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Poor Safety and Tolerability Hamper Reaching a Potentially Therapeutic Dose in the Use of Thalidomide for Alzheimer's Disease: Results from a Double-Blind, Placebo-Controlled Trial

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Abstract

Introduction—To date there is no cure for Alzheimer's disease (AD). After amyloid beta immunotherapies have failed to meet primary endpoints of slowing cognitive decline in AD subjects, the inhibition of the beta-secretase BACE1 appears as a promising therapeutic approach. Pre-clinical data obtained in APP23 mice suggested that the anti-cancer drug thalidomide decreases brainBACE1 and Aβ levels. This prompted us to develop an NIH-supported Phase IIa clinical trial to test the potential of thalidomide for AD. We hypothesized that thalidomide can decrease or stabilize brain amyloid deposits, which would result in slower cognitive decline in drug- versus placebo-treated subjects.

Methods—This was a 24-week, randomized, double-blind, placebo-controlled, parallel group study with escalating dose regimen of thalidomide with a target dose of 400mg daily in patients with mild to moderate AD. The primary outcome measures were tolerability and cognitive performance assessed by a battery of tests.

Results—A total of 185 subjects have been pre-screened, out of which25 were randomized. Mean age of the sample at baseline was 73.64 (±7.20) years; mean education was 14.24 (±2.3) years; mean MMSE score was 21.00 (±5.32); and mean GDS score was 2.76 (±2.28).Among the 25 participants, 14 (56%) terminated early due to adverse events, dramatically decreasing the power of the study. In addition, those who completed the study (44%) never reached the estimated therapeutic dose of 400 mg/day thalidomide because of reported adverse events. The cognitive data showed no difference between the treated and placebo groups at the end of the trial.

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Conclusion—This study demonstrates AD patients have poor tolerability for thalidomide, and are unable to reach a therapeutic dose felt to be sufficient to have effects on BACE1. Because of poor tolerability, this study failed to demonstrate a beneficial effect on cognition.

Keywords

Adverse events; Alzheimer's Disease; clinical trial; cognitive tests; thalidomide; tolerability

Introduction

Alzheimer's disease (AD) is a severely debilitating progressive neurological disorder which incidence increases as the worldwide population ages [1]. Considering the devastating course of the disease and associated health care costs, there is an urgent need for developing therapeutic approaches that target primary pathologic mechanisms in AD. Continuing research has identified several molecular mechanisms involved in AD, providing hope for the development of novel disease-modifying therapies rather than merely symptomatic treatments. However, the safety and tolerability of each promising therapeutic agent must be scrutinized through clinical trials before planning large scale administration.

The progressive formation of amyloid plaques and vascular deposits consisting of the 4 kDa amyloid β-peptide (Aβ) has long been considered as one of the major pathological hallmark of AD [2-4]. Amyloidogenesis stems from the sequential proteolytic processing of the amyloid precursor protein (APP) by two key enzymatic activities. To produce Aβ, APP must first be cleaved by a beta-secretase, generating C89-99 transmembrane fragments and releasing soluble APPβ; C89-99 are further cleaved by γ-secretase to produce Aβ. Beta amyloid Converting Enzyme 1 (BACE1) was shown to be the primordial beta-secretase involved in AD. Recent discoveries suggest that BACE1 protein levels and activity are increased in sporadic AD brain samples and CSF [5-10]. Thus BACE1 modulation represents a promising therapeutic target for AD and tremendous efforts have been placed in the past 15 years to develop BACE1 inhibitors that can cross the blood brain barrier [11].

