

ANTI-N3pGlu AMYLOID BETA PEPTIDE ANTIBODIES AND USES THEREOF

The present invention relates to treatment of a disease with anti-N3pGlu A β antibodies, wherein the disease is characterized by deposition of Amyloid Beta (A β) in a patient. More specifically, the present invention relates to a short term induction treatment with N3pGlu A β antibodies of a disease characterized by deposition of A β in the brain, including Alzheimer's disease (AD), Down's syndrome, and cerebral amyloid angiopathy (CAA).

The deposits found in plaques of human patients are comprised of a heterogeneous mixture of A β peptides. N3pGlu A β , also referred to as N3pE A β , A β pE3-42, or A β _{p3-42}, is a truncated form of A β peptide and is found only in plaques. N3pGlu A β lacks the first two amino acid residues at the N-terminus of human A β and has a pyroglutamate which was derived from the glutamic acid at the third amino acid position. Although N3pGlu A β peptide is a minor component of the deposited A β in the brain, studies have demonstrated that N3pGlu A β peptide has aggressive aggregation properties and accumulates early in the deposition cascade.

Antibodies to N3pGlu A β are known in the art. For example, U.S. Patent Number 8,679,498 discloses anti-N3pGlu A β antibodies and methods of treating diseases such as Alzheimer's disease, with the antibodies. Passive immunization by long term chronic administration of antibodies against the A β , including N3pGlu A β , found in deposits has been shown to disrupt the A β aggregates and promote the clearance of plaques in the brain in various animal models. However, in humans long term chronic administration of A β antibodies has led to adverse events that include amyloid-related imaging abnormalities (ARIA), suggestive of vasogenic edema and sulcal effusions (ARIA-E), as well as microhaemorrhages and hemosiderin deposits (ARIA-H) as well as infusion site reactions and risk of immunogenicity. See Piazza and Winblad, "Amyloid-Related Imaging Abnormalities (ARIA) in Immunotherapy Trials for Alzheimer's Disease: Need for Prognostic Biomarkers?" Journal of Alzheimer's Disease, 52 (2016) 417-420.

Summary

In one aspect of the present disclosure, there is provided an anti-N3pGlu A β antibody for use in the treatment of a disease characterized by A β deposits in the brain, wherein the anti-N3pGlu A β antibody is to be administered to a patient at an induction dose of 10 to 60 mg/kg for a period of 6 months or less.

In another aspect of the present disclosure, there is provided an anti-N3pGlu A β antibody for use in slowing cognitive decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease, wherein the anti-N3pGlu A β antibody is to be administered to a patient at an induction dose of 10 to 60 mg/kg for a period of 6 months or less.

In a further aspect of the present disclosure, there is provided an anti-N3pGlu A β antibody for use in reducing A β plaque load in the brain of a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is to be administered to a patient at an induction dose of 10 to 60 mg/kg for a period of 6 months or less.

In another aspect of the present disclosure, there is provided a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for the treatment and prevention of a disease characterized by A β deposits in the brain, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody which is to be administered to a patient for a period of 6 months or less.

In a further aspect of the present disclosure, there is provided a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for reducing A β plaque load in the brain of a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody which is to be administered to a patient for a period of 6 months or less.

In another aspect of the present disclosure, there is provided a use of an anti-N3pGlu A β antibody for the manufacture of a medicament for slowing cognitive decline in a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody which is to be administered to a patient for a period of 6 months or less.

Description

5 The present invention overcomes the problems associated with long term chronic
administration. Applicants found that short term induction treatment with relatively high doses of
anti-N3pGlu A β antibodies promotes significant clearance of plaques in the brain of patients with
A β deposits, and this clearance is surprisingly maintained for an extended period of time. The
short term induction treatment can include a one-time dose of an anti-N3pGlu antibody, a
biweekly dose of an anti-N3pGlu A β antibody for a period of 6 months, or a monthly dose of an
10 anti-N3pGlu A β antibody for a period of 6 months or less. In addition to reducing the adverse

WE CLAIM:

- 5 1. An anti-N3pGlu A β antibody for use in the treatment of a disease characterized by A β deposits in the brain, wherein the anti-N3pGlu A β antibody is to be administered to a patient at an induction dose of 10 to 60 mg/kg for a period of 6 months or less.
- 10 2. An anti-N3pGlu A β antibody for use in slowing cognitive decline in a patient diagnosed with pre-clinical Alzheimer's disease or clinical Alzheimer's disease, wherein the anti-N3pGlu A β antibody is to be administered to a patient at an induction dose of 10 to 60 mg/kg for a period of 6 months or less.
- 15 3. An anti-N3pGlu A β antibody for use in reducing A β plaque load in the brain of a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the anti-N3pGlu A β antibody is to be administered to a patient at an induction dose of 10 to 60 mg/kg for a period of 6 months or less.
- 20 4. The anti-N3pGlu A β antibody for use according to any one of claims 1-3, wherein the anti-N3pGlu A β antibody is to be administered one-time.
- 25 5. The anti-N3pGlu A β antibody for use according to any one of claims 1-3, wherein the anti-N3pGlu A β antibody is to be administered every two weeks for a period of 6 months.
- 30 6. The anti-N3pGlu A β antibody for use according to any one of claims 1-3, wherein the anti-N3pGlu A β antibody is to be administered monthly for a period of 6 months.
7. The anti-N3pGlu A β antibody for use according to any one of claims 1-6, wherein the induction dose of the anti-N3pGlu A β antibody which is to be administered to the patient is 10 to 40 mg/kg.

