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 aspects the invention provides multiple variable dose treatment regimen

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

[0005a] In one aspect, the present invention provides the use of an antibody that binds interferon gamma (IFNγ) in the manufacture of a medicament for the treatment of Macrophage Activation Syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (HLH) in a subject, wherein the antibody is to be administered at

i) a first dose of 6.0 mg/kg of the subject's body weight, and

ii) a second dose of 3.0 mg/kg to 10 mg/kg of the subject's body weight, and

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).

[0006] In one aspect, the invention provides 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] In another aspect, the invention provides 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] In a further aspect, the invention provides 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] In yet another aspect, the invention provides 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