

Several therapeutic amyloid targeted antibodies have demonstrated dose-response related increases in ARIA-E. See, *e.g.*, Brashear *et al.*, “Clinical Evaluation of Amyloid-related Imaging Abnormalities in Bapineuzumab Phase III Studies,” *J. of Alzheimer’s Disease* 66.4:1409-1424 (2018); Budd *et al.*, “Clinical Development of Aducanumab, an Anti-A β Human Monoclonal Antibody Being Investigated for the Treatment of Early Alzheimer’s Disease,” *The Journal of Prevention of Alzheimer’s Disease* 4.4: 255 (2017). In some instances, there is a higher incidence rate of ARIA-E in patients harboring the epsilon-4 allele of apolipoprotein E (referred to herein as *APOE4*, apoE4, or ApoE- ϵ 4).

To decrease the rate of ARIA-E adverse events while maintaining plaque clearance, some antibody treatment programs implement dose-titration schemes that included multiple dose escalations (3-4 steps) over a period of ~6-months prior to reaching their efficacious dose level. See, *e.g.*, Budd *et al.*, “Clinical Development of Aducanumab, an Anti-A β Human Monoclonal Antibody Being Investigated for the Treatment of Early Alzheimer’s Disease,” *The Journal of Prevention of Alzheimer’s Disease* 4.4:255 (2017) and Klein *et al.*, “Gantenerumab Reduces Amyloid- β Plaques in Patients with Prodromal to Moderate Alzheimer’s Disease: a PET Substudy Interim Analysis,” *Alzheimer’s Research & Therapy* 11.1:101 (2019). Such treatment regimens may not fully clear amyloid plaques or may delay clearance of amyloid plaque.

SUMMARY

In an aspect of the present disclosure, there is provided a use of an anti-N3pGlu A β antibody in the manufacture of a medicament for treating Alzheimer’s Disease (AD) in a subject in need thereof, wherein:

- (i) three first doses of 700 mg of the anti-N3pGlu A β antibody is to be administered to the subject, wherein each first dose of 700 mg is to be administered at a frequency of once every four weeks;
- (ii) magnetic resonance image (MRI) scan of the subject’s brain is to be evaluated for amyloid-related imaging abnormality (ARIA) after administration of the three first doses; and
- (iii) if the step of evaluating does not demonstrate ARIA, four weeks after administration of the three first doses, one or more second doses of 1400 mg of the anti-N3pGlu A β antibody is to be administered to the subject at a frequency of once every four weeks,

wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 1 and the HCVR consists of the amino acid sequence of SEQ ID NO: 2.

In another aspect of the present disclosure, there is provided a use of an anti-N3pGlu A β antibody in the manufacture of a medicament for treating Alzheimer's Disease (AD) in a subject in need thereof, wherein:

(i) three first doses of 700 mg of the anti-N3pGlu A β antibody is to be administered to the subject, wherein each first dose of 700 mg is to be administered at a frequency of once every four weeks;

(ii) magnetic resonance image (MRI) scan of the subject's brain is to be evaluated for ARIA after administration of the three first doses;

(iii) if the step of evaluating demonstrates ARIA, treatment with the anti-N3pGlu A β antibody is to be temporarily withheld until resolution of ARIA or radiographic stabilization on MRI; and

(iv) upon resolution of ARIA or radiographic stabilization on MRI, one or more second doses of 1400 mg of the anti-N3pGlu A β antibody is to be administered at a frequency of once every four weeks,

wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 1 and the HCVR consists of the amino acid sequence of SEQ ID NO: 2.

In a further aspect of the present disclosure, there is provided a use of an anti-N3pGlu A β antibody in the manufacture of a medicament for treating Alzheimer's Disease in a subject in need thereof, wherein

(i) three first doses of 700 mg of the anti-N3pGlu A β antibody are to be administered to the subject, wherein each first dose of 700 mg is to be administered at a frequency of once every four weeks;

(ii) magnetic resonance image (MRI) scan of the subject's brain is to be evaluated for ARIA after administration of the three first doses; and

(iii) if the step of evaluating demonstrates ARIA, treatment with the anti-N3pGlu A β antibody is to be discontinued,

wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 1 and the HCVR consists of the amino acid sequence of SEQ ID NO: 2.

