Current Issue in Management of Dementia

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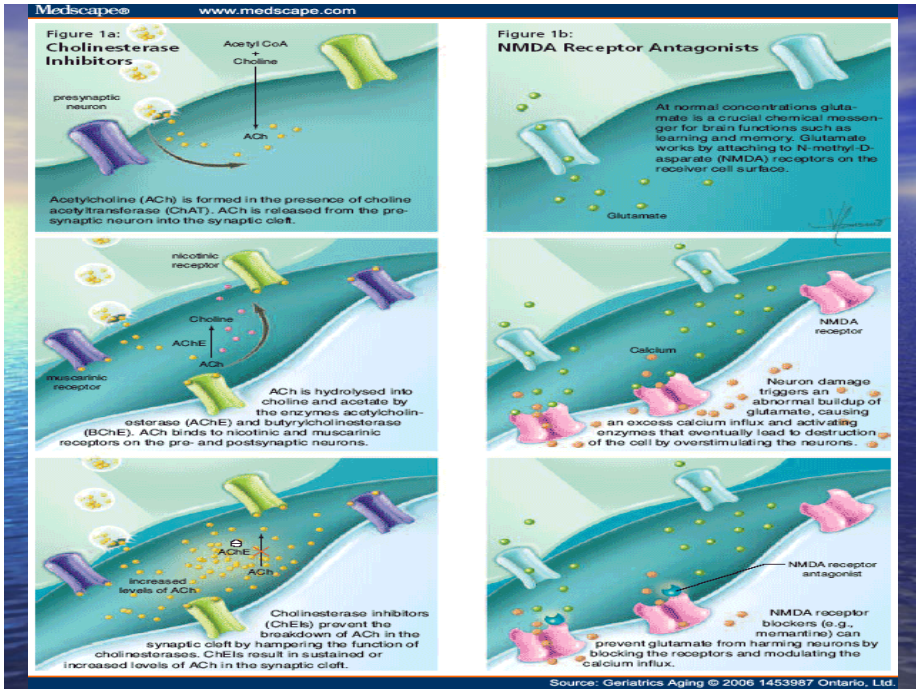


Outlines

- Current medications use in dementia management in Thailand.
- Medications that soon to be used in Thailand.
- Medications and treatment which are in the developing process.

Cholinesterase Inhibitors

- Donepezil
- Rivastigmine
- Galantamine

Table 1. Pharmacological characteristics of cholinesterase inhibitors.

Drug	Mechanism of action	Half-life	Protein-binding capacity	Metabolism
Donepezil	Selective reversible noncompetitive inhibitor of AChE*	58–90 hours	96%	CYP 2D6, CYP 3A4‡
Rivastigmine	Pseudo-irreversible inhibitor of AChE and BChE†	2 hours	40%	Non-hepatic, metabolized by AChE and BChE
Galantamine	Reversible inhibitor of AChE, presynaptic modulator of nicotinic AChE	5–7 hours	18%	CYP 2D6, CYP 3A4

*AChE = acetylcholinesterase
†BChE = butyrylcholinesterase
‡CYP = cytochrome P-450
Adapted from Hsiung GYR, Loy-English I[7]

Donepezil

- Dosage : 5 mg/day for at least 4 weeks then increase to 10 mg/day
- FDA Approved for mild-moderate-severe stage of dementia, Alzheimer type
- Adverse effects: GI symptoms (nausea/ vomitting/diarrhea), bradycardia, vivid dream

TABLE I

Characteristics and Properties of Acetylcholinesterase Inhibitors[a]

Drug Name	Starting Dose	Maintenance Dose	Serum Half-life	Taken with Food?	Tips for Use
Donepezil	5 mg	10 mg 23-mg once-daily tablet after patients are stable on a dose of 10 mg daily for 6 months	70 hours	No	Take in the morning or with lunch to lessen dreams/nightmares
Rivastigmine pill	1.5 mg bid	6 mg bid	2-8 hours	Yes	Must be swallowed whole—do not crush
Rivastigmine patch	4.6 mg/24 hours	9.5 mg/24 hours	N/A	N/A	
Galantamine	4 mg bid or 8 mg ER daily	12 mg bid or 24 mg ER daily	6-8 hours	Yes	Drink with plenty of water; may cause dizziness

Abbreviations: bid, twice a day; ER, extended release; N/A, not applicable.
[a] Contains information from reference 13.

