METHODS, COMPOSITIONS AND DOSING REGIMENS FOR TREATING OR PREVENTING INTERFERON-GAMMA RELATED INDICATIONS

Related Applications

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 62/411,783, filed October 24, 2016 the contents of which are incorporated herein by reference in its entirety

Field of the Invention

[0002] The disclosure relates generally to methods and compositions for treating, preventing and/or delaying the onset or progression of, or alleviating a symptom associated with elevated levels interferon gamma (IFNγ, IFN-gamma) such as for example, hemophagocytic lymphohistiocytosis (HLH), hemoragic fever, CAR-T cell therapy, transplant failure, transplant rejection, Graft-versus-host disease (GvHD), and/or an inflammatory disorder associated with transplant rejection. The disclosure also relates to methods and compositions for prolonging survival of transplanted biological material.

Background of the Invention

[0003] Human interferon gamma (IFNγ, IFN-gamma) is a lymphokine produced by activated T-lymphocytes and natural killer cells. It manifests anti-proliferative and immunomodulatory activities and binds to IFNγ-R, a heterodimeric receptor on most primary cells of the immune system, and triggers a cascade of events leading to inflammation. The immunomodulatory activity of IFNγ is known to have beneficial effects in a number of clinical conditions. However, there are many clinical settings in which IFNγ-activity is known to have deleterious effects. For example, autoimmune diseases are associated with high levels of IFNγ in the blood and diseased tissue from autoimmune patients. IFNγ-activity has also been linked to such disease states as cachexia and septic shock.

[0004] IFNγ has been implicated in a number of disorders; and anti-IFNγ agents are being developed as therapeutic agents..

Summary

[0005] In various embodiments the disclosure provides multiple variable dose treatment regimen

for the treatment of diseases, disorder or conditions associated with elevated IFN-g levels.

[0005a] In one aspect, there is provided use of the formulation as described herein in the manufacture of a medicament for treating a condition in a human subject, wherein the condition is primary hemophagocytic lymphohistiocytosis (HLH), secondary HLH, systemic Juvenile Idiopathic Arthritis (sJIA), Macrophage Activation Syndrome (MAS), transplant rejection, solid organ transplant disorder, bone marrow acute graft rejection, graft vs. host disease, paraneoplastic cerebellar degeneration, hemorrhagic fever, sarcoidosis or adult onset Still's disease.

[0005b] In another aspect, there is provided use of the unit dose vial as described herein in the manufacture of a medicament for treating a condition in a human subject, wherein the condition is primary hemophagocytic lymphohistiocytosis (HLH), secondary HLH, systemic Juvenile Idiopathic Arthritis (sJIA), Macrophage Activation Syndrome (MAS), transplant rejection, solid organ transplant disorder, bone marrow acute graft rejection, graft vs. host disease, paraneoplastic cerebellar degeneration, hemorrhagic fever, sarcoidosis or adult onset Still's disease.

[0006] Disclosed is a method for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) in a human by intravenously administering to a subject a first dose and second dose of an antibody that binds interferon gamma (IFNγ). The subject is an adult subject or a pediatric subject. The first dose is 1.0 or 3.0 mg/kg of the subject's body weight and the second dose is 3.0, 6.0 or 10.0 mg/kg of the subject's body weight. Optionally, a third dose of 1.0 mg/kg of the subject's body weight is administered.

[0007] Disclosed is a method for the treatment of secondary hemophagocytic lymphohistiocytosis (HLH) in a human pediatric subject by intravenously administering to a subject a first dose and second dose of an antibody that binds interferon gamma (IFNγ). The first dose is 6.0 mg/kg of the subject's body weight and the second dose is 3.0 mg/kg of the subject's body weight. Optionally, a third dose of 6.0 mg/kg of the subject's body weight is administered.

[0008] Disclosed is a method for the treatment of secondary hemophagocytic lymphohistiocytosis (HLH) in a human adult subject by intravenously administering to a subject a first dose and second dose of an antibody that binds interferon gamma (IFNγ). The first dose is 3.0 mg/kg or 6.0 mg/kg of the subject's body weight and the second dose is no more than 10 mg/kg of the subject's body weight. For example, the second dose is 1.0, 3.0, 6.0 or 10.0 mg/kg. Optionally, a third dose of less than 10.0 mg/kg of the subject's body weight is administered. For example the third dose is 1.0, 3.0, or 6.0 mg/kg of the subject's body weight.