Another pathological hallmark of AD is chronic brain inflammation. Particularly, tumor necrosis factor-α (TNF-α) signaling is of primary interest because it regulates many other cytokines and proteins (see the TNF-α review in this special edition). One clinical study suggests that the TNF fusion protein antagonist Etanercept was beneficial to one AD patient [12]. However, Etanercept is a molecule of a large size unable to cross the brain blood barrier (BBB), thus requiring peri-cervical injections, which carry potential risks for patients. In addition, several lines of evidence indicate that TNF-α signaling exacerbates amyloidogenesis, including up-regulation of BACE1 expression (see the TNF-α review paper in this Special Edition). Thalidomide is a very potent TNF-α inhibitor and immunomodulator used in the treatment of oncologic [13, 14], cardiovascular [15], dermatologic [16], and neurodegenerative [17] conditions. This prompted us to test the potential of thalidomide on APP23 mice, a transgenic model of AD, which resulted in a significant reduction of Aβ production (unpublished data). Given the preclinical and clinical evidence that TNF-α inhibition might be beneficial for AD, we hypothesized that thalidomide might be able to reduce CNS inflammation and amyloidogenesis in AD

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subjects, which would translate into better cognitive outcomes in patients after several months of treatment. However, thalidomide is notorious for inducing adverse events in oncologic populations [18], thus safety and tolerability must be assessed first in AD patients.

In the present study, our primary objective was to evaluate the safety and tolerability of thalidomide administered for 24 weeks to patients with mild to moderate dementia of the Alzheimer's type. The secondary objective was to determine the effects of thalidomide treatment on cognitive functions in AD patients.

Methods

Study Design

The study was an NIH-supported (ClinicalTrials.gov ID #NCT01094340) 24-week, randomized, double-blind, placebo-controlled, parallel group study of the effect of escalating dose regimens of thalidomide and placebo on safety and tolerability, as well as cognitive outcome measures, in patients with mild to moderate AD. The study was conducted at a single site. The protocol was approved by a central Institutional Review Board/Ethics Board and written informed consent was obtained for all patients before enrollment in this clinical trial. If the patient had a legally authorized representative (LAR), the LAR reviewed and signed the informed consent (IC) form. If the patient did not have a LAR, the patient himself or herself was able to provide informed consent as well as review and sign the informed consent form. In addition, each patient informant (as defined above) signed the informed consent form. If the LAR and the patient's informant was the same individual, he/she signed under both designations. Participants resided in the community and supervision was available for the administration of all study medication.

This was a double-blinded study with both the investigators and research participants being blinded. All samples were coded. Investigators were not aware of group assignment until all biomarkers have been measured and recorded in a double blind manner. All other study personnel were blinded. Patients were randomized to one of two groups. Group 1 received the drug thalidomide and Group 2 received placebo. Subjects were assigned by the unblinded pharmacist with a ratio of 2:1 (drug:placebo). Patients received escalating dose regimens of thalidomide (50-400 mg/day; provided by Celgene Corp.) or placebo. The maximum dose of 400 mg/day was determined based on oncological studies [19] and tests conducted on APP23 mice (unpublished data).

Subjects and Inclusion Criteria

Patients were recruited in the local Community which is very supportive of clinical trials. To be considered eligible for enrollment they had to meet the following requirements: male or female outpatients who were at least 50 years of age. Females were surgically or post-menopausal for at least two years. Participants had a diagnosis of probable AD for at least one year prior based on the NINCDS-ADRDA criteria, and the severity of AD was mild to moderate with a documented Mini Mental State Exam (MMSE) score between 12-26 at both the screening and baseline visits (visits 1 and 2). The CT or MRI scan of the brain obtained during the course of the dementia was consistent with the diagnosis and showed no evidence

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of significant focal lesions or of pathology which could contribute to dementia. If neither a CT nor an MRI scan were available, a CT scan fulfilling the requirements was obtained before randomization. Patient vision and hearing were sufficient to comply with study procedures and all were able to take oral medications. Patient's Hachinski scores were ≤ 4 and each participant scored ≤ 10 on the Geriatric Depression Scale. For inclusion in this study, participants had received a cholinesterase inhibitor and/or memantine for at least 4 months and were maintained on a stable dose for at least two months prior to randomization. They continued on a stable dose for the remainder of the study period, unless they demonstrated an intolerance to or lack of efficacy from these medications. Each participant had an adult informant who had significant direct contact with them at least three days per week, was willing to accompany them to all clinic visits, and was present during all phone visits.

