

[0006] Accordingly, there is a need for therapeutic anti-CD33 antibodies to treat diseases, disorders, and conditions associated with undesired CD33 activity.

[0007] Novel therapeutic antibodies targeting CD33 are one solution to treating diseases associated with CD33 activity, such as Alzheimer's disease. Systemically administered monoclonal antibodies normally exhibit a biphasic pharmacokinetic profile, being first distributed relatively quickly and then eliminated more slowly (Ovacik, M and Lin, L, (2018) *Clin Transl Sci* 11, 540-552). Circulation of systemically administered antibodies is typically confined to the vasculature and interstitial space (Ovacik, M and Lin, L, (2018) *Clin Transl Sci* 11, 540-552). This is because of their size, polarity, recycling and clearance kinetics, and typically relatively long half-lives, which are often 11-30 days in humans (Ovacik, M and Lin, L, (2018) *Clin Transl Sci* 11, 540-552).

[0008] Administration of monoclonal antibodies presents a challenge for therapeutic use. Monoclonal antibodies have limited oral bioavailability, so they are typically administered intravenously, subcutaneously, or intramuscularly (Ovacik, M and Lin, L, (2018) *Clin Transl Sci* 11, 540-552). Intravenous administration is particularly challenging for patients with neurodegenerative diseases, such as Alzheimer's disease. These diseases affect patients for long periods of time and thus require regular treatment over the course of many years. As intravenous administration cannot be done at home, patients must be transported to infusion centers on a regular basis, which is a burden on both the patient and caregiver. Finally, the memory loss, mood swings, aggression, and other behavioral symptoms of these diseases make patient compliance difficult.

[0009] Accordingly, there is a further need for identifying methods of treating patients with the appropriate dose and frequency of administration of anti-CD33 antibodies for treating and/or delaying the progression of a disease or injury, such as Alzheimer's disease, while facilitating patient compliance.

[0010] All references cited herein, including patents, patent applications and publications, are hereby incorporated by reference in their entirety.

SUMMARY

[0011] In one ~~aspect~~example, provided herein is a method of treating and/or delaying the progression of a disease or injury in an individual, including administering to the individual an anti-CD33 antibody intravenously at a dose of at least about 1.6 mg/kg, wherein the antibody is administered about once every twelve weeks or more frequently; and wherein the antibody includes: a heavy chain variable region that includes an HVR-H1 including the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), an HVR-H2 including the amino acid sequence FIYPSNRITG (SEQ ID NO: 119), and an HVR-H3 including the amino acid sequence SDVDYFDY (SEQ ID NO: 122); and a light chain variable region that includes an HVR-L1 including the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 including the amino acid sequence YASNLES (SEQ ID NO: 135), and an

HVR-L3 including the amino acid sequence QHSWEIPLT (SEQ ID NO: 146). In some [embodimentexamples](#), the anti-CD33 antibody is administered at a dose of between about 1.6 mg/kg and about 15 mg/kg. In some [embodimentexamples](#), the anti-CD33 antibody is administered at a dose of about 1.6 mg/kg, about 5 mg/kg, about 7.5 mg/kg, about 10 mg/kg, or about 15 mg/kg. In some [embodimentexamples](#), the anti-CD33 antibody is administered once every two weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every nine weeks, once every ten weeks, once every eleven weeks, or once every twelve weeks. In some [embodimentexamples](#), the anti-CD33 antibody is administered once every two weeks at a dose of about 1.6 mg/kg. In some [embodimentexamples](#), the anti-CD33 antibody is administered once every four weeks at a dose of about 1.6 mg/kg. In some [embodimentexamples](#), the anti-CD33 antibody is administered once every four weeks at a dose of about 15 mg/kg. In some [embodimentexamples](#), the anti-CD33 antibody is administered once every five weeks at a dose of about 15 mg/kg. In some [embodimentexamples](#), the anti-CD33 antibody is administered once every six weeks at a dose of about 15 mg/kg. In some [embodimentexamples](#), the anti-CD33 antibody is administered once every seven weeks at a dose of about 15 mg/kg. In some [embodimentexamples](#), the anti-CD33 antibody is administered once every eight weeks at a dose of about 15 mg/kg.