Rivastigmine

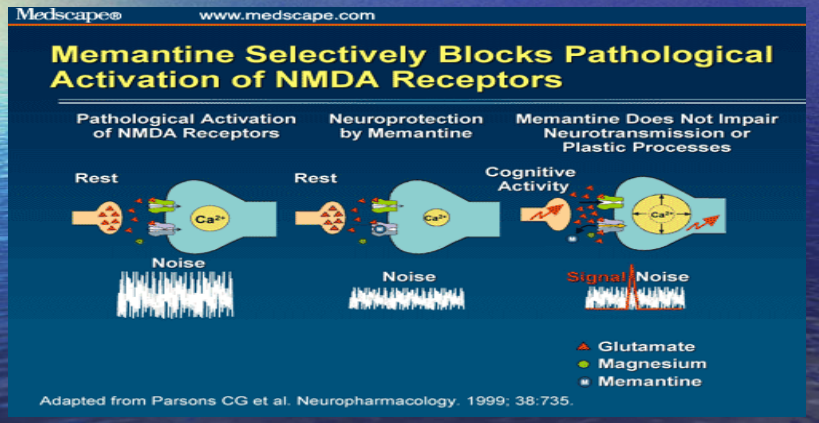
- Dosage: pill : 1.5 mg bid then increase every 2-4 weeks till reach the dose of 6 mg bid
  : patch : 4.6mg(5mg)/24hrs for 1 month then increase to 9.5mg(10mg)/24 hours
- FDA approved for mild-moderate stage of dementia, Alzheimer type and mild to moderate dementia related with Parkinson's disease
- Adverse effects: nausea, vomitting, rash

Galantamine

- Dosage: IR: 4 mg bid for 4 weeks then increase to 8 mg bid for 4 weeks then increase to 12 mg bid
  : ER: 8 mg/d for 4 weeks then increase to 16 mg/d for 4 weeks then increase to 24 mg/d
- FDA approved for mild-moderate stage of dementia, alzheimer type. Also have several studies on mild-moderate vascular dementia.

NMDA Antagonist

- Memantine



Galantamine

- Adverse effects : GI side effects, bradycardia, syncope

Memantine

- Dosage: 5 mg/d for 1 week, then 5 mg bid for 1 week, then 10 mg ac-5 mg pc, then increase to 10 mg bid
- FDA approved for moderate to severe stage of Alzheimer's disease.
- Adverse effects: confusion, dizziness, drowsiness, headache, insomnia, agitation, hallucination

Combination Rx for mod-severe stage of dementia

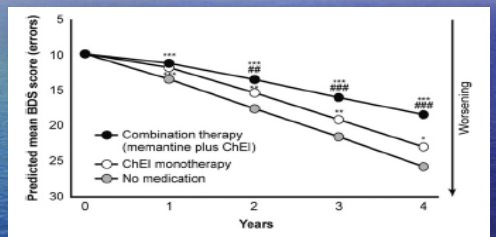


Fig. 1. Model for prediction of rate of decline in cognitive ability (Blessed Dementia Scale) in memory clinic patients receiving treatment for AD. *P* values are of difference in Cohen *d* effect size estimates at each time point: $^{*}P < .05$ versus no medication; $^{**}P < .01$ versus no medication; $^{***}P < .001$ versus no medication; $^{\#\#}P < .01$ versus ChEI monotherapy; $^{\#\#\#}P < .001$ versus ChEI monotherapy. Reproduced with permission from Atri A, Shaughnessy LW, Locascio JJ, Growdon JH. Long-term course and effectiveness of combination therapy in Alzheimer's disease. Alzheimer Dis Assoc Disord 2008;22:209–21.