[0009] Disclosed is a method for the treatment of a condition in a human subject by intravenously administering to a subject a first dose and second dose of an antibody that binds interferon gamma (IFNγ). The subject is an adult subject or a pediatric subject. The condition is transplant rejection such as solid organ transplant disorder or bone marrow acute graft rejection. The condition is graft vs. host disease, paraneoplastic cerebellar degeneration, hemorrhagic fever, sarcoidosis, or adult onset Still's disease. Alternatively, the method is administered to a subject after receiving CART cell therapy. The first dose is between 1.0 to 10 mg/kg of the subject's body weight and the second dose is between 1.0 to 10 mg/kg of the subject's body weight e subject's body weight. For example, the second dose is 1.0, 3.0, 6.0 or 10.0 mg/kg. Preferably, the second dose is higher or lower than the first dose. Optionally, a third dose of between 1.0 to 10 mg/kg of the subject's body weight is administered. For example, the first, second, or third dose is 1.0, 3.0, 6.0 or 10.0 mg/kg of the subject's body

weight.

[0010] The antibody that binds interferon gamma (IFNγ) includes: a variable heavy chain complementarity determining region 1 (VH CDR1) comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); and a variable heavy chain complementarity determining region 3 (VH CDR3) comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a variable light chain complementarity determining region 2 (VL CDR2) region comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable light chain complementarity determining region 3 (VL CDR3) region comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6). For example the antibody comprises the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47, and the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.

[0011] The dose of the antibody is administered within 1, hr, 6 hrs or 12 hrs.

[0012] The second dose is administered for a first treatment period of every three days after the first dose. Additionally, the second dose is administered for a second treatment period after completion of the first treatment period. The the second treatment period is for example twice weekly.

[0013] The antibody dose is administered as a single injection.

[0014] The antibody is administered as a monotherapy or a co-therapy.

[0015] Optionally, the methods of the disclosure further includes administering dexamethasone immediately prior to the dosing of the antibody. the dexamethasone is administered at a dose of at least 10 mg/m2 or at least 5 mg/m2.

[0016] The subject has not previously been treated for HLH.

[0017] In various embodiments, the method further includes comprises administering at least a second agent to the subject. The second agent is a therapeutic agent, an anti-inflammatory agent, and/or an immunosuppressive agent.

[0018] Also included in the disclosure is an injectable pharmaceutical formulation comprising per mL: 5 mg or 25 mg of a fully human anti-interferon gamma (IFNγ) monoclonal antibody; 1.55 mg L-histidine, 3.14 mg L-histidine monohydrochloride, monohydrate, 7.31 mg sodium chloride (NaCl), and 0.05 mg Polysorbate 80, where the pH is between 5.8 and 6.2.

[0018a] In another aspect, there is provided an injectable pharmaceutical formulation comprising per mL: a) 5 mg of a fully human anti-interferon gamma (IFNγ) monoclonal antibody; and b) about 1.55 mg L-histidine, about 3.14 mg L-histidine monohydrochloride, monohydrate, and about 0.05 mg Polysorbate 80, where the pH is between 5.8 and 6.2.

[0019] Disclosed is a unit dose vial containing 20 ml of a fully human anti-interferon gamma (IFNγ) monoclonal antibody solution suitable for injection where the concentration of antibody is 5 mg/ml or 25 mg/ml and the pH of the solution is between 5.8 and 6.2. The antibody is solubilized in the solution such that the solution is clear, colorless, and without precipitate.

[0020] Disclosed is a unit dose vial containing 10 ml or 20 ml of a fully human anti-interferon gamma (IFNγ) monoclonal antibody solution suitable for injection where the concentration of antibody is at 25 mg/ml, and he pH of the solution is between 5.8 and 6.2. The antibody is solubilized in the solution such that the solution is clear, colorless, and without precipitate.

[0021] Disclosed is a unit dose vial containing 2 ml or 10 ml of a fully human anti-interferon gamma (IFNγ) monoclonal antibody solution suitable for injection where the concentration of antibody is 5 mg/ml and the pH of the solution is between 5.8 and 6.2. The antibody is solubilized in the solution such that the solution is clear, colorless, and without precipitate.

[0021a] In another aspect, there is provided a unit dose vial comprising, 2 ml or 10 ml of a fully human anti-interferon gamma (IFNγ) monoclonal antibody solution suitable for injection wherein the concentration of antibody is at 5 mg/ml, wherein the pH of the solution is between 5.8 and 6.2.

[0022] The antibody that binds interferon gamma (IFNγ) includes: a variable heavy chain complementarity determining region 1 (VH CDR1) comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); and a variable heavy chain complementarity determining region 3 (VH CDR3) comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a variable light chain complementarity determining region 2 (VL CDR2) region comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable light chain complementarity determining region 3 (VL CDR3) region comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6). For example the antibody comprises the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47, and the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.

[0022a] Any of the above aspects or embodiments may be combined with any other aspect or embodiment.

[0022b]Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure

pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety. In cases of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples described herein are illustrative only and are not intended to be limiting.

[0023] Other features and advantages of the disclosure will be apparent from and encompassed by the following detailed description and claims.