In another aspect of the present disclosure, there is provided a use of an anti-N3pGlu A β antibody in the manufacture of a medicament for treating Alzheimer's Disease in a subject in need thereof, wherein:

(i) up to three first doses are to be administered to the subject, each first dose comprising 700 mg of the anti-N3pGlu A β antibody which is to be administered at a frequency of one first dose every four weeks, wherein the subject is evaluated for ARIA after each dose, and if ARIA is observed, administration of the anti-N3pGlu A β antibody is temporarily discontinued until resolution of ARIA symptoms or radiographic stabilization on MRI; and

(ii) upon resolution of ARIA or radiographic stabilization on MRI, the remaining first doses or one or more second doses of 1400 mg of the anti-N3pGlu A β antibody is to be administered at a frequency of once every four weeks,

wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 1 and the HCVR consists of the amino acid sequence of SEQ ID NO: 2.

In a further aspect of the present disclosure, there is provided a use of an anti-N3pGlu A β antibody in the manufacture of a medicament for treating Alzheimer's Disease in a subject in need thereof, wherein:

(i) up to three first doses are to be administered to the subject, each first dose comprising 700 mg of the anti-N3pGlu A β antibody which is to be administered at a frequency of one first dose every four weeks, wherein the subject is evaluated for ARIA after each first dose; and

(ii) one or more second doses of 1400 mg of the anti-N3pGlu A β antibody is to be administered at a frequency of once every four weeks,

wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the

amino acid sequence of SEQ ID NO: 1 and the HCVR consists of the amino acid sequence of SEQ ID NO: 2.

DESCRIPTION

Thus, a need exists for improved doses, dosing regimens, or methods that properly treat subjects without causing or increasing problematic adverse events.

One aspect of the present disclosure provides for doses and dosing regimens that circumvent problematic adverse events, such as ARIA with vasogenic edema, that have been observed in patients receiving therapeutic antibodies that bind to deposited amyloid and have been dose limiting for some clinical development programs.

The antibodies of the present disclosure bind selectively to N3pGlu A β found primarily in deposited amyloid plaque. The prevalence of the N3pGlu A β peptide in deposited parenchymal plaque is very low relative to other A β peptide species (~1 to 2%) where the majority is full-length A β ₁₋₄₂. Thus, the total number of binding sites for the antibodies of the present disclosure relative to other plaque binding A β antibodies is dramatically lower. Biochemical analysis of CAA, the amyloid depositing along CNS blood vessels, demonstrated a similar low prevalence of N3pGlu peptides (~2%).

WE CLAIM:

1. Use of an anti-N3pGlu A β antibody in the manufacture of a medicament for treating Alzheimer's Disease (AD) in a subject in need thereof, wherein:

(i) three first doses of 700 mg of the anti-N3pGlu A β antibody is to be administered to the subject, wherein each first dose of 700 mg is to be administered at a frequency of once every four weeks;

(ii) magnetic resonance image (MRI) scan of the subject's brain is to be evaluated for amyloid-related imaging abnormality (ARIA) after administration of the three first doses; and

(iii) if the step of evaluating does not demonstrate ARIA, four weeks after administration of the three first doses, one or more second doses of 1400 mg of the anti-N3pGlu A β antibody is to be administered to the subject at a frequency of once every four weeks,

wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 1 and the HCVR consists of the amino acid sequence of SEQ ID NO: 2.

2. Use of an anti-N3pGlu A β antibody in the manufacture of a medicament for treating Alzheimer's Disease (AD) in a subject in need thereof, wherein:

(i) three first doses of 700 mg of the anti-N3pGlu A β antibody is to be administered to the subject, wherein each first dose of 700 mg is to be administered at a frequency of once every four weeks;

(ii) magnetic resonance image (MRI) scan of the subject's brain is to be evaluated for ARIA after administration of the three first doses;

(iii) if the step of evaluating demonstrates ARIA, treatment with the anti-N3pGlu A β antibody is to be temporarily withheld until resolution of ARIA or radiographic stabilization on MRI; and

(iv) upon resolution of ARIA or radiographic stabilization on MRI, one or more second doses of 1400 mg of the anti-N3pGlu A β antibody is to be administered at a frequency of once every four weeks,

wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 1 and the HCVR consists of the amino acid sequence of SEQ ID NO: 2.