Domino study, NEJM, 2012

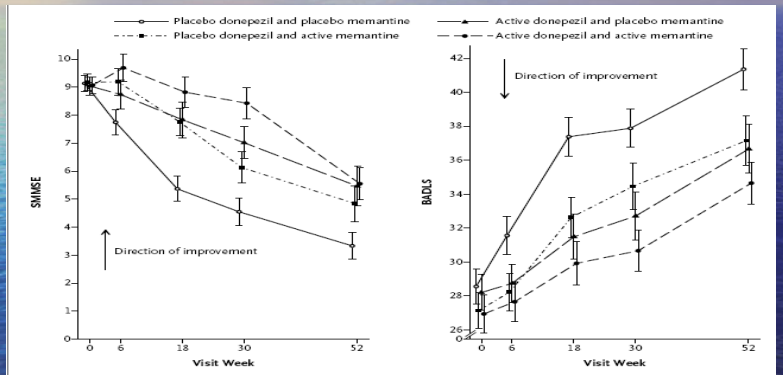


Figure 3. Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group.
Scores on the SMMSE range from 0 to 30, with higher scores indicating better cognitive function; scores on the BADLS range from 0 to 60, with higher scores indicating greater impairment. Shown are raw estimates of the mean score at each visit. I bars denote the standard error.

Combination Rx for mod-severe stage of dementia

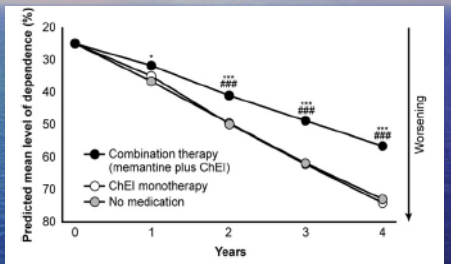


Fig. 2. Model for prediction of rate of decline in functional ability (Weintraub Activities of Daily Living Scale) in memory clinic patients receiving treatment for AD. *P* values are of difference in Cohen *d* effect size estimates at each time point: $^{*}P < .05$ versus no medication; $^{***}P < .001$ versus no medication; $^{\#\#\#}P < .001$ versus ChEI monotherapy. Reproduced with permission from Atri A, Shaughnessy LW, Locascio JJ, Growdon JH. Long-term course and effectiveness of combination therapy in Alzheimer's disease. Alzheimer Dis Assoc Disord 2008;22:209–21.

In-coming medications

- Donepezil 23 mg
- Memantine ER
- Medical food : Axona

Donepezil 23 mg

- Patient should be on donepezil 10 mg for at least 3 months.
- Adverse efffects : more GI effects compared to donepezil 10 mg, bradycardia, fainting, weight loss, seizure

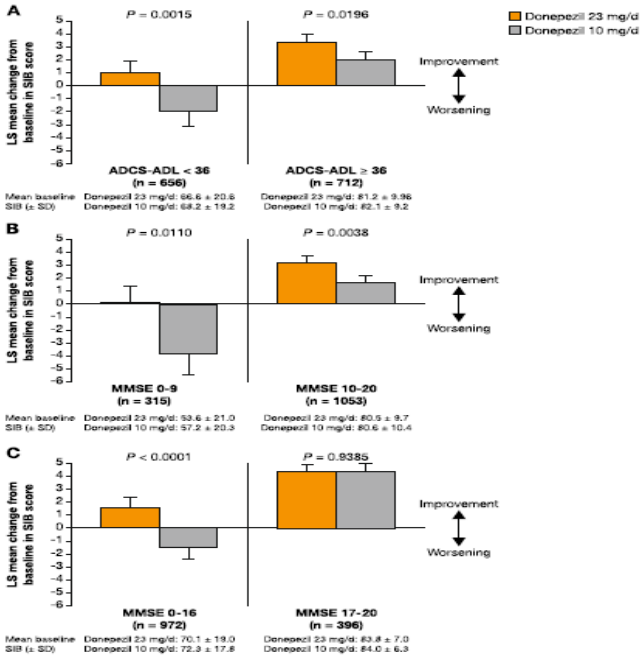


Figure 1 Effect of disease characteristics on the efficacy of donepezil 23 mg/d or 10 mg/d measured by LS mean change in SIB score from baseline to Week 24. **A**, Functional level. **B**, Severity, MMSE 0–9 or 10–20. **C**, Severity, MMSE 0–16 or 17–20.

