

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 haemosiderin 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 a use of an anti-N3pGlu A β antibody in the manufacture of a medicament for reducing amyloid beta (A β) deposits in the brain of a patient in need thereof, wherein the medicament comprises an intravenous dose of 10 to 60 mg/kg of the anti-N3pGlu A β antibody, wherein the medicament is administered more than one time to the patient at a frequency of once every month, and wherein the anti-N3pGlu A β antibody

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comprises a light chain variable region (LCVR) of SEQ ID NO: 25 and a heavy chain variable region (HCVR) of SEQ ID NO:26.

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WE CLAIM:

1. Use of an anti-N3pGlu A β antibody in the manufacture of a medicament for reducing amyloid beta (A β) deposits in the brain of a patient in need thereof, wherein the medicament comprises an intravenous dose of 10 to 60 mg/kg of the anti-N3pGlu A β antibody, wherein the medicament is administered more than one time to the patient at a frequency of once every month, and wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) of SEQ ID NO: 25 and a heavy chain variable region (HCVR) of SEQ ID NO:26.
2. The use according to claim 1, 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.
3. The use according to claim 1, wherein the medicament is to be administered at a frequency of once every month for 1-12 separate doses.
4. The use according to claim 1, wherein the medicament is to be administered at a frequency of once every month for a period of 72 weeks.
5. The use according to claim 1, wherein 6 separate doses of the medicament are to be administered to the patient at a frequency of once every month.
6. The use according to claim 1, wherein the patient has preclinical Alzheimer's disease (AD), clinical Alzheimer's disease, Down's syndrome, clinical cerebral amyloid angiopathy, or pre-clinical cerebral amyloid angiopathy.
7. The use according to claim 1, wherein the patient has preclinical AD, prodromal AD, mild AD, moderate AD, or severe AD.
8. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is from 10 to 40 mg/kg.
9. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is from 10 to 20 mg/kg.
10. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is from 15 to 30 mg/kg.
11. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is selected from 10 mg/kg, 15 mg/kg, 20 mg/kg and 40 mg/kg.
12. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is 10 mg/kg.

13. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is 20 mg/kg.
- 5 14. The use according to claim 1, wherein the intravenous dose of the anti-N3pGlu A β antibody to be administered to the patient is 40 mg/kg.
15. The use according to claim 1, wherein the A β deposits in the brain of the patient are reduced by 35-100% within 6 months post treatment.
- 10 16. The use according to claim 1, wherein the A β deposits in the brain of the patient are reduced by 50% within 6 months post treatment.
17. The use according to claim 1, wherein the reduction of A β deposit in the brain of the patient is maintained for a period of 2 to 10 years post treatment.
- 15 18. The use according to claim 1, wherein the reduction of A β deposit in the brain of the patient is maintained for a period of 3 to 5 years post treatment.
- 20 19. The use according to claim 1, wherein the intravenous dose of the N3pGlu A β antibody to be administered to the patient is 700 mg per dose for a patient weighing 70 kg.
- 25 20. The use according to claim 1, wherein amyloid PET imaging scans are used to determine whether the patient is positive for amyloid deposits in the brain.
21. The use according to claim 1, wherein the patient carries one or two APOE ϵ 4 alleles.
- 30 22. The use according to claim 1, wherein the anti-N3pGlu A β antibody is a humanized antibody.