3. The use of claim 1 or 2, wherein the second doses are to be administered until:
 - (i) the A β plaques are cleared;
 - (ii) the A β plaques in the subject are 25 centiloids or lower as measured by two consecutive amyloid PET imaging scans, wherein the two consecutive amyloid PET imaging scans are at least 6 months apart;
 - (iii) the A β plaques in the subject are 11 centiloids or lower as measured by a single amyloid PET imaging scan;
 - (iv) the subject is amyloid negative; or
 - (v) the A β plaque level of <24.1 CL is reached as measured by amyloid PET imaging scan.
4. The use of any one of claims 1 to 3, wherein the anti-N3pGlu A β antibody doses are to be administered over a period of no more than 72 weeks.
5. The use of any one of claims 1-4, wherein a baseline MRI scan is further obtained prior to the administration of three first doses to the subject.
6. The use of any one of claims 1-5, wherein:
 - (i) disease progression is slowed by at least 15% as compared to being untreated estimated by Disease Progression Model (DPM), wherein disease progression is measured by Integrated Alzheimer's Disease Rating Scale (iADRS) or Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB);
 - (ii) disease progression is slowed by at least 15% as compared to being untreated estimated by a mixed-model repeated-measures analysis (MMRM), wherein disease progression is measured by iADRS or CDR-SB;
 - (iii) disease progression is slowed by at least 15% as compared to being untreated, wherein disease progression is measured by iADRS;

(iv) disease progression is slowed by at least 3 as compared to being untreated, wherein disease progression is measured by iADRS;

(v) disease progression is slowed by at least 20% as compared to being untreated, wherein the disease progression is measured by CDR-SB;

(vi) the level of A β plaque is reduced in the brain of the subject by at least 40% as measured by amyloid PET imaging;

(vii) tau accumulation in the frontal lobe is slowed by at least 50% as compared to being untreated;

(viii) increase in the subject's frontal lobe tau over 72 weeks is limited to less than 0.04 SUVR (standardized uptake value ratio) as measured by tau PET imaging;

(ix) plasma P-tau 217 is reduced by at least 5% from baseline; or

(x) glial fibrillary acidic protein (GFAP) is reduced by at least 5% from baseline.

7. The use of claim 1 or 2, wherein administration of the anti-N3pGlu A β antibody reduces A β plaques by about an average of about 50 centiloids to about 100 centiloids as compared to A β plaques prior to administration of the one or more first doses, wherein the A β plaques are measured by amyloid PET imaging scan.

8. The use of claim 1 or 2, wherein 24 weeks of administration of the anti-N3pGlu A β antibody reduces the A β plaque by at least 60%.

9. The use of any one of claims 1-8, wherein each of the first doses and second doses are to be administered intravenously at a concentration of 4 mg/mL to 10 mg/mL over at least 30 minutes.

10. The use of claim 1 or 2, wherein the subject's hippocampal volume is not reduced.

11. The use of claim 1 or 2, wherein A β plaque levels in the brain of the subject are sustained at normal levels for at least 52 weeks after said step of administration of one or more second doses.
12. The use of claim 1 or 2, wherein if after 24 weeks of administration of the anti-N3pGlu A β antibody, A β plaque levels in the brain of the subject reach normal levels or stop reducing, said step of administration of one or more second doses is discontinued.
13. The use of claim 1 or 2, wherein A β plaque levels in the brain of the subject are sustained at normal levels for at least 52 weeks after said step of administration of one or more second doses is discontinued.
14. The use of claim 1 or 2, wherein the level of A β plaques in the brain of the subject is reduced to normal levels by 24 weeks.
15. The use of claim 14, wherein the level of A β plaques in the brain of the subject is sustained at normal levels for at least 52 weeks after said step of administration of one or more second doses is stopped.
16. The use of any one of claims 12-15, wherein the subject has an increase in tau level in a parietal lobe of less than 0.06 SUVR 76 weeks after said step of administration of one or more second doses is stopped, wherein the brain tau level is measured by tau PET imaging scan.
17. The use of any one of claims 12-16, wherein the subject has a brain tau level of less than 0.4 SUVR in a frontal lobe region 76 weeks after said step of administration of one or more second doses is discontinued, wherein the brain tau level is measured by tau PET imaging scan.
18. Use of an anti-N3pGlu A β antibody in the manufacture of a medicament for treating Alzheimer's Disease in a subject in need thereof, wherein