Exclusion Criteria

Subjects were excluded from this study if there was current evidence or history within the last three years of a neurological or psychiatric illness that could contribute to dementia, including (but not limited to) epilepsy, focal brain lesion, Parkinson's disease, seizure disorder, head injury with loss of consciousness, DSM IV criteria for any major psychiatric disorder including psychosis, major depression and bipolar disorder, and alcohol or substance abuse. In addition, potential participants were excluded if they lived alone or had any of the following conditions: poorly controlled hypertension; a history of myocardial infarction or signs or symptoms of unstable coronary artery disease within the last year (including revascularization procedure/angioplasty); severe pulmonary disease (including chronic obstructive pulmonary disease) requiring more than two hospitalizations within the past year, a requirement for home oxygen use or sleep apnea; any thyroid disease (unless euthyroid on treatment for at least 6 months); active neoplastic disease (except for skin tumors other than melanoma); a history of multiple myeloma; an absolute neutropenia down to750/mm^3 (normal range: 1,500-8,000/mm3); a history of neutropenia; a history of or current thromboembolism (including deep venous thrombosis); or any clinically significant hepatic or renal disease (including presence of Hepatitis B or C antigen/antibody or an elevated transaminase levels of greater than two times the upper limit of normal (ULN) or creatinine greater than 1.5 × ULN). Patients with stable prostate cancer were able to be included at the discretion of the Medical Monitor. To be enrolled in this trial, patients did not have any clinically significant hematologic or coagulation disorder including any unexplained anemia or a platelet counts less than 100,000/mL at screening. Individuals on an investigational drug within 30days or within five half-lives of the investigational agent, whichever was longer, were excluded from this study. Participation required that there wasn't use of an investigational medical device within two weeks before or after the study. Females who were either pregnant or of child bearing age were excluded. Other diseases or conditions that, in the opinion of the Investigators, made the patient unsuitable to participate in this clinical trial (including inability to undergo a lumbar puncture for any reason) were also excluded.

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Cognitive Tests

Cognitive functions in AD patients were assessed through administration of the following tests before treatment, at baseline and at the end of treatment: The Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog);Clinical Dementia Rating Scale- Sum of boxes (CDR-SOB); Mini Mental State Examination (MMSE); Neuropsychiatric Inventory (NPI) and Alzheimer's Disease Collaborative Study-Activities of Daily Living (ADCS-ADL).

Screening Visit (Day -14: Visit 1)

After providing informed consent, subjects underwent evaluations within 14 days of randomization. These evaluations included a SNAP test, vital signs and body weight, MMSE, blood and urine samples, full medical history, 12-lead ECG, a full physical examination, neurological examination and concomitant medications, and an assessment of inclusion/exclusion criteria. After examinations were completed (physical exams, CBC, CMP, Hep B and Hep C assessments and urinalyses) and a CT scan or MRI were not found to be significant, subjects were randomized. Complete physical examinations (with neurological exam) were performed at the Screening Visit and at Visit 8 or end of study visit, including Early-Termination visit (see below). An abbreviated physical examination was also performed at visits 3-7, which included an ophthalmic (routine fundoscopic) examination and routine examination of the heart, lungs, abdomen, skin, and oral cavity.

Baseline Visit (Day 1, Visit 2)

Baseline evaluations were performed on subjects randomized into the study. These evaluations included: assessment of concomitant therapy and inclusion/exclusion criteria, vital signs and bodyweight, blood samples, lumbar puncture to draw CSF, and cognitive assessments. In addition the ADAS-Cog, ADCS-ADL, FAQ, NPI and CDR Sum-of-Boxes were administered. At end of the visit, subjects were given a sufficient supply of study medication to last until Visit 3 (two weeks later) along with instructions for use. Patients were instructed to take their first dose of study medication on day of Visit 2. Each patient was also instructed to take their medication every evening thereafter at or around the same time of day.