Table 1 Demographics and baseline characteristics of the intent-to-treat population

Characteristic	Donepezil 23 mg/d	Donepezil 10 mg/d
Age, years		
Number of patients	909	462
Mean (± SD)	73.8 (8.48)	73.8 (8.55)
Median	75.0	75.0
Range	47–89	49–90
Gender		
Number of patients	909	462
Males, n (%)	335 (36.9)	175 (37.9)
Females, n (%)	574 (63.1)	287 (62.1)
Weight, kg		
Number of patients	908	462
Mean (± SD)	66.7 (14.8)	66.2 (14.4)
Median	65.5	64.5
MMSE		
Number of patients	908	462
Mean (± SD)	13.1 (4.99)	13.1 (4.72)
Median	14.0	14.0
ADCS-ADL-sev		
Number of patients	908	461
Mean (± SD)	34.1 (10.88)	34.5 (11.19)
Median	36.0	36.0
SIB		
Number of patients	907	462
Mean (± SD)	74.2 (17.58)	75.6 (16.28)
Median	81.0	82.0
CIBIS-plus		
Number of patients	904	461
Mean (± SD)	4.42 (0.85)	4.38 (0.89)
Median	4.0	4.0
Duration of prestudy donepezil 10 mg/d, weeks		
Number of patients	909	462
Mean (±SD)	113.4 (108.4)	104.9 (99.2)
Median	71.9	66.3

MMSE = Mini-Mental State Examination; ADCS-ADL-sev = Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory, severe version; SIB = Severe Impairment Battery; CIBIS-plus = Clinician's Interview-Based Impression of Severity plus caregiver input; SD = standard deviation.

Memantine ER 28 mg

- Dosage: start at 7 mg/day and increase weekly in 7 mg increment until reach the dose of 28 mg/day.

  If a patient is switching from 10 mg twice daily conventional memantine to memantine ER, the patient may transition to the 28-mg dose of memantine ER immediately instead of following the titration schedule.

Adverse effects: headache, somnolence, dizziness

- International,multicenter, randomized, double-blind, placebo-controlled,parallel-group design study of 24 weeks' duration included 667 participants who were at least 50 years of age with a diagnosis of probable Alzheimer's disease with MMSE 3-12.
- 342 patients were randomized to receive memantine ER 28 mg and ChEI; and 335 patients were randomized to receive placebo and ChEI.

Medical food : Axona

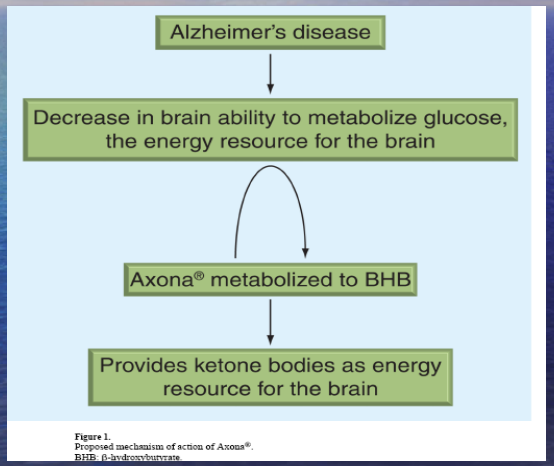


Figure 1.
Proposed mechanism of action of Axona®.
BHB: β-hydroxybutyrate.

- At week 24, patients treated with memantine ER 28 mg/ChEI showed a statistically significant improvement (LOCF) over the placebo/ChEI group on both the SIB (p = 0.001) and CIBIC-plus (p = 0.008).
- Patients treated with memantine ER 28 mg/ChEI also showed statistically significant benefits at the end of the study versus the placebo/ChEI group on outcomes of behavior as measured by the NPI (p = 0.005), and on the verbal fluency test (p = 0.004) compared with patients who were receiving placebo/ChEI.