[0011a] In one aspect, the present disclosure refers to use of an anti-CD33 antibody in the manufacture of a medicament for treating and/or delaying the progression of a disease or injury in an individual, wherein the anti-CD33 antibody is to be administered intravenously at a dose of at least about 1.6 mg/kg, wherein the antibody is to be administered about once every twelve weeks or more frequently; and wherein the antibody comprises: a heavy chain variable region that comprises an HVR-H1 comprising the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), an HVR-H2 comprising the amino acid sequence FIYPSNRITG (SEQ ID NO: 119), and an HVR-H3 comprising the amino acid sequence SDVDYFDY (SEQ ID NO: 122); and a light chain variable region that comprises an HVR-L1 comprising the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the amino acid sequence YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the amino acid sequence QHSWEIPLT (SEQ ID NO: 146).

[0012] In some [embodimentexamples](#), which may be combined with any of the preceding [embodimentexamples](#), the cell surface level of CD33 is reduced by at least about 70% compared to the cell surface level of CD33 prior to administration of the anti-CD33 antibody. In some [embodimentexamples](#), the cell surface level of CD33 is reduced by at least about 80% compared to the cell surface level of CD33 prior to administration of the anti-CD33 antibody. In some [embodimentexamples](#), the cell surface level of CD33 is reduced by at least about 85% compared to the cell surface level of CD33 prior to administration of the anti-CD33 antibody. In some [embodimentexamples](#), the cell surface level of CD33 is reduced by at least about 90% compared to the cell surface level of CD33 prior to administration of the anti-CD33 antibody. In some [embodimentexamples](#), the reduction in the cell surface level of CD33 is present for at least about 12 days after administration of the anti-CD33 antibody. In some [embodimentexamples](#), the reduction in the cell surface level of CD33 is present for at least about 17 days after administration of the anti-CD33 antibody. In some [embodimentexamples](#), the reduction in the cell surface level of CD33 is present for at least about 29 days after administration of the anti-CD33 antibody. In some [embodimentexamples](#), the reduction in the cell surface level of CD33 is present for at least about 42 days after administration of the anti-CD33 antibody. In some [embodimentexamples](#), the reduction in the cell surface level of CD33 is present for at least about 56 days after administration of the anti-CD33 antibody. In some [embodimentexamples](#), the reduction in cell surface level of CD33 includes a reduction in the cell surface level of CD33 on peripheral blood monocytes of the individual.

[0013] In some [embodimentexamples](#), which may be combined with any of the preceding [embodimentexamples](#), the antibody includes a heavy chain variable region including the amino acid sequence of SEQ ID NO: 59 and a light chain variable region including the amino acid sequence of SEQ ID NO: 86. In some [embodimentexamples](#), the antibody has an IgG2 isotype. In some [embodimentexamples](#), the antibody includes a

heavy chain including the amino acid sequence of SEQ ID NO: 180 or SEQ ID NO: 201, and a light chain including the amino acid sequence of SEQ ID NO: 185.

[0014] In some embodimentexamples, which may be combined with any of the preceding embodimentexamples, the terminal half-life of the anti-CD33 antibody in plasma is about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, or about 12 days. In some embodimentexamples, the terminal half-life of the anti-CD33 antibody in plasma is about 10 days.

[0015] In some embodimentexamples, which may be combined with any of the preceding embodimentexamples, the disease or injury is selected from dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, tauopathy disease, infections, and cancer. In some embodimentexamples, the disease or injury is Alzheimer's disease.

[0016] In some embodimentexamples, which may be combined with any of the preceding embodimentexamples, the individual is diagnosed with Alzheimer's disease, or has a clinical diagnosis of probable Alzheimer's disease dementia. In some embodimentexamples, the individual has a Mini-Mental State Examination (MMSE) score of between about 16 points to about 28 points. In some embodimentexamples, the individual has a Clinical Dementia Rating-Global Score (CDR-GS) of about 0.5, about 1.0, or about 2.0. In some embodimentexamples, the individual has a positive amyloid-PET scan. In some embodimentexamples, the individual is taking a stable dose of a cholinesterase inhibitor and/or a memantine therapy for Alzheimer's disease. In some embodimentexamples, the individual does not carry two copies of the *rs12459419^T* allele.