Treatment Visits (Visits 3,4,5,6, 7, 8 and 9; Phone Visits at Weeks 11 and 17)

On Visits 3-7, several assessments were completed: assessment of concomitant therapy, brief physical and neurological examination, vital signs and body weight, blood samples collection, and CBC and CMP, urinalysis, medication compliance (pill count) and an assessment for any adverse events. Prior to leaving the clinic, subjects continuing in the study were given a sufficient supply of study medication to last until the next visit. Subjects were instructed to take their medication prior to bedtime. Subjects were informed that they could split their study medication and take half at dinner time and half at bedtime. Only the Principal Investigator (PI) or a Sub-Investigator (Sub-I), who have completed the S.T.E.P.S. training dispensed the study drug and educated the subject/study partner on the handling of study drug. If any worsening or new events were documented, the site asked subjects to come to the clinic for an unscheduled visit to assess the event.

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Withdrawal of Individual Subjects Prior to Study Completion

After randomization and administration of the first dose of study drug on Day 1 of the first treatment period, subjects were withdrawn from the study prior to completion for using any investigational drug (other than the study drug), participation in any other clinical trial, using any drug listed in excluded drug list, development of adverse events, development of an ALT, AST, or LDH more than 2.5 × the upper limit of the laboratory reference range for two consecutive visits confirmed with a repeat assessment within 48 hours of the second abnormal reading. Total bilirubin >2 mg/dL (repeated within 48 hours) that, in the opinion of the Investigator, was thought to be probably related or related to study drug was consideration of study withdrawal. Development of neutropenia or of any other abnormal laboratory value that, in the opinion of the investigator, was clinically significant and thought to be probably related or related to study drug was cause for early termination. Other causes for withdrawal were pregnancy, the subject did not consent to participate for any reason, and non-compliance such as missing >20% of study medication (must be ≥80%). Additional follow-up of any ongoing adverse event (including any clinically significant laboratory abnormality) was conducted at appropriate intervals, as determined by the Investigator, until the condition was deemed not clinically meaningful or there was a return to baseline. If a patient discontinued (dropped out or withdrawn after randomization) from this trial, the patient was not replaced. If a subject withdrew from the study early, the subject was asked to continue to taking study drug (if safe to do so) until the Termination Visit.

Premature End-of-Trial/Final Visit prior to Day 168 (Visit 8)

If a study subject withdrew from the trial before Day 168, all of the End-of-Trial evaluations were completed as soon as possible after the last dose of study medication was given. The same evaluations as the baseline visit were performed with the addition of an assessment for any adverse events, and a pill count for medication compliance.

Premature End-of-Trial/Final Visit After Day 168

Participants who withdrew from the study after Day 168 were asked to return four weeks following the premature-end-of-trial/final visit to complete evaluations, including concomitant therapy assessment, physical and neurological exams, vital sign monitoring, blood and urine sample acquisition, SNAP test and an assessment of any adverse events.

Lumbar Puncture (LP)

Some participants volunteered to undergo lumbar puncture at Visit 1 and at termination. Fifteen cubic centimeters of cerebral spinal fluid (CSF) was collected each time. A post lumbar puncture telephone check was completed the day after. CSF was used for biomarker evaluation (study in progress which will be reported later).

Blood Collection

Collection of 10 mL of whole blood in tubes containing ethylenediaminetetraacetic acid (EDTA) was done for each participant at each visit. Like for CSF, blood was processed to investigate some biomarkers (study in progress which will be reported later).

