Examen de l'UE O5 Session 1 2014-15

M2pro Pharmacologie et métiers du médicament (durée de l'épreuve 2 hrs)

Les documents ci-joints sont extraits d'un article publié dans le New England Journal of Medicine en janvier 2014 [Doody et al, N Engl J Med 370 ;4 January 23, 2014] intitulé :

Phase 3 Trials odf Solanezumab for Mild-toModerate Alzheimer's Disease.

ABSTRACT

BACKGROUND

Alzheimer's disease is characterized [redacted]. Solanezumab, a humanized monoclonal antibody, preferentially binds soluble forms of amyloid and in preclinical studies promoted its clearance from the brain.

METHODS

In two phase 3, double-blind trials (EXPEDITION 1 and EXPEDITION 2), we [redacted] assigned 1012 and 1040 patients, respectively, with mild-to-moderate Alzheimer's disease to receive placebo or solanezumab (administered intravenously at a dose of 400 mg) every 4 weeks for 18 months. The [redacted] were the changes from baseline to week 80 in scores on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11; range, 0 to 70, with higher scores indicating greater cognitive impairment) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL; range, 0 to 78, with lower scores indicating worse functioning). After analysis of data from EXPEDITION 1, the primary outcome for EXPEDITION 2 was revised to the change in scores on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90, with higher scores indicating greater impairment), in patients with mild Alzheimer's disease.

RESULTS

Neither study showed significant improvement in the primary outcomes. The modeled difference between groups (solanezumab group minus placebo group) in the change from baseline was −0.8 points for the ADAS-cog11 score (95% confidence interval [CI], −2.1 to 0.5; P=0.24) and −0.4 points for the ADCS-ADL score (95% CI, −2.3 to 1.4; P=0.64) in EXPEDITION 1 and −1.3 points (95% CI, −2.5 to 0.3; P=0.06) and 1.6 points (95% CI, −0.2 to 3.3; P=0.08), respectively, in EXPEDITION 2. Between-group differences in the changes in the ADAS-cog14 score were −1.7 points in patients with mild Alzheimer's disease (95% CI, −3.5 to 0.1; P=0.06) and −1.5 in patients with moderate Alzheimer's disease (95% CI, −4.1 to 1.1; P=0.26). In the combined safety data set, the incidence of amyloid-related imaging abnormalities with edema or hemorrhage was 0.9% with solanezumab and 0.4% with placebo for edema (P=0.27) and 4.9% and 5.6%, respectively, for hemorrhage (P=0.49).

CONCLUSIONS

Solanezumab, a humanized monoclonal antibody that binds amyloid, failed to improve cognition or functional ability. (Funded by Eli Lilly; EXPEDITION 1 and 2 ClinicalTrials.gov numbers, NCT00905372 and NCT00904683.)

From the Alzheimer's Disease and Memory Disorders Center, Department of Neurology, Baylor College of Medicine, Houston (R.S.D.); Alzheimer's Disease Cooperative Study, Department of Family and Preventive Medicine (R.G.T., R.R., X.S.), and the Department of Neurosciences (R.G.T., R.R., P.S.A., R.M.), University of California at San Diego, San Diego; Indiana Alzheimer Disease Center, Indiana University (M.F.), and Eli Lilly (E.S., H.L.-S., R.M.) — both in Indianapolis; the Department of Neuropathology, School of Medicine, and the Department of Neuropathology and Neuroscience, School of Pharmacological Science, University of Tokyo, Tokyo (T.I.); Gerontopole, Unité Mixte de Recherche 1027, Centre Hospitalier Universitaire Toulouse, Toulouse, France (B.V.); the Department of Medical Ethics and Health Policy, University of Pennsylvania, Philadelphia (S.J.); and the Center for Human Experimental Therapeutics, University of Rochester Medical Center, Rochester, NY (K.K.). Address reprint requests to Dr. Doody at the Department of Neurology, Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, 1977 Butler Blvd., Suite E 5.101, Houston, TX 77030, or at rdoody@bcm.edu.

