cerebrospinal fluid of multiple sclerosis patients." J *Neuroimmunol*, 180(1-2):63-70 (2006); Bar-Or A. *et al.*, "Safety, pharmacodynamics, and activity of Rituximab in patients with relapsing-remitting multiple sclerosis: a phase I, multicentre, open-label clinical trial." *Ann Neurol* 63(3):395-400 (2008); Hauser S. *et al.*, "B-cell depletion with Rituximab in relapsing-remitting multiple sclerosis." *NEJM*, 358(7):676-88, (2008); Hawker K *et al.*, "Efficacy and Safety of rituximab in patients with primary progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled, multicenter trial." *Multiple Sclerosis* 14(1):S299 (2008), Abstract; Hawker K *et al.*, "Efficacy and Safety of rituximab in patients with primary progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled, multicenter trial." *Neurology* 72(S3):A254 (2009), Abstract.

BRIEF SUMMARY

[0021a] In one aspect, there is provided use of an effective amount of an anti-CD20 antibody in the manufacture of a medicament for the treatment of multiple sclerosis in a patient, wherein an effective amount of the anti-CD20 antibody is adapted to be administrable to the patient to provide an initial antibody exposure of between about 0.3 to about 0.6 grams followed by a second antibody exposure of between about 0.3 to about 0.6 grams, the second exposure not being provided until from about 16 to 60 weeks from the initial exposure, and each of the antibody exposures is to be provided to the patient as one or two doses of antibody, wherein the anti-CD20 antibody is a human IgG1 antibody that comprises a VH domain comprising the amino acid set forth in SEQ ID NO: 8 and a VL domain comprising the amino acid sequence set forth in SEQ ID NO: 2.

[0022] The present disclosure provides methods of treating progressive multiple sclerosis in a patient comprising administering to the patient an effective amount of an anti-CD20 antibody, wherein treatment is based upon the patient having one or more characteristics selected from the group consisting of (a) an age less than about 55 years, (b) one or more gadolinium staining lesions, (c) at least about a one point increase in Expanded Disability Status Scale (EDSS) over two years prior to starting treatment, and (d) a Multiple Sclerosis Severity Score (MSSS) greater than about 5 points.

[0022a] Also disclosed is use of a composition comprising an anti-CD20 antibody for the manufacture of a medicament for treating progressive multiple sclerosis in a patient, wherein treatment is based upon the patient having an age less than about 55 years and one or more characteristics selected from the group consisting of: (a) one or more gadolinium staining lesions and (b) an EDSS when starting treatment is between about 3.0 and about 6.5.

[0044] In some embodiments, the effective amount of the anti-CD20 antibody is administered to the patient to provide an initial anti-CD20 antibody exposure of between about 0.3 to about 4.0 grams followed by a second anti-CD20 antibody exposure of between about 0.3 to about 4.0 grams. In some embodiments, the initial anti-CD20 antibody exposure and/or the second anti-CD20 antibody exposure is between about 0.3 to about 1.5 grams. In some embodiments, the second exposure not being provided until from about 16 to 60 weeks from the initial exposure. In some embodiments, each of the anti-CD20 antibody exposures is provided to the patient as one or two doses of anti-CD20 antibody.

[0045] In some embodiments, the anti-CD20 antibody comprises: a) a heavy chain variable region comprising SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12, and b) a light chain variable region comprising SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6. In some embodiments, the anti-CD20 antibody is ocrelizumab. In some embodiments, the anti-CD20 antibody is rituximab. In some embodiments, the anti-CD20 antibody is ofatumumab. In some embodiments, the anti-CD20 antibody is TRU-015 or SBI-087. In some embodiments, the anti-CD20 antibody is GA101. In some embodiments, the anti-CD20 antibody is hA20.

[0045a] Disclosed is use of one or more characteristics selected from the group consisting of (a) an age less than about 55 years; (b) one or more gadolinium staining lesions; and (c) an EDSS when starting treatment is between about 3.0 and about 6.5 for assessing whether a patient with progressive multiple sclerosis will respond to treatment with an anti-CD20 antibody wherein one or more of the characteristics in the patient indicates the patient will be responsive to the treatment.