- 5 8. The anti-N3pGlu A β antibody for use according to any one of claims 1-7, wherein the induction dose of the anti-N3pGlu A β antibody which is to be administered to the patient is 10 to 20 mg/kg.
- 10 9. The anti-N3pGlu A β antibody for use according to any one of claims 1-7, wherein the induction dose of the anti-N3pGlu A β antibody which is to be administered to the patient is between 15 to 30 mg/kg.
- 15 10. The anti-N3pGlu A β antibody for use according to any one of claims 1-7, wherein the induction dose of the anti-N3pGlu A β antibody which is to be administered to the patient is selected from 10 mg/kg, 15 mg/kg, 20 mg/kg and 40 mg/kg.
- 20 11. The anti-N3pGlu A β antibody for use according to claim 10, wherein the induction dose of the anti-N3pGlu A β antibody which is to be administered to the patient is 10 mg/kg.
- 25 12. The anti-N3pGlu A β antibody for use according to claim 10, wherein the induction dose of the anti-N3pGlu A β antibody which is to be administered to the patient is 20 mg/kg.
- 30 13. The anti-N3pGlu A β antibody for use according to claim 10, wherein the induction dose of the anti-N3pGlu A β antibody which is to be administered to the patient is 40 mg/kg.
14. The anti-N3pGlu A β antibody for use according to any one of claims 1-13, wherein the A β deposit in the brain of the patient is reduced by 35-100%, within 6 months post induction dose treatment.
15. The anti-N3pGlu A β antibody for use according to claim 14, wherein the A β deposit in the brain of the patient is reduced by 50%, within 6 months of post induction dose treatment.

- 5 16. The anti-N3pGlu A β antibody for use according to any one of claims 14-15, wherein the reduction of A β deposit in the brain of the patient is maintained for a period of 2 to 10 years post induction dose treatment.
- 10 17. The anti-N3pGlu A β antibody for use according to any one of claims 14-16, wherein the reduction of A β deposit in the brain of the patient is maintained for 3 to 5 years post induction dose treatment.
- 15 18. The anti-N3pGlu A β antibody for use according to any one of claims 1-17, wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR and HCVR is selected from the group consisting of:
- a) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 26;
 - b) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 27;
 - c) LCVR of SEQ ID NO: 32 and HCVR of SEQ ID NO: 34;
 - d) LCVR of SEQ ID NO: 9 and HCVR of SEQ ID NO: 8; and
 - e) LCVR of SEQ ID NO: 10 and HCVR of SEQ ID NO: 8
- 20 19. The anti-N3pGlu A β antibody for use according to any one of claims 1-17, wherein the anti-N3pGlu A β antibody comprises a light chain (LC) and a heavy chain (HC), wherein said LC and HC is selected from the group consisting of:
- a) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 29;
 - 25 b) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 30;
 - c) LC of SEQ ID NO: 33 and HC of SEQ ID NO: 35;
 - d) LC of SEQ ID NO: 12 and HC of SEQ ID NO: 11; and
 - e) LC of SEQ ID NO: 13 and HC of SEQ ID NO: 11.
- 30 20. The anti-N3pGlu A β antibody for use according to claim 19, wherein the anti-N3pGlu A β antibody comprises a light chain (LC) of SEQ ID NO: 28 and a heavy chain (HC) of SEQ ID NO: 29

21. The anti-N3pGlu A β antibody for use according to any one of claims 1-20, wherein the induction dose which is to be administered to the patient is to be followed by a maintenance dose with the same anti-N3pGlu A β antibody every 2, 3, 5 or 10 years post completion of the induction dose treatment.
22. The anti-N3pGlu A β antibody for use according to any one of claims 1-21, wherein the induction dose is to be administered to the patient in simultaneous, separate, or sequential combination with an effective amount of a BACE inhibitor.
23. The anti-N3pGlu A β antibody for use according to any one of claims 1-22, wherein the induction dose is to be administered to the patient in simultaneous, separate, or sequential combination with an effective amount of a symptomatic agent for the treatment of Alzheimer's disease.
24. The anti-N3pGlu A β antibody for use according to any one of claims 1-23, wherein the patient is positive for amyloid plaques in the brain, as determined by amyloid PET imagining scans.
25. Use of an anti-N3pGlu A β antibody for the manufacture of a medicament for the treatment and prevention of a disease characterized by A β deposits in the brain, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody which is to be administered to a patient for a period of 6 months or less.
26. Use of an anti-N3pGlu A β antibody for the manufacture of a medicament for reducing A β plaque load in the brain of a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody which is to be administered to a patient for a period of 6 months or less.