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ALZHEIMER'S DISEASE IS ASSOCIATED with [redacted]. One approach to reducing brain amyloid involves increasing the clearance of Aβ by means of prolonged treatment with monoclonal antibodies directed against this peptide. In preclinical studies, a murine antibody that targeted the central domain of Aβ and was selective for soluble forms slowed Aβ deposition in a transgenic mouse model[1]; in another transgenic murine model, Aβ–antibody complexes were present in the cerebrospinal fluid (CSF) and plasma, and behavioral deficits were reversed without a decrease in amyloid plaques, as assessed by immunohistochemical analysis.[2] Solanezumab, the humanized analogue of the murine antibody, was tested in clinical phase 1 and 2 studies.[3,4] These studies showed dose-related increases in total (bound plus unbound) plasma Aβ and similar CSF alterations (increased total Aβ and, at the highest dose [400 mg weekly], decreased unbound Aβ1-40 but increased unbound Aβ1-42),[4] findings that suggest solanezumab might have efficacy in Alzheimer's disease through a central effect[5] or through promotion of Aβ efflux from the central nervous system to the peripheral circulation. Eli Lilly conducted two phase 3, randomized, double-blind, placebo-controlled trials (EXPEDITION 1 and EXPEDITION 2), which were analyzed and are reported here by the Alzheimer's Disease Cooperative Study (ADCS) Data Analysis and Publication Committee.

METHODS

PATIENTS AND STUDY-DRUG REGIMENS

Both trials involved otherwise healthy patients 55 years of age or older who had mild-to-moderate Alzheimer's disease without depression. Mild-to-moderate Alzheimer's disease was documented on the basis of a score of 16 to 26 on the Mini–Mental State Examination (MMSE; score range, 0 to 30, with higher scores indicating better cognitive function)[6] and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association.[7] The absence of depression was documented on the basis of a score of 6 or less on the Geriatric Depression Scale (score range, 0 to 15, with higher scores indicating more severe depression).[8] Participants were randomly assigned to receive solanezumab (400 mg) or placebo, administered as an intravenous infusion of approximately 70 ml over a period of 30 minutes, once every 4 weeks for 18 months. Concomitant treatment with cholinesterase inhibitors, memantine, or both was allowed.

OVERSIGHT

The study protocol was approved by the institutional review board at each participating institution, and all participants provided written informed consent. (The study protocol is available with the full text of this article at NEJM.org.) The Data Analysis and Publication Committee of the ADCS, an academic consortium funded by the National Institute on Aging, was funded by a contract between Eli Lilly and the University of California at San Diego as a fiduciary for the ADCS. Eli Lilly designed and conducted the study. The manuscript was written by the committee chair and was revised and approved by the voting members of the Data Analysis and Publication Committee, the ADCS steering committee, and all the authors. All the authors vouch for the completeness and veracity of the data and data analysis and for the fidelity of this report to the study protocol, with modifications and additions to the statistical analysis plan as explained in this report and in the Supplementary Appendix, available at NEJM.org.

SAFETY ASSESSMENTS

Safety was assessed on the basis of measurements of vital signs and weight, physical examination, serum biochemical measurements, hematologic analysis, measurement of electrolytes, urinalysis, and electrocardiography. Adverse events were assessed at each visit.

CLINICAL OUTCOME MEASURES

Efficacy measures included the 11- or 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11 [score range, 0 to 70] and ADAS-cog14 [score range, 0 to 90], with higher scores indicating greater cognitive impairment),[9] the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale (score range, 0 to 78, with lower scores indicating worse functioning),[10] the Clinical Dementia Rating–Sum of Boxes (CDR-SB),[11,12] the Neuropsychiatric Inventory (NPI),[13] the Resource Utiliza-

tion in Dementia Lite (RUD-Lite) scale,[14] the European Quality of Life–5 Dimensions (EQ-5D) scale (proxy version),[15] the Quality of Life in Alzheimer's Disease (QOL-AD) scale,[16,17] and the MMSE.[7]

BIOLOGIC MARKERS AND NEUROIMAGING OUTCOME MEASURES

[redacted] genotypes were determined. Plasma levels of Aβ were assessed at multiple time points, and CSF levels of [redacted] were measured in a subset of patients. Brain volumetric magnetic resonance imaging (MRI) was performed; amyloid imaging by means of positron-emission tomography (PET) with the use of ^{18}F-florbetapir was performed at baseline and week 80 or at early termination in a subset of patients.

