INEBILIZUMAB AND METHODS OF USING THE SAME FOR SUSTAINED B-CELL DEPLETION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 63/369,590, filed July 27, 2022, incorporated by reference herein in its entirety for all purposes.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (HOPA_045_01WO_SeqList_ST26.xml; Size: 10,611 bytes; and Date of Creation: September 19, 2022) is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[0003] The present disclosure is related to compositions comprising Inebilizumab and methods of using the same for sustained B-cell depletion.

BACKGROUND

[0004] Inebilizumab is an anti-CD19 monoclonal antibody approved in Japan and the USA for the treatment of neuromyelitis optica spectrum disorder (NMOSD). However, the relationship between B-cell, plasma cell, and immunoglobulin depletion after inebilizumab treatment, and reductions in NMOSD disease activity after inebilizumab treatment remains unclear and further elucidation of the relationship warrants analysis to elucidate optimized methods of treatment for subjects with NMOSD.

BRIEF SUMMARY

[0005] In one aspect, the present disclosure provides for a use of an anti-CD19 antibody in the manufacture of a medicament for treating or preventing Neuromyelitis Optica Spectrum Disorder (NMOSD) in a subject, wherein the subject has a level of B-cells of less than about 4 cells/μL of blood, and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5. The description provides methods of treating or preventing Neuromyelitis Optica Spectrum Disorder (NMOSD), the method comprising administering Inebilizumab to a subject in need that has a level of B-cells of less than about 4 cells/μL of blood, thereby treating the NMOSD.

In examples, the subject in need's Fc Gamma Receptor IIIa (*FCGR3A)* gene comprises a rs396991 polymorphism. In examples, the subject in need comprises a V allele as determined by a V/F or V/V genotype.

[0006] In another aspect, the present disclosure provides for a use of an anti-CD19 antibody in the manufacture of a medicament for treating of an autoimmune disease, wherein the presence of a rs396991 polymorphism in a *FCGR3A* gene of a subject is to be determined, and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5. Provided are methods of treatment, the methods comprising assaying a blood sample from a subject in need to determine presence of a rs396991 polymorphism of the *FCGR3A*

gene and administering Inebilizumab to the subject in need if the determination is positive for the rs396991 polymorphism. In examples, the subject in need has an autoimmune disease. In examples, the autoimmune disease is selected from the group consisting of: Neuromyelitis Optica Spectrum Disorder (NMOSD), Myasthenia Gravis (MG), and IgG4RD. In examples, the autoimmune disease is NMOSD. In examples, the autoimmune disease is MG. In examples, the autoimmune disease is IgG4RD. In examples, the subject in need has at least two autoimmune diseases. In examples, the at least two autoimmune diseases are selected from the group consisting of: Neuromyelitis Optica Spectrum Disorder (NMOSD), Myasthenia Gravis (MG), and IgG4RD.

[0007] Provided are methods of treating Neuromyelitis Optica Spectrum Disorder (NMOSD), the method comprising administering Inebilizumab to a subject in need that comprises a rs396991 polymorphism of the *FCGR3A* gene, wherein the administering is more effective in reducing B-cell or plasma-cell levels in the subject in need that comprises the rs396991 polymorphism of the *FCGR3A* gene as compared to an otherwise comparable subject lacking the rs396991polymorphism.

[0008] In examples, levels of B-cells or plasma-cells are determined at least 1, 2, 4, 8, 12, 16, 22, 28, and/or 32 weeks after the administering. In examples, the administering is effective in reducing a criteria selected from the group consisting of: Annualized Attack Rate (AAR), incidence of disability as assessed by Expanded Disability Status Scale (EDSS) score, incidence of hospitalization, magnetic resonance imaging (MRI) lesions, and combinations thereof. In examples, the administering is effective in reducing the AAR, wherein the reduction is at least about 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 97%, or up to about 100%. In examples, the administering is effective in reducing the MRI lesions, wherein the reduction is at least about 20%, 30%, 40%, 50%, 60%, 70%, 73%, 75%, 80%, 85%, 90%, 95%, 97%, or up to about 100%. In examples, the administering is repeated. In examples, the administering is repeated daily, monthly, or yearly. In examples, the administering is repeated monthly. In examples, the administering is repeated every 6 months. In examples, the administering is continued for at least about 1 year, 2 years, 3 years, 4 years, 5 years, or up to about the lifetime of the subject in need. In examples, the subject in need was previously administered Inebilizumab. In examples, administering is intravenous. In examples, the administering is by intravenous infusion. In examples, Inebilizumab is administered at a dose of about 300 mgs.