[0017] In some embodimentexamples, which may be combined with any of the preceding embodimentexamples, the disease or injury is Alzheimer's disease, and treatment and/or delay of the progression of Alzheimer's disease is assessed using one or more clinical assessments selected from the Mini-Mental State Examination (MMSE), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Clinical Dementia Rating (CDR) assessment, amyloid brain positron emission tomography (PET), translocator protein (TSPO)-PET imaging, and any combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0019] **FIG. 1** shows the effect of anti-CD33 antibody AB-64.1.2 on CD33 levels on peripheral monocytes over time following a single intravenous administration of the antibody at a dose of 1.6 mg/kg or 15 mg/kg.

CLAIMS

What is claimed is:

1. Use of an anti-CD33 antibody in the manufacture of a medicament for~~A method of~~ treating and/or delaying the progression of a disease or injury in an individual, ~~comprising administering to the individual an~~wherein the anti-CD33 antibody is to be administered intravenously at a dose of at least about 1.6 mg/kg, wherein the antibody is to be administered about once every twelve weeks or more frequently; and wherein the antibody comprises: a heavy chain variable region that comprises an HVR-H1 comprising the amino acid sequence GYTFTDYNLH (SEQ ID NO: 105), an HVR-H2 comprising the amino acid sequence FIYPSNRITG (SEQ ID NO: 119), and an HVR-H3 comprising the amino acid sequence SDVDYFDY (SEQ ID NO: 122); and a light chain variable region that comprises an HVR-L1 comprising the amino acid sequence RASQSVSTSTYSYMH (SEQ ID NO: 127), an HVR-L2 comprising the amino acid sequence YASNLES (SEQ ID NO: 135), and an HVR-L3 comprising the amino acid sequence QHSWEIPLT (SEQ ID NO: 146).
2. The ~~method-use~~ of claim 1, wherein the anti-CD33 antibody is to be administered at a dose of between about 1.6 mg/kg and about 15 mg/kg.
3. The ~~method-use~~ of claim 1 or claim 2, wherein the anti-CD33 antibody is to be administered at a dose of about 1.6 mg/kg, about 5 mg/kg, about 7.5 mg/kg, about 10 mg/kg, or about 15 mg/kg.
4. The ~~method-use~~ of any one of claims 1-3, wherein the anti-CD33 antibody is to be administered once every two weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks, once every eight weeks, once every nine weeks, once every ten weeks, once every eleven weeks, or once every twelve weeks.
5. The ~~method-use~~ of any one of claims 1-4, wherein the anti-CD33 antibody is to be administered once every two weeks at a dose of about 1.6 mg/kg.
6. The ~~method-use~~ of any one of claims 1-4, wherein the anti-CD33 antibody is to be administered once every four weeks at a dose of about 1.6 mg/kg.