Plasma and CSF concentrations of total (bound and unbound) [redacted] were determined by means of INNOTEST immunoassays (Innogenetics) that were modified and validated for use with biologic specimens containing variable levels of solanezumab, as reported previously.[19]

STATISTICAL ANALYSIS

The statistical analysis plan followed by the Data Analysis and Publication Committee was consistent with the Eli Lilly statistical analysis plans for the two trials, although it differed in some details (see Table S1 in the Supplementary Appendix). Mixed-model repeated-measures analyses were used to assess between-group differences in the modeled change in scores from baseline to week 80. The dependent variable in each analysis was the change from the baseline score. Fixed effects were baseline scores on outcome measures, study-drug assignment (solanezumab or placebo), MMSE score at screening (categorical variable [mild or moderate Alzheimer's disease]), visit and treatment-by-visit interaction, concomitant use of cholinesterase inhibitors or memantine at baseline (yes or no), and age at baseline.

there was at least one postbaseline observation. A secondary analysis was performed for all randomly assigned participants who completed the period of treatment with the study medication.

The primary outcomes for EXPEDITION 1 and the original primary outcomes for EXPEDITION 2 were the change in scores on the ADAS-cog11 and the ADCS-ADL scale from baseline to week 80 (end point). Secondary outcomes were the change from baseline in scores on the CDR-SB, MMSE, NPI, EQ-5D scale, RUD-Lite scale, and QOL-AD scale; the values for plasma and CSF levels of Aβ and for CSF levels of tau and phospho-tau; MRI brain volumetric measurements; and evidence of amyloid accumulation on imaging studies performed with ^{18}F-florbetapir–PET. Safety analyses were based on the full intention-to-treat population, and all biomarker analyses were calculated with the use of data from patients with at least one postbaseline value. The baseline characteris-

Table 1. **Demographic and Baseline Clinical Characteristics of the Patients**

Characteristic	EXPEDITION 1	
	Placebo (N=506)	Solanezumab (N=506)
Age — yr	74.4±8.0	75.0±7.9
Male sex — no. (%)	219 (43.3)	207 (40.9)
Race or ethnic group — no. (%)†		
White	427 (84.4)	420 (83.0)
Black	25 (4.9)	20 (4.0)
Asian	49 (9.7)	65 (12.8)
American Indian or Alaska Native	2 (0.4)	0
More than one	3 (0.6)	1 (0.2)
Education — yr	12.8±3.9	12.6±4.2
Antidementia therapy at baseline — no. (%)		
Acetylcholinesterase inhibitor alone	218 (43.1)	229 (45.3)
Memantine alone	33 (6.5)	21 (4.2)
Acetylcholinesterase inhibitor and memantine	196 (38.7)	197 (38.9)
None	59 (11.7)	59 (11.7)
MMSE score‡	21±3	21±4
ADAS-cog11 score§	22±9	22±8
APOE ε4 carrier — no./total no. (%)	288/470 (61.3)	266/464 (57.3)

Table 3. **Primary and Secondary Outcomes in EXPEDITION 2, Intention-to-Treat Population.***

