrome; multifocal motor neuropathy; Myasthenia Gravis; Moersch-Woltmann syndrome; secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency); specific antibody deficiency; Acute disseminated encephalomyelitis; ANCA-positive systemic necrotizing vasculitis; Autoimmune haemolytic anaemia; Bullous pemphigoid; Cicatricial pemphigoid; Evans syndrome (including autoimmune haemolytic anaemia with immune thrombocytopenia); Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT); Haemophagocytic syndrome; High-risk allogeneic haemopoietic stem cell transplantation; IgM paraproteinaemic neuropathy; kidney transplantation; multiple sclerosis; Opsoclonus myoclonus ataxia; Pemphigus foliaceus; Pemphigus vulgaris; Post-transfusion purpura; Toxic epidermal necrolysis/Steven Johnson syndrome (TEN/SJS); Toxic shock syndrome; Alzheimer's Disease; Systemic lupus erythematosus; multiple myeloma; sepsis; B cell tumors; trauma; and a bacterial, viral or fungal infection.

12. The combination or use of claim 11, wherein the IG-treatable disease or condition is an immunodeficiency and the immunodeficiency is selected from among common variable immunodeficiency (CVID), congenital agammaglobulinemia, Wiskott-Aldrich syndrome, severe combined immunodeficiency (SCID), primary hypogammaglobulinemia, primary immunodeficiency diseases with antibody deficiency, X-linked agammaglobulinemia (XLA), hypogammaglobulinemia of infancy, and paraneoplastic cerebellar degeneration with no antibodies.

13. The combination or use of claim 11, wherein the IG-treatable disease or condition is acquired hypogammaglobulinemia secondary to hematological malignancies and the hematological malignancy is selected from among chronic lymphocytic leukemia (CLL), multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL).

14. The combination of claim 11, wherein the IG-treatable disease or condition is an inflammatory myopathy and the inflammatory myopathy is selected from among polymyositis, dermatomyositis and inclusion body myositis.

15. The combination of claim 11, wherein the IG-treatable disease or condition is a bacteria, viral or fungal condition and the bacterial, viral or fungal condition is selected from among *Haemophilus influenzae* type B, *Psuedomonas aeruginosa* types A and B, *Staphylococcus aureus*, Group B Streptococcus, *Streptococcus pneumoniae* types 1, 3, 4, 6, 7, 8, 9, 12, 14, 18, 19, and 23, Adenovirus types 2 and 5, Cytomegalovirus, Epstein Barr virus VCA, Hepatitis A virus, Hepatitis B virus, Herpes simplex virus-1, Herpes simplex virus-2, Influenza A, Measles, Parainfluenza types 1, 2 and 3, Polio, Varicella zoster virus, *Apergillus* and *Candida albicans*.

Claims

1. A combination for use in increasing the bioavailability of subcutaneously administered immune globulin (IG) for the treatment of an IG-treatable disease or condition in a subject, comprising:

a first composition comprising IG formulated for subcutaneous single dosage administration of 0.5 grams (g) to 70 g, wherein:

the concentration of IG is 5 to 15% w/v

the IG is formulated in a volume of liquid that is 50 mL to 700 mL; and

a second composition, comprising a soluble hyaluronidase, formulated for direct subcutaneous single dosage administration in an amount that is at a ratio of 10-500 Units (U) hyaluronidase per gram (g) of the IG, wherein:

the soluble hyaluronidase is formulated in a volume of liquid that is 5 to 30 mL;

the hyaluronidase is formulated separately from the IG for administration prior to administration of the IG and at the same site as the IG;

the IG and hyaluronidase are formulated for administration every 3-4 weeks or monthly; and

the amount of hyaluronidase effects increased bioavailability of the IG when administered in combination with the IG to at least 90% of the bioavailability of the same single dosage of IG administered via intravenous administration for treatment of the same IG-treatable disease or condition.