7. The ~~method~~-use of any one of claims 1-4, wherein the anti- CD33 antibody is to be administered once every four weeks at a dose of about 15 mg/kg.
8. The ~~method~~-use of any one of claims 1-4, wherein the anti- CD33 antibody is to be administered once every five weeks at a dose of about 15 mg/kg.
9. The ~~method~~-use of any one of claims 1-4, wherein the anti- CD33 antibody is to be administered once every six weeks at a dose of about 15 mg/kg.
10. The ~~method~~-use of any one of claims 1-4, wherein the anti-CD33 antibody is to be administered once every seven weeks at a dose of about 15 mg/kg.
11. The ~~method~~-use of any one of claims 1-4, wherein the anti-CD33 antibody is to be administered once every eight weeks at a dose of about 15 mg/kg.
12. The ~~method~~-use of any one of claims 1-11, wherein the cell surface level of CD33 is reduced by at least about 70% compared to the cell surface level of CD33 prior to administration of the anti-CD33 antibody.
13. The ~~method~~-use of any one of claims 1-12, wherein the cell surface level of CD33 is reduced by at least about 80% compared to the cell surface level of CD33 prior to administration of the anti-CD33 antibody.
14. The ~~method~~-use of any one of claims 1-13, wherein the cell surface level of CD33 is reduced by at least about 85% compared to the cell surface level of CD33 prior to administration of the anti-CD33 antibody.
15. The ~~method~~-use of any one of claims 1-14, wherein the cell surface level of CD33 is reduced by at least about 90% compared to the cell surface level of CD33 prior to administration of the anti-CD33 antibody.
16. The ~~method~~-use of any one of claims 12-15, wherein the reduction in the cell surface level of CD33 is present for at least about 12 days after administration of the anti-CD33 antibody.
17. The ~~method~~-use of any one of claims 12-16, wherein the reduction in the cell surface level of CD33 is present for at least about 17 days after administration of the anti-CD33 antibody.

18. The method-use of any one of claims 12-17, wherein the reduction in the cell surface level of CD33 is present for at least about 29 days after administration of the anti-CD33 antibody.
19. The method-use of any one of claims 12-18, wherein the reduction in the cell surface level of CD33 is present for at least about 42 days after administration of the anti-CD33 antibody.
20. The method-use of any one of claims 12-19, wherein the reduction in the cell surface level of CD33 is present for at least about 56 days after administration of the anti-CD33 antibody.
21. The method-use of any one of claims 12-20, wherein the reduction in cell surface level of CD33 comprises a reduction in the cell surface level of CD33 on peripheral blood monocytes of the individual.
22. The method-use of any one of claims 1-21, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 59 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 86.
23. The method-use of any one of claims 1-22, wherein the antibody has an IgG2 isotype.
24. The method-use of any one of claims 1-23, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 180 or SEQ ID NO: 201, and a light chain comprising the amino acid sequence of SEQ ID NO: 185.
25. The method-use of any one of claims 1-24, wherein the terminal half-life of the anti-CD33 antibody in plasma is about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, or about 12 days.
26. The method-use of any one of claims 1-25, wherein the terminal half-life of the anti-CD33 antibody in plasma is about 10 days.
27. The method-use of any one of claims 1-26, wherein the disease or injury is selected from the group consisting of dementia, frontotemporal dementia, Alzheimer's disease, vascular dementia, mixed dementia, tauopathy disease, infections, and cancer.
28. The method-use of any one of claims 1-26, wherein the disease or injury is Alzheimer's disease.

29. The ~~method~~-use of any one of claims 1-28, wherein the individual is diagnosed with Alzheimer's disease, or has a clinical diagnosis of probable Alzheimer's disease dementia.
30. The ~~method~~-use of any one of claims 1-29, wherein the individual has a Mini-Mental State Examination (MMSE) score of between about 16 points to about 28 points.
31. The ~~method~~-use of any one of claims 1-30, wherein the individual has a Clinical Dementia Rating-Global Score (CDR-GS) of about 0.5, about 1.0, or about 2.0.
32. The ~~method~~-use of any one of claims 1-31, wherein the individual has a positive amyloid-PET scan.
33. The ~~method~~-use of any one of claims 1-32, wherein the individual is taking a stable dose of a cholinesterase inhibitor and/or a memantine therapy for Alzheimer's disease.
34. The ~~method~~-use of any one of claims 1-33, wherein the individual does not carry two copies of the *rs12459419^T* allele.
35. The ~~method~~-use of any one of claims 1-34, wherein the disease or injury is Alzheimer's disease, and wherein treatment and/or delay of the progression of Alzheimer's disease is to be assessed using one or more clinical assessments selected from the group consisting of the Mini-Mental State Examination (MMSE), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Clinical Dementia Rating (CDR) assessment, amyloid brain positron emission tomography (PET), translocator protein (TSPO)-PET imaging, and any combination thereof.