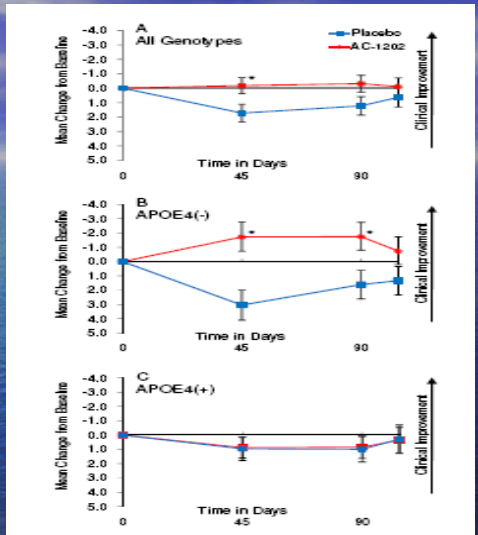


Figure 2
Mean change in ADAS-Cog scores from Baseline in the ITT population w/LOCF and stratified by APOE4 carriage status. Y axis is change from Baseline. X axis is time in days. Red circles and lines represent subjects taking AC-1202. Blue squares and lines represent subjects taking Placebo. Error bars represent standard error of the mean.

Medications and treatment which are in the developing process

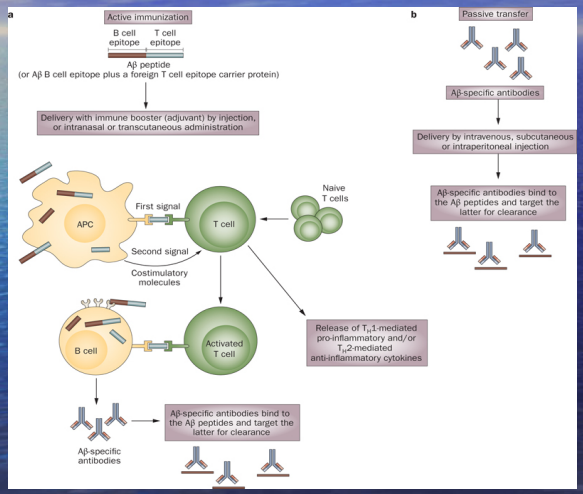
- Active Immunotherapy: vaccine
- Passive Imunotherapy: monoclonal Ab, IVIG
- Others: Gamma Secretase Inhibition, Metal-protein interaction attenuation, statins, DM drugs, drugs that target tau protein, eternacept, drugs that stimulate cholinergic receptors (M1 receptor agonist, nicotinic receptor agonist) etc.

As of 2012, >300 clinical trials under way to understand and treat AD and 30 of these were in human phase III trials.

Active Immunotherapy

- First vaccine, AN-1792,in 20002, had to be terminated due to meningoncephalitis.
- ACC-001, a modified version of AN-1792 is in phase II study.
- Others: CAD-106, ACI-24,UB-31,V950, affitopes AD-01/AD-02 are in early developing phase.

Immunotherapy



Passive Immunotherapy

- Monoclonal Ab: bapineuzumab, solanezumab, gantenerumab, etc.
- Intravenous Immunoglobulin (IVIG)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

ABSTRACT

BACKGROUND

Bapineuzumab, a humanized anti–amyloid-beta monoclonal antibody, is in clinical development for the treatment of Alzheimer's disease.

METHODS

We conducted two double-blind, randomized, placebo-controlled, phase 3 trials involving patients with mild-to-moderate Alzheimer's disease — one involving 1121 carriers of the apolipoprotein E (*APOE*) ε4 allele and the other involving 1331 noncarriers. Bapineuzumab or placebo, with doses varying by study, was administered by intravenous infusion every 13 weeks for 78 weeks. The primary outcome measures were scores on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11, with scores ranging from 0 to 70 and higher scores indicating greater impairment) and the Disability Assessment for Dementia (DAD, with scores ranging from 0 to 100 and higher scores indicating less impairment). A total of 1090 carriers and 1114 noncarriers were included in the efficacy analysis. Secondary outcome measures included findings on positron-emission tomographic amyloid imaging with the use of Pittsburgh compound B (PiB-PET) and cerebrospinal fluid phosphorylated tau (phospho-tau) concentrations.