2. Use of a combination for formulation of a medicament for increasing the bioavailability of subcutaneously administered immune globulin (IG) to at least 90% of the bioavailability of the same single dosage of IG administered via intravenous administration for treating an IG-treatable disease or condition in a subject, wherein the combination comprises:

a first composition comprising IG formulated for subcutaneous single dosage administration of 0.5 grams (g) to 70 g every 3-4 weeks or monthly, wherein the concentration of IG is 5 to 15% w/v; and

a second composition comprising a soluble hyaluronidase formulated for subcutaneous single dosage administration every 3-4 weeks or monthly prior to administration of, and at the same site as, the IG in a volume that is 5 to 30 mL and in an amount that is a ratio of 10-500 Units (U) hyaluronidase per gram (g) of the IG; wherein:

the soluble hyaluronidase is formulated separately from the IG for administration prior to administration of the IG and at the same site as the IG; and

the hyaluronidase effects increased bioavailability of the IG when administered in combination with the IG to at least 90% of the bioavailability of the same single dosage of IG administered via intravenous administration for treatment of the same IG-treatable disease or condition.

3. The use of claim 2, wherein the IG in the composition is between 20 to 30 grams (g), 21 g to 42 g, 27 g to 61 g or 25.5 g to 61.2 g of IG.

4. The use of claim 2 or claim 3, wherein the amount of hyaluronidase in the formulation is between 1000 Units to 10,000 Units or 5000 Units to 7500 Units.

5. The use of any of claims 2-4, wherein the soluble hyaluronidase is a PH20, or a PH20 lacking all or a portion of the GPI anchor attachment signal sequence, such that upon expression, the hyaluronidase is soluble.

6. The use of claim 5, wherein the PH20 is selected from an ovine PH20, bovine PH20 or human PH20, wherein the human PH20 lacks all or a portion of the GPI anchor attachment signal sequence, such that upon expression, the hyaluronidase is soluble.

7. The use of claim 6, wherein the PH20 is a human PH20 selected from among polypeptides having the sequence of amino acids set forth in any of SEQ ID NOS:4-9, or a sequence of amino acids that exhibits at least 91% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOS:4-9.

8. The use of any of claims 5-7, wherein the soluble hyaluronidase is designated rHuPH20.

9. The use of any of claims 2-8, wherein the IG has a protein concentration that is 6 to 15% w/v, or 8 to 12% w/v of IG composition.

10. The use of any of claims 2-9, wherein the soluble hyaluronidase is designated rHuPH20.

11. The use of any of claims 2-10, wherein the IG-treatable disease or condition is selected from among immunodeficiency; acquired hypogammaglobulinemia secondary to hematological malignancies; Kawasaki's disease; chronic inflammatory demyelinating polyneuropathy (CIDP); Guillain-Barre Syndrome; Idiopathic thrombocytopenic purpura; inflammatory myopathies; Lambert-Eaton myasthenic syndrome; multifocal motor neuropathy; Myasthenia Gravis; Moersch-Woltmann syndrome; secondary hypogammaglobulinaemia (including iatrogenic immunodeficiency); specific antibody deficiency; Acute disseminated encephalomyelitis; ANCA-positive systemic necrotizing

vasculitis; Autoimmune haemolytic anaemia; Bullous pemphigoid; Cicatricial pemphigoid; Evans syndrome (including autoimmune haemolytic anaemia with immune thrombocytopenia); Foeto-maternal/neonatal alloimmune thrombocytopenia (FMAIT/NAIT); Haemophagocytic syndrome; High-risk allogeneic haemopoietic stem cell transplantation; IgM paraproteinaemic neuropathy; kidney transplantation; multiple sclerosis; Opsoclonus myoclonus ataxia; Pemphigus foliaceus; Pemphigus vulgaris; Post-transfusion purpura; Toxic epidermal necrolysis/Steven Johnson syndrome (TEN/SJS); Toxic shock syndrome; Alzheimer's Disease; Systemic lupus erythematosus; multiple myeloma; sepsis; B cell tumors; trauma; and a bacterial, viral or fungal infection.

