INEBILIZUMAB AND METHODS OF USING THE SAME IN THE TREATMENT OR PREVENTION OF IgG4-RELATED DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

[1] This application claims priority to U.S. Provisional Patent Application No. 63/232,131, filed August 11, 2021, and U.S. Provisional Patent Application No. 63/285,297, filed December 2, 2021, each of which is entirely incorporated herein by reference for all purposes.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[2] The contents of the electronic sequence listing (HOPA_035_01WO_SeqList_ST26.xml; Size: 10,635 bytes; and Date of Creation: August 3, 2022) is herein incorporated by reference in its entirety.

TECHNICAL FIELD

[3] The present disclosure is related to compositions and methods of treating or preventing IgG4 related disease comprising administering an anti-CD19 antibody to a subject in need.

BACKGROUND

[4] There are currently no medicinal products approved for the treatment of immunoglobulin G4-related disease (IgG4-RD), a rare disease. The majority of cases follow a relapsing course that can lead to permanent tissue damage with attendant morbidity and potential mortality. Glucocorticoids (GCs) are widely and effectively used for acute treatment of initial disease activity and of recurrent episodes (flares), but GCs do not prevent recurrence of active disease during their taper or after their discontinuation. Moreover, GCs are associated with substantial toxicity.

[5] Thus, there is a high unmet medical need for therapies that prevent disease recurrence and limit GC exposure.

SUMMARY

[6] Provided herein are methods of treating Immunoglobulin G4-related disease (IgG4-RD), comprising administering to a subject in need thereof an effective amount of Inebilizumab, wherein the administering is sufficient to reduce or eliminate an IgG4-RD flare, thereby treating the IgG4-RD. In one aspect, the present disclosure refers to a use of an effective amount of anti-CD19 antibody in the manufacture of a medicament for treating Immunoglobulin G4-related disease (IgG4-RD) in a subject in need thereof, 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, wherein 300 mg of the anti-CD19 antibody is to be administered intravenously, comprising a first dose of 300 mg, a second dose of 300 mg two weeks after the first dose, and subsequent doses of 300 mg every 6 months following the first initial dose; and wherein the effective amount is sufficient to reduce the IgG4-RD flare, as determined by: a. reduced incidence of the IgG4-RD flare; b. increased time to the IgG4-RD flare; or c. a. and b. In examples, the administering is sufficient to reduce the IgG4-RD flare, as determined by: (a) reduced incidence of the IgG4-RD flare; (b) increased time to the IgG4-RD flare; or (c) a. and b. In examples, the incidence of the IgG4-RD flare

flare, lymph node flare, lung flare, blood vessel flare, retroperitoneum flare, mediastinum flare, mesentery flare, pancreatic flare, bile duct flare, kidney flare, skin disease flare, and combinations thereof. In examples, from about 200-400 mg of the Inebilizumab is administered. In examples, from about 250-350 mg of the Inebilizumab is administered. In examples, about 300 mg of the Inebilizumab is administered. In examples, two weeks prior to administering the 300 mg Inebilizumab every 6 months, an initial 300 mg Inebilizumab dose is administered to the subject. In examples, the administering is intravenous. In examples, a method comprises: a second administering of the Inebilizumab, a third administering of the Inebilizumab, or both a second and third administering of the Inebilizumab. In examples, each of the administering, the second administering, or the third administering are separated by at least about 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 8 months, 10 months, or up to about 1 year.

[10] In examples, pachymeningitis flare may be present when the subject shows new or worsening symptoms or physical examination consistent with IgG4-RD pachymeningitis in combination with (a) a CSF detection consistent with IgG4-RD pachymeningitis or with (b) an imaging finding confirming new or worsening meningeal involvement.

[11] Provided are methods of treating Immunoglobulin G4-related disease (IgG4-RD), comprising administering to a subject in need thereof: (a) a pharmaceutical composition that comprises a corticosteroid in an amount sufficient to reduce an immune response in the subject; and (b) a pharmaceutical composition that comprises Inebilizumab in an amount sufficient to reduce a level of at least one of CD19 positive B cells, plasmablasts, plasma cells, or any combination thereof in the subject in need thereof, thereby treating the IgG4-RD. In another aspect, the present disclosure refers to a use of: (a.) a pharmaceutical composition that comprises a corticosteroid in an amount sufficient to reduce an immune response in the subject in the manufacture of a first medicament; and (b.) a pharmaceutical composition that comprises an anti-CD19 antibody in an amount sufficient to reduce a level of at least one of CD19 positive B cells, plasmablasts, plasma cells, or any combination thereof in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination therapy for treating Immunoglobulin G4-related disease (IgG4-RD) in a subject in need thereof, 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; wherein the pharmaceutical composition is to be administered intravenously with a first initial dose of 300 mg, a second initial dose of 300 mg two weeks after the first initial dose, and subsequent doses of 300 mg every 6 months following the first initial dose. In examples, the corticosteroid is a glucocorticoid. In examples, the glucocorticoid is selected from the group consisting of: prednisone, methylprednisolone, hydrocortisone, betamethasone, dexamethasone, and combinations thereof. In examples, the glucocorticoid is prednisone. In examples, from about

origin of disease, high frequency of atopy, multiple organs are typically affected (for example, one or more of lymph nodes, lacrimal gland, major salivary glands, pancreas, bile ducts, kidney, lung pituitary and paranasal sinus. Proliferative subtypes patients typical have high levels of IgG4, IgG1 and IgE. Eosinophilia and hypocomplementemia are also common. They may also show produce autoantibodies to one or more of laminin-511, galectin-3, annexin A11, and prohibitin. In lymphoplasmacytic infiltrates they may exhibit over 50 or over 100 IgG4-positive cells per HPF.