RESULTS

There were no significant between-group differences in the primary outcomes. At week 78, the between-group differences in the change from baseline in the ADAS-cog11 and DAD scores (bapineuzumab group minus placebo group) were −0.2 (P= 0.80) and −1.2 (P= 0.24), respectively, in the carrier study; the corresponding differences in the noncarrier study were −0.3 (P= 0.64) and 2.8 (P= 0.07) with the 0.5-mg-per-kilogram dose of bapineuzumab and 0.4 (P= 0.62) and 0.9 (P= 0.55) with the 1.0-mg-per-kilogram dose. The major safety finding was amyloid-related imaging abnormalities with edema among patients receiving bapineuzumab, which increased with bapineuzumab dose and *APOE* ε4 allele number and which led to discontinuation of the 2.0-mg-per-kilogram dose. Between-group differences were observed with respect to PiB-PET and cerebrospinal fluid phospho-tau concentrations in *APOE* ε4 allele carriers but not in noncarriers.

CONCLUSIONS

Bapineuzumab did not improve clinical outcomes in patients with Alzheimer's disease, despite treatment differences in biomarkers observed in *APOE* ε4 carriers. (Funded by Janssen Alzheimer Immunotherapy and Pfizer; Bapineuzumab 301 and 302 ClinicalTrials.gov numbers, NCT00575055 and NCT00574132, and EudraCT number, 2009-012748-17.)

Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial

Richard Dodel, Axel Rominger, Peter Bartenstein, Frederik Barkhof, Kaj Blennow, Stefan Förster, Yaroslav Winter, Jan-Philipp Bach, Julius Popp, Judith Alferink, Jens Wiltfang, Katharina Buerger, Markus Otto, Piero Antuono, Michael Jacoby, Ralph Richter, James Stevens, Isaac Melamed, Jerome Goldstein, Stefan Haag, Stefan Wietek, Martin Farlow, Frank Jessen