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Statistical Analysis

Statistical analyses were performed using PROC GLIMMIX in SAS. Descriptive statistics were utilized to characterize study sample. A general linear model suitable for small sample with repeated measures was utilized for the primary analyses. Differences between proportions were tested with the χ^2 test or Fisher's Exact Test as indicated. A $p<0.05$ was considered statistically significant.

Results

Subject Enrollment

The primary objective of this study was to evaluate the safety and tolerability of thalidomide administered in an escalating dose regimen for 24 weeks to patients with mild to moderate dementia of the Alzheimer's disease type (ClinicalTrials.gov ID #NCT01094340). A total of 185 subjects from the local Community were contacted by phone. Over 120 subjects refused participation because of thalidomide stigma or reluctance to undergo lumbar puncture. Among the 65 subjects pre-screened at the study site, 40 were not selected because they met one or several exclusion criteria (see Methods). Therefore, 25 individuals were recruited for randomization.

Demographics and Baseline Statistics

The demographics and baseline statistics are summarized in Table 1. Of the 25 study participants in our sample population, the majority were male (n=16; 64%). The proportion of males completing the study (n=8; 50%) was higher than for females (n=3, 33%); however, this difference was not statistically significant. Mean age for the sample was 73.64 years (SD=7.2 years). Females were non-significantly older (Mean=75.0 years, SD=6.14; Range: 66-84 years) than males (Mean=72.9; SD=7.8; Range 50-86). Age difference between those who completed and those who did not was not significant (73.5 years compared to 73.8 years, respectively). Mean level of education was 14.1 years (SD=2.3 years). There were no significant differences found for education between individuals who received treatment and those that did not on baseline assessments. Additionally, there were no significant differences on baseline assessments between individuals with early terminations and those who completed the trial.

Safety and Tolerability of Thalidomide in AD Patients

As precaution to limit strong adverse events (AEs) in our sample population, we opted to administer thalidomide in an escalating dose regimen which consisted in starting at 100 mg/day on Visit 2 (first day of treatment; see Methods section for details) and going up to 400 mg/day starting from Visit 5, by 100 mg increments (50 mg increments when patients reported severe AEs early). The average dose reached in our sample population was 250 mg/day, with a few individuals (n=3) reaching the maximum dose of 400 mg/day for a 2-4 weeks before dose reduction after reported AEs. From the 25 individuals enrolled in the study, 11 (44.0%) completed the 24 week trial and 14 (56.0%) terminated participation early. Overall, adverse events were high in the sample with almost 80% (actual 79.2%) of study participants reporting at least one adverse event. Among those receiving the study drug,

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88.2% (n=15/17) experienced adverse effects with 10 of 15 terminating the study early compared to 50% (n=2/4) for the placebo group. As anticipated, the placebo group had a higher completion rate than the treatment group (Fisher's Exact Test, p=0.04).

Adverse Events

All adverse events (AE) were assessed and documented by the Principal Investigator. A total of 19 subjects (79.2%) experienced one or more AEs during the study, including 15/17 (88%) in the study drug group. Overall, there were 55 adverse events reported, 48 in the study drug group, including one death, and 7 in the placebo group. Adverse events (AE) were categorized into organ systems as shown in Table 2. The most common AE was neurological, accounting for approximately one-third of all AEs (n=18, 32.7%), followed by urinary/renal (n=8, 14.5%), gastrointestinal and skin at 9.1% (n=5 in each group). Infections, oedema, and injury represented 7.3% each (n=4 in each group). There were two cardiovascular AEs (3.6%). Respiratory, cognitive, haematological, and procedure-related AEs each represented 1.8% (n=1 for each group) for the sample. There was one death that may or may not have been related to treatment. Overall, the majority of AEs were mild in nature (72.6%), 19.6% deemed to be moderate, and 7.8% were severe.