- (i) three first doses of 700 mg of the anti-N3pGlu A β antibody are to be administered to the subject, wherein each first dose of 700 mg is to be administered at a frequency of once every four weeks;
 - (ii) magnetic resonance image (MRI) scan of the subject's brain is to be evaluated for ARIA after administration of the three first doses; and
 - (iii) if the step of evaluating demonstrates ARIA, treatment with the anti-N3pGlu A β antibody is to be discontinued,
- wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 1 and the HCVR consists of the amino acid sequence of SEQ ID NO: 2.

19. The use of any one of claims 1-18, wherein the ARIA is ARIA-E.

20. The use of claim 19, wherein ARIA-E is moderate or severe.

21. The use of any one of claims 1-18, wherein the ARIA is ARIA-H.

22. The use of claim 21, wherein ARIA-H is moderate or severe.

23. The use of any one of claims 1-22, wherein prior to the step of administration of three first doses to the subject, the subject:

- (i) has a brain tau level of less than 1.46 standardized uptake value ratio (SUVr);
 - (ii) has a brain tau level of greater than 1.10 SUVr and less than 1.46 SUVr; or
 - (iii) has a negative brain tau imaging level in a frontal lobe brain region;
- wherein the brain tau level is measured by tau PET imaging scan.

24. The use of claim 23, wherein brain tau level is measured by ¹⁸F-flortaucipir PET imaging.

25. The use of any one of claims 1-24, wherein, prior to said step of administration of three first doses, the subject:

- (i) is identified as having early symptomatic Alzheimer's Disease;
- (ii) is identified as having at least one *APOE4* allele; or
- (iii) has a baseline MMSE (Mini-Mental State Exam) score of 20 to 28.

26. Use of an anti-N3pGlu A β antibody in the manufacture of a medicament for treating Alzheimer's Disease in a subject in need thereof, wherein:

(i) up to three first doses are to be administered to the subject, each first dose comprising 700 mg of the anti-N3pGlu A β antibody which is to be administered at a frequency of one first dose every four weeks, wherein the subject is evaluated for ARIA after each dose, and if ARIA is observed, administration of the anti-N3pGlu A β antibody is temporarily discontinued until resolution of ARIA symptoms or radiographic stabilization on MRI; and

(ii) upon resolution of ARIA or radiographic stabilization on MRI, the remaining first doses or one or more second doses of 1400 mg of the anti-N3pGlu A β antibody is to be administered at a frequency of once every four weeks,

wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the amino acid sequence of SEQ ID NO: 1 and the HCVR consists of the amino acid sequence of SEQ ID NO: 2.

27. Use of an anti-N3pGlu A β antibody in the manufacture of a medicament for treating Alzheimer's Disease in a subject in need thereof, wherein:

(i) up to three first doses are to be administered to the subject, each first dose comprising 700 mg of the anti-N3pGlu A β antibody which is to be administered at a frequency of one first dose every four weeks, wherein the subject is evaluated for ARIA after each first dose; and

(ii) one or more second doses of 1400 mg of the anti-N3pGlu A β antibody is to be administered at a frequency of once every four weeks,

wherein the anti-N3pGlu A β antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR consists of the

amino acid sequence of SEQ ID NO: 1 and the HCVR consists of the amino acid sequence of SEQ ID NO: 2.

28. The use of any one of claims 1-27, wherein the anti-N3pGlu A β antibody comprises a light chain (LC) and a heavy chain (HC), wherein the LC comprises the amino acid sequence of SEQ ID NO: 3 and the HC comprises the amino acid sequence of SEQ ID NO: 4.