	Intravenous immunoglobulin (n=21)			Placebo (n=7)	Placebo vs intravenous immunoglobulin (difference; 95% CI)		
	0·2 g/kg (n=6)	0·5 g/kg (n=8)	0·8 g/kg (n=7)		0·2 g/kg	0·5 g/kg	0·8 g/kg
$A\beta_{1-40}$ concentration (×10⁻³g/L)							
CSF*	561·7 (1195·5; n=6)	403·9 (588·1; n=8)	642·2 (1171·3; n=6)	42·0 (874·0; n=6)	−519·7 (−1866·7 to 827·4; p=0·4102)	−361·9 (−1210·4 to 486·6; p=0·3711)	−600·2 (−1929·5 to 729·2; p=0·3382)
Plasma	−20·3 (29·2; n=6)	15·7 (29·7; n=8)	−30·5 (42·3; n=6)	−6·0 (23·8; n=6)	14·3 (−19·9 to 48·6; p=0·3729)	−21·7 (−55·0 to 11·6; p=0·1788)	24·5 (−19·7 to 68·7; p=0·2446)
$A\beta_{1-42}$ concentration (×10⁻³g/L)							
CSF*	18·8 (40·3; n=6)	10·5 (40·9; n=8)	24·7 (43·2; n=6)	−5·2 (36·3; n=6)	−24·0 (−73·3 to 25·3; p=0·3037)	−15·7 (−61·6 to 30·3; p=0·4718)	−29·8 (−81·1 to 21·4; p=0·2239)
Plasma	−3·5 (5·8; n=6)	−0·1 (4·4; n=8)	−7·0 (6·2; n=6)	−2·0 (4·8; n=6)	1·5 (−5·3 to 8·3; p=0·6349)	−1·9 (−7·2 to 3·5; p=0·4606)	5·0 (−2·2 to 12·2; p=0·1509)
Anti-Aβ autoantibody concentration							
CSF* (relative units)	0·4 (1·4; n=6)	1·1 (1·5; n=8)	0·7 (2·3; n=6)	0·1 (0·3; n=6)	−0·3 (−1·6 to 1·1; p=0·6881)	−1·0 (−2·3 to 0·4; p=0·1083)	−0·6 (−2·7 to 1·5; p=0·5596)
Plasma (relative units)	96·7 (133·7; n=6)	256·6 (214·1; n=8)	501·3 (514·6; n=6)	−56·3 (58·3; n=6)	−153·0 (−285·6 to −20·4; p=0·0279)	−313·0 (−610·4 to −115·6; p=0·0039)	−557·7 (−1028·8 to −86·6; p=0·0450)
Total tau* (CSF; ×10⁻³g/L)	−141·8 (419·5; n=6)	1·3 (86·7; n=8)	131·3 (301·0; n=6)	−33·2 (69·7; n=6)	108·7 (−278·2 to 495·5; p=0·5575)	−34·4 (−128·6 to 59·8; p=0·4416)	−164·5 (−445·6 to 116·6; p=0·2438)
p-tau$_{181}$* (CSF; ×10⁻³g/L)	3·3 (21·2; n=6)	−2·5 (8·6; n=8)	10·2 (19·3; n=6)	−1·3 (10·1; n=6)	−4·7 (−26·0 to 16·7; p=0·6370)	1·2 (−9·7 to 12·0; p=0·8102)	−11·5 (−31·3 to 8·3; p=0·2243)
Alzheimer's disease assessment scale cognitive subscale score	5·3 (−4·7 to 8·7; n=6)	1·8 (−8·0 to 24·0; n=8)	−1·5 (−4·3 to 18·3; n=6)	0·3 (−3·3 to 5·0; n=5)	−3·8 (−9·3 to 4·0; p=0·2353)	−0·3 (7·0 to 5·7; p=0·8835)	0·8 (−13·3 to 7·3; p=0·6466)
Mini-mental state examination score	−3·0 (−8·0 to 2·0; n=6)	−1·5 (−4·0 to 1·0; n=8)	−1·5 (−7·0 to 2·0; n=6)	−1·5 (−11·0 to 4·0; n=6)	2·0 (−6·0 to 7·0; p=0·5725)	0·5 (−5·0 to 5·0; p=0·8453)	0·0 (−6·0 to 5·0; p=1·0000)
Clinical dementia rating—sum of boxes	0·5 (−1·0 to 3·0; n=6)	0·0 (−1·0 to 5·0; n=8)	0·3 (−1·5 to 3·0; n=6)	−0·5 (−6·0 to 0·0; n=5)	−1·5 (−6·5 to 0·0; p=0·0641)	−0·5 (−6·0 to 0·0; p=0·1879)	−1·3 (−5·5 to 0·5; p=0·1961)
Alzheimer's Disease Cooperative Study—activities of daily living inventory score	−3·0 (−31·0 to 11·0; n=6)	0·0 (−15·0 to 11·0; n=8)	−1·5 (−5·0 to 3·0; n=6)	−3·0 (−8·0 to 7·0; n=5)	−19·0 (−13·0 to −25·0; p=0·9273)	−4·5 (−14·0 to 7·0; p=0·3387)	−1·5 (−8·0 to 6·0; p=0·7144)
Normalised whole brain volume (cm³)	−1·4 (1·8; n=6)	−1·1 (1·0; n=8)	−1·6 (1·1; n=6)	−0·9 (0·8; n=4)	0·5 (−1·7 to 2·7; p=0·6196)	0·2 (−1·1 to 1·5; p=0·7794)	0·7 (−0·7 to 2·2; p=0·2851)
Left hippocampus volume (mm³)	−191·2 (111·7; n=6)	−188·4 (228·2; n=8)	−153·5 (91·2; n=6)	−137·0 (114·8; n=5)	54·2 (−100·8 to 209·1; p=0·4494)	51·4 (−193·0 to 295·7; p=0·6526)	16·5 (−123·7 to 156·7; p=0·7961)
Right hippocampus volume (mm³)	−140·8 (60·3; n=6)	−193·1 (137·7; n=8)	−230·5 (165·8; n=6)	−132·4 (122·1; n=5)	8·4 (−118·9 to 135·8; p=0·8842)	60·7 (−105·2 to 226·6; p=0·4375)	98·1 (−104·6 to 300·8; p=0·3021)

Data for treatment groups are mean (SD) or median (range). Change is from baseline to week 22 ± 1 day unless stated otherwise. Differences between treatment groups were assessed by t test (two-sided, α=0·05) for biomarkers and MRI results and by calculating Hodges-Lehmann estimates and non-parametric 95% CIs, compared with Wilcoxon rank sum test (normal approximation, two-sided, α=0·05) for the cognitive and functional scales. Aβ=amyloid β. *At the seventh visit (last infusion at week 20 + 1 day).