[0046] The present disclosure also provides methods of assessing whether a patient with progressive multiple sclerosis will respond to treatment with an anti-CD20 antibody comprising assessing one or more characteristics selected from the group consisting of (a) an age less than about 55 years, (b) one or more gadolinium staining lesions, (c) at least about a one point increase in Expanded Disability Status Scale (EDSS) over two years prior to starting treatment, and (d) a Multiple Sclerosis Severity Score (MSSS) greater than about 5 points, wherein one or more of the characteristics in the patient indicates the patient will be responsive to the treatment.

about 5.0 for less than about 10 years. In some embodiments, the increase in EDSS over two years prior to starting treatment is not attributable to relapse. In some embodiments, the increase in EDSS is at least about a 1.5 point increase in EDSS over two years prior to starting treatment. In some embodiments, the at least about a 1.5 point increase in EDSS over two years prior to starting treatment is not attributable to relapse. In some embodiments, the patient further had two or more relapses within two years prior to starting treatment. In some embodiments, the EDSS when starting treatment is between about 3.0 and about 6.5.

[0050] In some embodiments, the age of the patient is less than about 51.

[0051] In some embodiments, the method further comprises advising a patient.

[0052] In some embodiments, the anti-CD20 antibody comprises: a) a heavy chain variable region comprising SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12, and b) a light chain variable region comprising SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6. In some embodiments, the anti-CD20 antibody is ocrelizumab. In some embodiments, the anti-CD20 antibody is rituximab. In some embodiments, the anti-CD20 antibody is ofatumumab. In some embodiments, the anti-CD20 antibody is TRU-015 or SBI-087. In some embodiments, the anti-CD20 antibody is GA101. In some embodiments, the anti-CD20 antibody is hA20.

[0052a] Disclosed is use of one or more characteristics selected from the group consisting of (a) an age less than about 55 years; (b) one or more gadolinium staining lesions; and (c) an EDSS when starting treatment is between about 3.0 and about 6.5 for identifying a patient with progressive multiple sclerosis likely to respond to anti-CD20 antibody treatment, wherein one or more of the characteristics in the patient indicates the patient will be responsive to the treatment.

[0079] In some embodiments of any of the methods or articles of manufacture described herein, the patients have one or more characteristics selected from the group consisting of (a) an age less than about 55 years, (b) one or more gadolinium staining lesions, and (c) at least about a one point increase in Expanded Disability Status Scale (EDSS) over two years prior to starting treatment.

[0080] The disclosure further provides methods of treating multiple sclerosis in a patient comprising administering an effective amount of ocrelizumab to the patient to provide an initial ocrelizumab exposure of between about 0.3 to about 0.6 grams followed by a second ocrelizumab exposure of between about 0.3 to about 0.6 grams, the second exposure not being provided until from about 16 to 60 weeks from the initial exposure, and each of the ocrelizumab exposures is provided to the patient as one or two doses of ocrelizumab.

[0080a] Disclosed is use of a composition comprising ocrelizumab for the manufacture of a medicament for treating multiple sclerosis in a patient, wherein an effective amount of ocrelizumab is to be administered to the patient to provide an initial ocrelizumab exposure of between about 0.3 to about 0.6 grams followed by a second ocrelizumab exposure of between about 0.3 to about 0.6 grams, the second exposure not being provided until from about 16 to 60 weeks from the initial exposure, and each of the ocrelizumab exposures is to be provided to the patient as one or two doses of ocrelizumab.