[0009] In another aspect, the present disclosure provides for a use of an anti-CD19 antibody in the manufacture of a medicament for treating or preventing an autoimmune disease, wherein 300 mg of the anti-CD19 antibody is to be administered to a subject that has a level of B-cells of less than about 4 cells/μL of blood, wherein the administering is repeated every 6 months, and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5. Provided are methods of treating or preventing an autoimmune disease, the method comprising administering 300 mg of Inebilizumab to a subject in need that has a level of B-cells of less than about 4 cells/μL of blood, wherein the administering is repeated every 6

months. In examples, the autoimmune disease is selected from the group consisting of: Neuromyelitis Optica Spectrum Disorder (NMOSD), Myasthenia Gravis (MG), and IgG4RD. In examples, the autoimmune disease is NMOSD. In examples, the autoimmune disease is MG. In examples, the autoimmune disease is IgG4RD.

[0010] In another aspect, the present disclosure provides for a use of an anti-CD19 antibody in the manufacture of a medicament for treating or preventing Neuromyelitis Optica Spectrum Disorder (NMOSD), wherein 300 mg of the anti-CD19 antibody is to be administered to a subject that has a level of B-cells of less than about 4 cells/μL of blood, wherein the administering is repeated every 6 months, and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5. Provided are methods of treating or preventing Neuromyelitis Optica Spectrum Disorder (NMOSD), the method comprising administering 300 mg of Inebilizumab to a subject in need that has a level of B-cells of less than about 4 cells/μL of blood, wherein the administering is repeated every 6 months.

[0011] In another aspect, the present disclosure provides for a use of an anti-CD19 antibody in the manufacture of a medicament for treating or preventing an autoimmune disease, wherein 300 mg of an anti-CD19 antibody is to be administered to a subject that has a level of B-cells of less than about 4 cells/μL of blood, wherein the administering is repeated every 6 months, wherein the autoimmune disease is selected from the group consisting of: Neuromyelitis Optica Spectrum Disorder (NMOSD), Myasthenia Gravis (MG), and IgG4RD, and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5. Provided are methods of treating or preventing an autoimmune disease, the method comprising administering 300 mg of Inebilizumab to a subject in need that has a level of B-cells of less than about 4 cells/μL of blood, wherein the administering is repeated every 6 months, and wherein the autoimmune disease is selected from the group consisting of: Neuromyelitis Optica Spectrum Disorder (NMOSD), Myasthenia Gravis (MG), and IgG4 related disease (IgG4RD). In examples, the administering is continued for at least about 2.5 years.

[0012] In another aspect, the present disclosure provides for a use of an anti-CD19 antibody in the manufacture of a medicament for treating neuromyelitis optica spectrum disorder in a subject, wherein the subject has no anti-aquaporin 4 immunoglobulin G antibodies (AQP4-IgG−) and has immunoglobulin G antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG+), and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5.

Provided are methods of treating neuromyelitis optica spectrum disorder, the methods comprising administering Inebilizumab to a subject in need, wherein the subject has no anti-aquaporin 4 immunoglobulin G antibodies (AQP4-IgG−) and has immunoglobulin G antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG+). In examples, about 300 mg of Inebilizumab is administered. In examples, the administration is continued for at least 6 months, 1 year, 2 years, or 3 years. In examples, the administration is continued indefinitely. In examples, the administration is continued for at least 2 years. In examples, the subject in need has increased serum autoreactivity to an autoantibody that is not related to NMOSD as compared to a healthy control subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1A is a graphic of a study design. **FIG. 1B** shows attack free probability of newly diagnosed subjects during RCP. **FIG. 1C** shows attack free probability of subjects with ≥ 2 prior NMOSD relapses.