Adverse Events in the Study Drug Group

Selecting on subjects who received treatment, approximately 43.2% of adverse events were thought not to be drug-related, 11.4% unlikely, and 45.5% possible (Table 3). No action was required for almost 60% (n=25, 56.8%) of AEs experienced by the study drug group. Drug dose was reduced for 25% (n=11 AEs), delayed for one subject (2.3%), and discontinued for 15.9% (n=7). Duration of AEs was one to 60 days. The majority of AEs were not serious in nature (n=38, 86.4%), but 11.4% required hospitalization (n=5), and there was a single death. Other actions were required for 31.8% of the AEs for this group and included use of concomitant medication (n=5, 11.4%), hospitalization (n=3, 6.8%), and procedure required (n=1, 2.3%). Five patients were withdrawn (n=5, 11.4%) because of poorly tolerated AEs.

Cognitive Assessments

In addition to safety and tolerability, we investigated the effect of thalidomide on cognition in AD patients using a battery of tests (see Methods). It was suggested previously that thalidomide induces cognitive impairments in oncologic populations [20], however to our knowledge no assessment has been reported for individuals suffering AD. Our observations are summarized in Tables 1 and 4. Across the tests, we did not observe any statistically relevant difference in scores between study drug and placebo groups. In details, we calculated the score variation at the end of study versus baseline (Table 4). The individual test results showed no significant difference for ADAS-COG (p=0.3462), CDR-SOB (p=0.1619), ADCS-ADL (p=0.7437), NPI (p=0.1408), or MMSE (p=0.6946). These results suggest that, at the dose tolerated by AD patients, thalidomide neither improved, nor deteriorated cognitive performance in the two study groups.

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Discussion

Since chronic brain inflammation exacerbates amyloidogenesis, a potential treatment option is to modulate inflammation. We explored this hypothesis in a Phase IIa clinical trial using the very potent immunomodulator thalidomide in mild to moderate AD subjects. Thalidomide was selected because of pre-clinical work showing reduction of TNFα and Aβ; it has a known safety and toxicity trial; and it had the inherent appeal of repurposing an already approved drug. In this study, we observed that thalidomide is very poorly tolerated by patients suffering AD, as confirmed by the disproportionately high AE rate in the treatment group. Ultimately the safety and tolerability impeded the ability to titrate the dose to the theoretical target felt to be appropriate for a biological and cognitive effect. We conclude that thalidomide is not a safe drug to use in AD subjects. However, the absence of a significant cognitive impairment in the drug-treated group (compared to previous reports in oncologic populations) encourages the testing of additional anti-inflammatory agents in better designed clinical trials.

Many factors could have caused our lack of positive results in this study. While we followed a standard design at the time we developed our clinical trial (2009), very recent discussions suggest that our sample population might not have been optimal for thalidomide testing. Indeed, it is currently thought that AD neuropathological features likely develop over one to three decades before cognitive symptoms appear [21]. This implies that at the mild to moderate stages of AD 1- amyloid plaques are present in large numbers; and 2- numerous neurons have died and synaptic connections disappeared. Because our intended use of thalidomide was to modulate BACE1 and reduce amyloidogenesis, mild to moderate AD might be too late into the disease to test our hypothesis. Therefore, it might be difficult to detect any cognitive improvement using such sample population, although a slower cognitive decline compared to the placebo-treated group would have suggested positive drug effects. Furthermore, older individuals are vulnerable to side effects, and individuals with AD even more so with increased sensitivities and co-morbidities resulting in high withdrawal rates from clinical trials. For future clinical trials testing agents or methods that could potentially slow down amyloidogenesis we suggest to select a sample population at earlier stages of AD to provide healthier patients and better assess cognitive decline prevention. For example, subjects included in future studies could be suffering mild cognitive impairment (MCI), which was recently classified as early AD by the Alzheimer's working group [22]; or showing low to moderate amyloid loads by fluorbetapir or Pittsburg compound B imaging.

Second, thalidomide has been studied extensively in cancer patients and found to be poorly tolerated. When compared to other compounds, cancer patients preferred to drop out of treatment than continuing with thalidomide [23]. A long list of adverse events, most of which were observed in the present study, has been drawn over the past decades [18]. This explains why most drug-treated subjects terminated the study early.