[0081] In some embodiments, the initial ocrelizumab exposure is about 0.6 grams. In some embodiments, the second ocrelizumab exposure is about 0.6 grams. In some embodiments, the second exposure is administered from about 24 weeks from the initial exposure. In some embodiments, one or more of the ocrelizumab exposures are provided to the patient as one dose of ocrelizumab. In some embodiments, one or more of the ocrelizumab exposures are provided to the patient as two doses of ocrelizumab. In some embodiments, the initial ocrelizumab exposure comprises a first dose and a second dose of ocrelizumab, wherein the first dose and second dose of ocrelizumab is about 0.3 grams. In some embodiments, the second ocrelizumab exposure comprises a single dose of ocrelizumab, wherein the single dose of ocrelizumab is 0.6 grams. In some embodiments, the methods further comprising providing a third ocrelizumab exposure. In some embodiments, the methods further comprising providing a fourth ocrelizumab exposure. In some embodiments, the methods further comprising providing a fifth ocrelizumab exposure. In some embodiments of any of the methods, the methods further comprising providing between about one to about three subsequent ocrelizumab exposures.

[0081a] In one aspect, there is provided an article of manufacture comprising:

(a) a container comprising an anti-CD20 antibody, which anti-CD20 antibody is a human IgG1 antibody that comprises a VH domain comprising the amino acid set forth in SEQ ID NO: 8 and a VL domain comprising the amino acid sequence set forth in SEQ ID NO: 2; and (b) a package insert with instructions for treating multiple sclerosis in a patient, wherein the instructions indicate that an amount of anti-CD20 is to be administered to the patient that is effective to provide an initial antibody exposure of between about 0.3 to about 0.6 grams followed by a second antibody exposure of between about 0.3 to about 0.6 grams, the second exposure not being administered until from about 16 to 60 weeks from the initial exposure, and each of the antibody exposures is to be provided to the patient as one or two doses of antibody.

[0082] Also disclosed is an article of manufacture comprising: (a) a container comprising ocrelizumab; and (b) a package insert with instructions for treating multiple sclerosis in a patient, wherein the instructions indicate that an amount of ocrelizumab is to be administered to the patient that is effective to provide an initial ocrelizumab exposure of between about 0.3 to about 0.6 grams followed by a second ocrelizumab exposure of between about 0.3 to about 0.6 grams, the second exposure not being administered until from about 16 to 60 weeks from the initial exposure, and each of the ocrelizumab exposures is provided to the patient as one or two doses of ocrelizumab.

CLAIMS

1. Use of an effective amount of an anti-CD20 antibody in the manufacture of a medicament for the treatment of multiple sclerosis in a patient, wherein an effective amount of the anti-CD20 antibody is adapted to be administrable to the patient to provide an initial antibody exposure of between about 0.3 to about 0.6 grams followed by a second antibody exposure of between about 0.3 to about 0.6 grams, the second exposure not being provided until from about 16 to 60 weeks from the initial exposure, and each of the antibody exposures is to be provided to the patient as one or two doses of antibody, wherein the anti-CD20 antibody is a human IgG1 antibody that comprises a VH domain comprising the amino acid set forth in SEQ ID NO: 8 and a VL domain comprising the amino acid sequence set forth in SEQ ID NO: 2.

2. The use of claim 1, wherein the initial antibody exposure is about 0.6 grams and the second antibody exposure is about 0.6 grams.

3. The use of claim 1 or claim 2, wherein the initial antibody exposure comprises a first dose and a second dose of anti-CD20 antibody, wherein the first dose and second dose of anti-CD20 antibody is about 0.3 grams.

4. The use of claim 3, wherein the second dose is to be administered from about 3 to 17 days from the time the first dose was administered.

5. The use of claim 3, wherein the second dose is to be administered from about 6 to 16 days from the time the first dose was administered.

6. The use of claim 3, wherein the second dose is to be administered from about 13 to 16 days from the time the first dose was administered.

7. The use of claim 3, wherein the second dose is to be administered 15 days from the time the first dose was administered.

8. The use of any one of claims 1-7, wherein the second antibody exposure comprises a single dose of anti-CD20 antibody, wherein the single dose of anti-CD20 antibody is 0.6 grams.

9. The use of any one of claims 1-8, wherein the second antibody exposure is to be provided approximately 24 weeks after the initial antibody exposure.