[0014] FIG. 2A shows serum autoreactivity to at least one autoantigen in subjects with NMOSD in all subclasses, IgG subclass, IgM subclass, IgA subclass and IgE subclass. **FIG. 2B** shows subjects with NMOSD who were IFNGS (type 1 interferon-inducible gene signature)-positive at baseline. **FIG. 2C** shows the proportion of IFNGS-negative and IFNGS-positive subjects with NMOSD reactive to at least one anti-ribonucleoprotein (RNP) IgG. **FIG.**

CLAIMS

1. Use of an anti-CD19 antibody in the manufacture of a medicament for treating or preventing Neuromyelitis Optica Spectrum Disorder (NMOSD) in a subject, wherein the subject has a level of B-cells of less than about 4 cells/μL of blood, and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5.

2. The use of claim 1, wherein the subject has a Fc Gamma Receptor IIIa (*FCGR3A)* gene that comprises a rs396991 polymorphism.

3. The use of claim 2, wherein the subject comprises a V allele as determined by a V/F or V/V genotype at amino acid position 158 of the *FCGR3A* gene.

4. The use of any one of claims 1-3, wherein the antibody is inebilizumab.

5. Use of an anti-CD19 antibody in the manufacture of a medicament for treating of an autoimmune disease, wherein the presence of a rs396991 polymorphism in a *FCGR3A* gene of a subject is to be determined, and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5.

6. The use of claim 4, wherein the autoimmune disease is NMOSD.

7. The use of claim 4, wherein the autoimmune disease is Myasthenia Gravis (MG).

8. The use of claim 4, wherein the autoimmune disease is IgG4RD.

9. The use of claim 4, wherein the subject has at least two autoimmune diseases.

10. The use of any one of claims 1-9, wherein the antibody is inebilizumab.

11. The use of any one of claims 1-10, wherein the medicament is effective in reducing a criteria selected from the group consisting of: Annualized Attack Rate (AAR), incidence of disability as assessed by Expanded Disability Status Scale (EDSS) score, incidence of hospitalization, a number of lesions as detected by magnetic resonance imaging, and combinations thereof.

12. The use of any one of claims 1-11, wherein the antibody is to be administered at a dose of about 300 mg every 6 months.

13. Use of an anti-CD19 antibody in the manufacture of a medicament for treating or preventing an autoimmune disease, wherein 300 mg of the anti-CD19 antibody is to be administered to a subject that has a level of B-cells of less than about 4 cells/μL of blood, wherein the administering is repeated every 6 months, and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5.

14. The use of claim 13, wherein the autoimmune disease is NMOSD.

15. The use of claim 13, wherein the autoimmune disease is MG.

16. The use of claim 13, wherein the autoimmune disease is IgG4RD.

17. The use of any one of claims 13-16, wherein the antibody is inebilizumab.

18. Use of an anti-CD19 antibody in the manufacture of a medicament for treating or preventing Neuromyelitis Optica Spectrum Disorder (NMOSD), wherein 300 mg of the anti-CD19 antibody is to be administered to a subject that has a level of B-cells of less than about 4 cells/μL of blood, wherein the administering is repeated every 6 months, and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5.

19. Use of an anti-CD19 antibody in the manufacture of a medicament for treating or preventing an autoimmune disease, wherein 300 mg of an anti-CD19 antibody is to be administered to a subject that has a level of B-cells of less than about 4 cells/μL of blood, wherein the administering is repeated every 6 months, wherein the autoimmune disease is selected from the group consisting of: Neuromyelitis Optica Spectrum Disorder (NMOSD), Myasthenia Gravis (MG), and IgG4RD, and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5.

20. Use of an anti-CD19 antibody in the manufacture of a medicament for treating neuromyelitis optica spectrum disorder in a subject, wherein the subject has no anti-aquaporin 4 immunoglobulin G antibodies (AQP4-IgG−) and has immunoglobulin G antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG+), and wherein the anti-CD19 antibody comprises a variable heavy chain comprising SEQ ID NO: 1 and a variable light chain comprising SEQ ID NO: 5.

21. The use of claim 20, wherein about 300 mg of the anti-CD19 antibody is to be administered, wherein the anti-CD19 antibody is Inebilizumab.

22. The use of any one of claims 1-21, wherein the subject has increased serum autoreactivity to an autoantibody that is not related to NMOSD as compared to a healthy control subject.

23. The use of any one of claims 1-22, wherein the antibody is inebilizumab.