Table 4: Mean change from baseline in the intention-to-treat population (4-week dosing interval)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

ABSTRACT

BACKGROUND

Alzheimer's disease is characterized by amyloid-beta plaques, neurofibrillary tangles, gliosis, and neuronal loss. 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 randomly 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 primary outcomes 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.

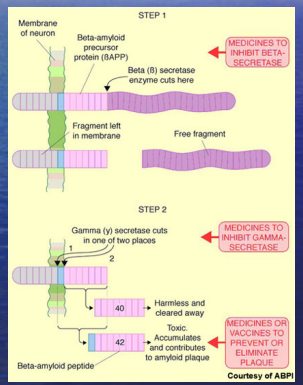
RESULTS

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.)

Gamma Secretase Inhibitor



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Phase 3 Trial of Semagacestat for Treatment of Alzheimer's Disease

ABSTRACT

BACKGROUND

Alzheimer's disease is characterized by the presence of cortical amyloid-beta (Aβ) protein plaques, which result from the sequential action of β-secretase and γ-secretase on amyloid precursor protein. Semagacestat is a small-molecule γ-secretase inhibitor that was developed as a potential treatment for Alzheimer's disease.

METHODS

We conducted a double-blind, placebo-controlled trial in which 1537 patients with probable Alzheimer's disease underwent randomization to receive 100 mg of semagacestat, 140 mg of semagacestat, or placebo daily. Changes in cognition from baseline to week 76 were assessed with the use of the cognitive subscale of the Alzheimer's Disease Assessment Scale for cognition (ADAS-cog), on which scores range from 0 to 70 and higher scores indicate greater cognitive impairment, and changes in functioning were assessed with the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) scale, on which scores range from 0 to 78 and higher scores indicate better functioning. A mixed-model repeated-measures analysis was used.

RESULTS

The trial was terminated before completion on the basis of a recommendation by the data and safety monitoring board. At termination, there were 189 patients in the group receiving placebo, 153 patients in the group receiving 100 mg of semagacestat, and 121 patients in the group receiving 140 mg of semagacestat. The ADAS-cog scores worsened in all three groups (mean change, 6.4 points in the placebo group, 7.5 points in the group receiving 100 mg of the study drug, and 7.8 points in the group receiving 140 mg; P=0.15 and P=0.07, respectively, for the comparison with placebo). The ADCS-ADL scores also worsened in all groups (mean change at week 76, −9.0 points in the placebo group, −10.5 points in the 100-mg group, and −12.6 points in the 140-mg group; P=0.14 and P<0.001, respectively, for the comparison with placebo). Patients treated with semagacestat lost more weight and had more skin cancers and infections, treatment discontinuations due to adverse events, and serious adverse events (P<0.001 for all comparisons with placebo). Laboratory abnormalities included reduced levels of lymphocytes, T cells, immunoglobulins, albumin, total protein, and uric acid and elevated levels of eosinophils, monocytes, and cholesterol; the urine pH was also elevated.

CONCLUSIONS

As compared with placebo, semagacestat did not improve cognitive status, and patients receiving the higher dose had significant worsening of functional ability. Semagacestat was associated with more adverse events, including skin cancers and infections. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT00594568.)

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Tau Aggregation Inhibitor(TAI)

- methylthioninium chloride, MTC, in a large phase 2 study in 321 subjects, was found to stabilize the progression of AD over 50 weeks in both mild and moderate AD.
- A stable, reduced version of methylthioninium (LMTX) has been developed which has better tolerability and absorption than MTC and can be administered orally twice daily.
- LMTX is the active agent in three parallel phase 3 studies in AD and frontotemporal dementia now ongoing in 250 centres in 22 countries world-wide, including 140 centres in the US.

Metal protein attenuation compounds

- Clioquinol/PBT1, PBT2
- PBT1 trial found no benefit on cognition and neurological effects (visual acuity and color blindness) that resolved on cessation of treatment. The planned phase III trial of PBT1 has been abandoned and this compound has been withdrawn from development.
- PBT2 trial showed that after 12 weeks this compound appeared to be safe and well tolerated in people with mild Alzheimer's dementia. This drug has been in a phase II trial.

Take Home Message

Are we on the right track of alzheimer's disease treatment ??