10. The use of claim any one of claims 1-8, wherein the second antibody exposure is to be provided about 6 months after the first antibody exposure.

11. The use of any one of claims 1-10, further comprising providing a third antibody exposure.

12. The use of claim 11, wherein the third antibody exposure is to be provided approximately 46 to 60 weeks from the initial antibody exposure.

13. The use of claim 11, wherein the third antibody exposure is to be provided approximately 46 to 54 weeks from the initial antibody exposure.

14. The use of claim 11, wherein the third antibody exposure is to be provided about 6 months from the second antibody exposure.

15. The use of any one of claims 11-14, further comprising providing a fourth antibody exposure.

16. The use of claim 15, wherein the fourth antibody exposure is to be provided about 6 months from the third exposure.

17. The use of claim 15 or claim 16, further comprising providing a fifth antibody exposure.

18. The use of claim 17, wherein the fifth antibody exposure is to be provided about 6 months from the fourth antibody exposure.

19. The use of claim 17 or claim 18, wherein subsequent antibody exposures are to be administered at intervals of approximately 6 months.

20. The use of any one of claims 1-19, wherein a second medicament is to be administered with the initial exposure or later exposures, wherein the anti-CD20 antibody is the first medicament.

21. The use of claim 20, wherein the second medicament is selected from the group consisting of an interferon, glatiramer acetate, a cytotoxic agent, a chemotherapeutic agent, mitoxantrone, methotrexate, cyclophosphamide, chlorambucil, azathioprine, gamma globulin, Campath, anti-CD4, cladribine, corticosteroid, mycophenolate mofetil (MMF), cyclosporine, a cholesterol-lowering drug of the statin class, estradiol, testosterone; a hormone replacement drug, a TNF inhibitor, a disease-modifying anti-rheumatic drug (DMARD), a non-steroidal anti-inflammatory drug (NSAID), levothyroxine, cyclosporin A, a somatastatin analogue, a cytokine or cytokine receptor antagonist, an anti-metabolite, an immunosuppressive agent, an integrin

antagonist or antibody, an LFA-1 antibody, efalizumab, an alpha 4 integrin antibody, natalizumab, and another B-cell surface marker antibody.

22. The use of any one of claims 1-21, wherein the multiple sclerosis is primary progressive multiple sclerosis (PPMS).

23. The use of any one of claims 1-21 wherein the multiple sclerosis is relapsing remitting multiple sclerosis (RRMS).

24. The use of any one of claims 1-23, wherein the subject has never been previously treated with an anti-CD20 antibody.

25. The use of any one of claims 1-27, wherein the anti-CD20 antibody is to be administered intravenously.

26. The use of any one of claims 1-19 and 21-25, wherein anti-CD20 antibody is the only medicament to be administered to the subject to treat multiple sclerosis.

27. The use of any one of claims 1-26, wherein the subject has elevated anti-myelin basic protein (MBP), anti-myelin oligodendrocytic glycoprotein (MOG), anti-ganglioside and/or anti-neurofilament antibody levels.

28. The use of any one of claims 1-27, wherein elevated levels of B cells are present in cerebrospinal fluid (CSF), multiple sclerosis lesion, or serum of the subject.

29. An article of manufacture comprising:

(a) a container comprising an anti-CD20 antibody, which anti-CD20 antibody is a human IgG1 antibody that comprises a VH domain comprising the amino acid set forth in SEQ ID NO: 8 and a VL domain comprising the amino acid sequence set forth in SEQ ID NO: 2; and

(b) a package insert with instructions for treating multiple sclerosis in a patient, wherein the instructions indicate that an amount of anti-CD20 is to be administered to the patient that is effective to provide an initial antibody exposure of between about 0.3 to about 0.6 grams followed by a second antibody exposure of between about 0.3 to about 0.6 grams, the second exposure not being administered until from about 16 to 60 weeks from the initial exposure, and each of the antibody exposures is to be provided to the patient as one or two doses of antibody.

30. The article of manufacture of claim 29, wherein the second exposure is to be provided about 6 months after the initial antibody exposure.