Brief Description of the Drawings

[0024] Figure 1 is a graph depicting correlations between predose serum CXCL9 levels and total IFNγ levels at 24 h post infusion with the NI-0501 antibody in an ongoing phase 2 pilot study in primary HLH patients.

[0025] Figure 2 is a graph depicting correlations between serum CXCL9 levels and total IFNγ predose levels at 24 h post infusion with the NI-0501 antibody in an ongoing phase 2 pilot study in primary HLH patients.

[0026] Figures 3A and 3B are a series of graphs depicting correlations between serum CXCL9 levels and IFNγ levels in patients with Macrophage Activation Syndrome (MAS) secondary to systemic Juvenile Idiopathic Arthritis (sJIA) and in patients with active sJIA.

[0027] Figures 4A-1, 4A-2, 4B-1, 4B-2, 4C-1, 4C-2, 4D-1, and 4D-2 are a series of graphs depicting correlations between IFNγ and serum CXCL9 levels and clinical parameters in patients with active sJIA and MAS secondary to sJIA.

[0028] Figure 5 is a graph depicting that IFNγ was fully neutralized as shown by undetectable levels of IFNγ-inducible chemokines.

[0029] Figure 6 is a graph depicting improvement of HLH disease activity during NI-0501 treatment (2 weeks and end of treatment): percent of patients with Platelet count >100 $x10^9$/L, Neutrophil count >$1x10^9$/L, Fibrinogen >1.5 g/L and ferritin decrease of at least 25%.

[0030] Figures 7A and 7B are a series of graphs depicting the correlation between pre-dose CXCL9 and total IFNγ levels at 24h after NI-0501 infusion. The insert shown in Figure 7B, depicts an example of individual IFNγ and CXCL9 profile during NI-0501 treatment.

[0031] Figures 8A, 8B, 8C, and 8D are a series of graphs depicting serum levels of IFNγ and of CXCL9, CXCL10 and CXCL11 in individual patients from whom paired samples were

What is claimed is:

1. An injectable pharmaceutical formulation comprising per mL:
   a) 5 mg of a fully human anti-interferon gamma (IFNγ) monoclonal antibody; and
   b) about 1.55 mg L-histidine, about 3.14 mg L-histidine monohydrochloride, monohydrate, and about 0.05 mg Polysorbate 80, where the pH is between 5.8 and 6.2.

2. The formulation of claim 1, wherein the antibody comprises a variable heavy chain complementarity determining region 1 (VH CDR1) comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); and a variable heavy chain complementarity determining region 3 (VH CDR3) comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a variable light chain complementarity determining region 2 (VL CDR2) region comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable light chain complementarity determining region 3 (VL CDR3) region comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6).

3. The formulation of claim 2, wherein the antibody comprises the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47, and the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.

4. A unit dose vial comprising, 2 ml or 10 ml of a fully human anti-interferon gamma (IFNγ) monoclonal antibody solution suitable for injection wherein the concentration of antibody is at 5 mg/ml, wherein the pH of the solution is between 5.8 and 6.2.

5. The unit dose vial of claim 4, wherein the antibody is solubilized in the solution such that the solution is clear, colorless, and without precipitate.

6. The unit dose vial of claim 4, wherein the antibody comprises a variable heavy chain complementarity determining region 1 (VH CDR1) comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); and

a variable heavy chain complementarity determining region 3 (VH CDR3) comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a variable light chain complementarity determining region 2 (VL CDR2) region comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable light chain complementarity determining region 3 (VL CDR3) region comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6).

7. The unit dose vial of claim 6, wherein the antibody comprises the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47, and the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.

8. Use of the formulation of claim 1 in the manufacture of a medicament for treating a condition in a human subject, wherein the condition is primary hemophagocytic lymphohistiocytosis (HLH), secondary HLH, systemic Juvenile Idiopathic Arthritis (sJIA), Macrophage Activation Syndrome (MAS), transplant rejection, solid organ transplant disorder, bone marrow acute graft rejection, graft vs. host disease, paraneoplastic cerebellar degeneration, hemorrhagic fever, sarcoidosis or adult onset Still's disease.

9. The use of claim 8, wherein the human subject is pediatric or adult.

10. Use of the unit dose vial of claim 4 in the manufacture of a medicament for treating a condition in a human subject, wherein the condition is primary hemophagocytic lymphohistiocytosis (HLH), secondary HLH, systemic Juvenile Idiopathic Arthritis (sJIA), Macrophage Activation Syndrome (MAS), transplant rejection, solid organ transplant disorder, bone marrow acute graft rejection, graft vs. host disease, paraneoplastic cerebellar degeneration, hemorrhagic fever, sarcoidosis or adult onset Still's disease.

11. The use of claim 10, wherein the human subject is pediatric or adult.

12. The injectable pharmaceutical formulation of claim 1, further comprising about 7.31mg sodium chloride (NaCl).