Variable	Mean Change from Baseline to Wk 80 (95% CI)		Mean Difference (95% CI)	P Value
	Placebo	Solanezumab		
ADAS-cog11 score†	6.6 (5.2 to 7.9)	5.3 (4.0 to 6.7)	−1.3 (−2.5 to 0.3)	0.06
ADAS-cog14 score†	7.5 (5.8 to 9.1)	5.9 (4.3 to 7.5)	−1.6 (−3.1 to 0.1)	0.04
ADCS-ADL score†	−10.9 (−12.7 to −9.1)	−9.3 (−11.2 to −7.5)	1.6 (−0.2 to 3.3)	0.08
CDR-SB score	1.9 (1.4 to 2.4)	1.6 (1.2 to 2.1)	−0.3 (−0.7 to 0.2)	0.17
NPI score	3.0 (0.8 to 5.1)	2.8 (0.7 to 5.0)	−0.2 (−1.8 to 1.5)	0.85
MMSE score	−2.8 (−3.6 to −2.0)	−2.1 (−2.8 to −1.3)	0.8 (0.2 to 1.4)	0.01
Free $A\beta_{40}$ in CSF — pg/ml	−649.0 (−2139.5 to 841.5)	−1258.1 (−2695.8 to 179.7)	−609.1 (−1228.4 to 10.2)	0.05
Free $A\beta_{42}$ in CSF — pg/ml	−35.1 (−129.5 to 59.3)	1.0 (−94.1 to 96.2)	36.1 (−1.0 to 73.3)	0.06
Total $A\beta_{40}$ in CSF — pg/ml	−876.4 (−4342.5 to 2589.8)	2156.8 (−1211.9 to 5525.4)	3033.1 (1628.4 to 4437.9)	<0.001
Total $A\beta_{42}$ in CSF — pg/ml	323.8 (86.2 to 561.5)	726.6 (489.4 to 963.9)	402.8 (307.7 to 497.8)	<0.001

* The methods used to analyze between-group differences in outcomes from baseline to week 80 were the same as those used in EXPEDITION 1. Measurements of $A\beta$ in the CSF were available at baseline and follow-up for 32 patients in the placebo group and 44 patients in the solanezumab group.

† The original primary outcomes were the changes from baseline to week 80 in scores on the ADAS-cog11 and the ADCS-ADL scale. After analysis of data from EXPEDITION 1, the primary outcome for EXPEDITION 2 was revised to the change in scores on the ADAS-cog14 in patients with mild Alzheimer's disease.

Questions:

1) Quels sont les éléments qui caractérisent la maladie d'Alzheimer et/ou les éléments qui sont associés à la maladie d'Alzheimer (cf. 1ères phrases masquées de l' »Abstract » et de l' »Introduction » ?

2) Quels sont l'adverbe et le terme correspondant aux 2 zones suivantes masquées de l' »Abstract » ?

3) Indiquer en quoi peut consister l'échelle ADAS-cog14 (cf. dernier paragraphe de la Page 2) et l'intérêt de cette échelle pour cette étude ?

4) Justifier le fait que ces deux essais (EXPEDITION 1 et EXPEDITION 2) ai été l'un et l'autre réalisés en double aveugle ?

5) Commenter le choix du placebo pour le groupe contrôle.

6) Quelle est la localisation des oedemes et hémorragies évoquées à la fin de l' « Abstract » ?

7) Justifier le schéma d'administration du solanezumab (cf. haut de la Page 2).

8) Justifier le fait que certains médicaments associés étaient autorisés (cf. haut de la Page 2). Néanmoins, quelles conditions étaient sans doute requises concernant ces traitements associés dans le protocole ?

9) Compléter les 3 groupes de termes masqués du paragraphe « Biologic markers » (Page 3).

10) Justifier le fait que la répartition des origines ethniques des patients inclus soit détaillée dans le Tableau 1. Le recueil de cette information est il aussi facile à réaliser dans tous les Pays ?

11) Pensez vous que l'analyse primaire d'efficacité « primary efficacy analysis » a été réalisée en intention de traiter ou uniquement pour les patients ayant reçu l'ensemble du traitement ? Quel est, néanmoins, l'intérêt de réaliser les deux analyses ?

12) Ces résultats signifient-ils un arrêt du développement du solanezumab ou, au contraire, peuvent-ils justifier la réalisation d'un (ou plusieurs) essai(s) clinique(s) cela dans une perspective d'enregistrement ?