27. Use of an anti-N3pGlu A β antibody for the manufacture of a medicament for slowing cognitive decline in a patient diagnosed with pre-clinical or clinical Alzheimer's disease, Down's syndrome, and clinical or pre-clinical cerebral amyloid angiopathy, wherein the medicament comprises an induction dose of 10 to 60 mg/kg of an anti-N3pGlu A β antibody which is to be administered to a patient for a period of 6 months or less.
28. The use according to any one of claims 25-27 wherein the medicament is to be administered one-time.
29. The use according to any one of claims 25-27 wherein the medicament is to be administered every two weeks for a period of 6 months.
30. The use according to any one of claims 25-27 wherein the medicament is to be administered monthly for a period of 6 months.
31. The use according to any one of claims 25-30, wherein the medicament comprises an induction dose of 10 to 40 mg/kg of an anti-N3pGlu A β antibody.
32. The use according to any one of claims 25-31, wherein the medicament comprises an induction dose of 10 to 20 mg/kg of an anti-N3pGlu A β antibody.
33. The use according to claims 31, wherein the medicament comprises an induction dose of 15 to 30 mg/kg of an anti-N3pGlu A β antibody.
34. The use according to any one of claims 25-30, wherein the medicament comprises an induction dose selected from 10 mg/kg, 15 mg/kg, 20 mg/kg and 40 mg/kg of an anti-N3pGlu A β antibody.
35. The use according to any one of claims 25-34, wherein the A β deposit in the brain of a patient is reduced by 35-100% within 6 months post induction dose treatment.

36. The use according to claim 35, wherein the A β deposit in the brain of the patient is reduced by 50% within 6 months post induction dose treatment.

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37. The use according to any one of claim 35-36, wherein the reduction of A β deposit in the brain of the patient is maintained for a period of 2 to 10 years post induction dose treatment.

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38. The use according to any one of claims 35-37, wherein the reduction of A β deposit in the brain of the patient is maintained for 3 to 5 years.

39. The use according to any one of claims 25-38, wherein the anti-N3pGlu A β antibody in the medicament is a human or humanized antibody.

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40. The use according to any one of claims 25-39, wherein the anti-N3pGlu A β antibody in the medicament comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein said LCVR and HCVR is selected from the group consisting of:

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- a) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 26;
- b) LCVR of SEQ ID NO: 25 and HCVR of SEQ ID NO: 27;
- c) LCVR of SEQ ID NO: 32 and HCVR of SEQ ID NO: 34;
- d) LCVR of SEQ ID NO: 9 and HCVR of SEQ ID NO: 8; and
- e) LCVR of SEQ ID NO: 10 and HCVR of SEQ ID NO: 8.

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41. The use according to any one of claims 25-39, wherein the anti-N3pGlu A β antibody in the medicament comprises a light chain (LC) and a heavy chain (HC), wherein said LC and HC is selected from the group consisting of:

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- a) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 29;
- b) LC of SEQ ID NO: 28 and HC of SEQ ID NO: 30;
- c) LC of SEQ ID NO: 33 and HC of SEQ ID NO: 35;
- d) LC of SEQ ID NO: 12 and HC of SEQ ID NO: 11; and
- e) LC of SEQ ID NO: 13 and HC of SEQ ID NO: 11.

- 5 42. The use according to claim 41, wherein the anti-N3pGlu A β antibody in the medicament comprises a light chain (LC) of SEQ ID NO: 28 and a heavy chain (HC) of SEQ ID NO: 29.
- 10 43. The use according to any one of claims 25-42, wherein the induction dose which is to be administered to the patient is to be followed by a maintenance dose with the same anti-N3pGlu A β antibody every 2, 3, 5 or 10 years post completion of the induction dose treatment.
- 15 44. The use according to any one of claims 25-43, wherein the induction dose is to be administered to the patient in simultaneous, separate, or sequential combination with an effective amount of a BACE inhibitor.
- 20 45. The use according to any one of claims 25-43, wherein the induction dose is to be administered to the patient in simultaneous, separate, or sequential combination with an effective amount of a symptomatic agent for the treatment of Alzheimer's disease.
46. The use according to any one of claims 25-45, wherein the patient is positive for amyloid plaques in the brain, as determined by amyloid PET imaging scans.