12. The use of claim 11, wherein the IG-treatable disease or condition is an immunodeficiency and the immunodeficiency is selected from among common variable immunodeficiency (CVID), congenital agammaglobulinemia, Wiskott-Aldrich syndrome, severe combined immunodeficiency (SCID), primary hypogammaglobulinemia, primary immunodeficiency diseases with antibody deficiency, X-linked agammaglobulinemia (XLA), hypogammaglobulinemia of infancy, and paraneoplastic cerebellar degeneration with no antibodies.

13. The use of claim 11, wherein the IG-treatable disease or condition is acquired hypogammaglobulinemia secondary to hematological malignancies and the hematological malignancy is selected from among chronic lymphocytic leukemia (CLL), multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL).

14. The use of claim 11, wherein the IG-treatable disease or condition is an inflammatory myopathy and the inflammatory myopathy is selected from among polymyositis, dermatomyositis and inclusion body myositis.

15. The use of claim 11, wherein the IG-treatable disease or condition is a bacteria, viral or fungal condition and the bacterial, viral or fungal condition is selected from among *Haemophilus influenzae* type B, *Psuedomonas aeruginosa* types A and B, *Staphylococcus aureus*, Group B Streptococcus, *Streptococcus pneumoniae* types 1, 3, 4, 6, 7, 8, 9, 12, 14, 18, 19, and 23, Adenovirus types 2 and 5, Cytomegalovirus, Epstein Barr virus VCA, Hepatitis A virus, Hepatitis B virus, Herpes simplex virus-1, Herpes simplex virus-2, Influenza A, Measles, Parainfluenza types 1, 2 and 3, Polio, Varicella zoster virus, *Apergillus* and *Candida albicans.*

16. The combination of claim 1, wherein the IG in the composition is between 20 to 30 grams (g), 21 g to 42 g, 27 g to 61 g or 25.5 g to 61.2 g of IG.

17. The combination of claim 1 or claim 16, wherein the amount of hyaluronidase in the formulation is between 1000 Units to 10,000 Units or 5000 Units to 7500 Units.

18. The combination of any of claims 1, 16 and 17, wherein the soluble hyaluronidase is a PH20, or a PH20 lacking all or a portion of the GPI anchor attachment signal sequence, such that upon expression, the hyaluronidase is soluble.

19. The combination of claim 18, wherein the PH20 is selected from an ovine PH20, bovine PH20 or human PH20, wherein the human PH20 lacks all or a portion of the GPI anchor attachment signal sequence, such that upon expression, the hyaluronidase is soluble.

20. The combination of claim 19, wherein the PH20 is a human PH20 selected from among polypeptides having the sequence of amino acids set forth in any of SEQ ID NOS:4-9, or a sequence of amino acids that exhibits at least 91% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOS:4-9.

21. The combination of any of claims 18-20, wherein the soluble hyaluronidase is designated rHuPH20.

22. The combination of any of claims 1 and 16-21, wherein the IG has a protein concentration that is 6 to 15% w/v, or 8 to 12% w/v of IG composition.

23. The combination of any of claims 1 and 16-22, wherein the soluble hyaluronidase is designated rHuPH20.

COMBINATIONS AND METHODS FOR SUBCUTANEOUS ADMINISTRATION OF IMMUNE GLOBULIN AND HYALURONIDASE

ABSTRACT

Provided are combinations, compositions and kits containing a immune globulin (IG) composition and a soluble hyaluronidase composition formulated for subcutaneous administration. Such products can be used in methods of treating IG- treatable diseases or conditions. Also provided are methods for subcutaneous administration of immune globulin whereby the dosing regimen is substantially the same as for intravenous administration of the same dosage for treatment of the same IG-treatable disease or condition.

No suitable figure