[14] The second subtype is called a fibrotic subtype. Fibrotic subtype patients show an origin of disease from extra glandular tissues rather than distinct organs. Fibrotic subtypes patient typical show slight elevation or normal levels of IgG4, IgG1 and IgE. Germinal center pathology is unusual. In lymphoplasmacytic infiltrates the fibrotic subtype patient may fewer than 50 IgG4-positive cells per HPF. Obliterative phlebitis is common. Germinal center pathology and storiform fibrosis are also common. Multiple organs are typically affected (for example, one or more of retroperitoneum, aorta and periaortic tissue, mesentery, pachymeninges, thyroid, and mediastinum.

[15] In examples, the IgG4-RD patient does not have one or more of the following: prominent neutrophilic infiltrate, necrotizing vasculitis, prominent necrosis, primarily granulomatous inflammation.

[16] Reducing flare incidence is particularly advantageous in these patients. The incidence of flares is about 35% annually; however, it can be about 20%, about 30%, about 40% or about 50%. The methods disclosed herein reduce the risk of flare by about 40%, about 50%, about 60%, about 65% or about 70%. Thus, an individual having a 35% incidence rate would have, on average, about 1 attack every 3 years.

[17] Provided are methods of treating a patient diagnosed with IgG4-RD, the method comprising: administering Inebilizumab to a patient diagnosed with IgG4-RD, wherein the Inebilizumab is administered intravenously with a first initial dose of 300 mg, a second initial dose of 300 mg two weeks after the first initial dose, and subsequent doses of 300 mg every 6 months following the first initial dose. In yet another example, the present disclosure refers to a use of an anti-CD19 antibody in the manufacture of a medicament for treating a patient diagnosed with Immunoglobulin G4-related disease (IgG4-RD), 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, wherein the medicament is to be administered intravenously with a first initial dose of 300 mg, a second initial dose of 300 mg two weeks after the first initial dose, and subsequent doses of 300 mg every 6 months following the first initial dose.

[18] These and other examples are described below.

Claims

1. Use of an effective amount of anti-CD19 antibody in the manufacture of a medicament for treating Immunoglobulin G4-related disease (IgG4-RD) in a subject in need thereof, 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;

wherein 300 mg of the anti-CD19 antibody is to be administered intravenously, comprising a first dose of 300 mg, a second dose of 300 mg two weeks after the first dose, and subsequent doses of 300 mg every 6 months following the first initial dose; and

wherein the effective amount is sufficient to reduce the IgG4-RD flare, as determined by:

a. reduced incidence of the IgG4-RD flare;

b. increased time to the IgG4-RD flare; or

c. a. and b.

2. The use of claim 1, wherein the anti-CD19 antibody comprises a heavy chain comprising SEQ ID NO: 9 and a light chain comprising SEQ ID NO: 10.

3. The use of claim 1, wherein the incidence of the IgG4-RD flare is reduced by at least 5%, as compared to an otherwise comparable subject lacking administering of the anti-CD19 antibody.

4. The use of any one of claims 1-3, wherein the subject in need thereof was previously administered a glucocorticoid.

5. The use of any one of claims 1-4, wherein the effective amount is effective in preventing new glucocorticoid administration in the subject in need thereof.

6. The use of any one of claims 1-3, further comprising that a corticosteroid is to be administered.

7. The use of any one of claims 1-3, further comprising that a steroid-sparing agent is to be administered, wherein the steroid-sparing agent is selected from the group consisting of: azathioprine and mycophenolate mofetil.

8. Use of:

a. a pharmaceutical composition that comprises a corticosteroid in an amount sufficient to reduce an immune response in the subject in the manufacture of a first medicament; and

b. a pharmaceutical composition that comprises an anti-CD19 antibody in an amount sufficient to reduce a level of at least one of CD19 positive B cells, plasmablasts, plasma cells, or any combination thereof in the manufacture of a second medicament, wherein the first and second medicament are to be used in combination therapy for treating Immunoglobulin G4-related disease (IgG4-RD) in a subject in need thereof, 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;

wherein the pharmaceutical composition is to be administered intravenously with a first initial dose of 300 mg, a second initial dose of 300 mg two weeks after the first initial dose, and subsequent doses of 300 mg every 6 months following the first initial dose.

9. The use of claim 8, wherein the corticosteroid is a glucocorticoid.

10. The use of claim 9, wherein the glucocorticoid is selected from the group consisting of: prednisone, methylprednisolone, hydrocortisone, betamethasone, dexamethasone, and combinations thereof.

11. The use of claim 8, wherein from 1 mg/day to 40 mg/day of the corticosteroid is to be administered.

12. The use of any one of claims 1-11, wherein the anti-CD19 antibody reduces the level of the at least one of CD19 positive B cells, plasmablasts, plasma cells, or any combination thereof by at least 1-fold as compared to an otherwise comparable subject lacking administering of the anti-CD19 antibody.

13. The use of any one of claims 8-11, wherein the corticosteroid is tapered, and wherein after the tapering, a reduction of IgG4-RD flare is observed as determined by:

a. reduced incidence of the IgG4-RD flare;

b. increased time to the IgG4-RD flare; or

c. a. and b.

14. The use of any one of claims 1-13, comprising determining a level of a marker in a sample of the subject in need thereof, wherein the marker is from a class selected from the group consisting of: immunoglobulin, complement, cellular, serum, RNA, DNA, and combinations thereof.

15. The use of any one of claims 1-14, further comprising that an antihistamine, an antipyretic, or both is/are to be administered.

16. The use of claim 15, comprising the antihistamine, antipyretic, or both are to be administered prior to the medicament that comprises the anti-CD19 antibody.