Third, a few reports suggested that thalidomide induces cognitive decline in cancer patients, which is reversible after a wash out period [20]. Here, we observed no statistical significance in cognitive performance between the drug- and placebo-treated groups. Because our study design included the administration of cognitive tests during and immediately at the

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completion of the trial, some improvements might have been noted if the final assessment was administered after 4-6 weeks of wash out. Several other hypotheses could be advanced to explain our results: 1- since no patient reach the maximum dose of 400 mg/kg, which is the dose commonly used for myeloplastic cancer treatment [19], the regimen received by patients in our study might not have been deleterious enough to induce cognitive impairments; 2- the tests used in our study are highly specific for Alzheimer's and likely more sensitive than the tests used in oncologic patients; 3- thalidomide might not be as toxic on the CNS of AD subjects as in cancer patients, although the recorded adverse events suggest otherwise; 4- since our sample population included mild to moderate AD patients, the neuronal loss may have been too advance for thalidomide to induce cognitive impairment by altering the physiology of neurons like it may happen in cancer patients who do not display advanced neuronal loss; 5- the difficulty to recruit and high rate of withdrawal from the study might not provide enough power to reach statistical significance. Whether thalidomide induces cognitive impairment or not in AD subjects remains an open question. In our opinion, future clinical trials testing disease-modifying therapies should include the administration of cognitive tests both immediately at the completion of the study and after a wash out a period of at least four weeks.

Clinical trial study design is currently under scrutiny for AD [24-27], and the scientific community is looking for improved designs to validate conclusions about treatment efficacy. After completing the present study, we do believe our design was sub-optimal for the pharmacological agent tested. As explained above, our sample population included mild to moderate AD subjects. Since we tested thalidomide as a blocker of amyloidogenesis, this sample population might be too advanced into the disease to measure potential drug efficacy. In addition, this population is known to be sensitive to drug side effects, which are a major issue with thalidomide. Thus, using a sample population at an earlier stage of the disease would likely provide better information about the effects of therapeutical approaches on cognitive outcomes and reduce the frequency of side effects. Furthermore, AD is suspected to develop over several decades, but most trials test interventions over a few months. Therefore, we are questioning whether using a high dose of thalidomide for six months was the best design for AD. To both reduce toxicity and improve the chances of success, maybe administering a lower dose (maximum of 200 instead of 400mg/kg) of the drug for a longer period of time (9-12 instead of 6 months) would have been more appropriate to tackle AD. Nonetheless, thalidomide remains a drug which induces adverse events in a cumulative manner. We conclude that, because of its poor tolerability and safety profile, thalidomide should not be tested any longer in AD clinical trials.

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Abbreviations

Aβ	Amyloid β protein
AD	Alzheimer disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living Scale
AE	Adverse Event
APP	Amyloid Precursor Protein
BACE1	Beta Amyloid Converting Enzyme 1
CDR-sb	Clinical Dementia Rating-sum of boxes
CSF	Cerebral Spinal Fluid
MMSE	Mini Mental State Exam
NPI	Neuropsychiatric Inventory
SAE	Serious Adverse event
TNF-α	Tumor necrosis factor-alpha

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Table 1
Demographic and clinical characteristics of subjects for treatment groups

	n	Thalidomide Group	n	Placebo Group
Age	17	73.6 (8.22)	8	73.6 (4.84)
Education	17	14.1 (2.30)	6	13.3 (1.97)
Visit 1 MMSE	17	21.8 (2.46)	7	22.0 (5.26)
Baseline ADAS-cog	17	22.7 (7.81)	7	26.9 (18.7)
Baseline CDR-sb	17	5.12 (2.50)	8	7.38 (5.36)
Baseline ADCS-ADL	17	57.8 (9.34)	8	51.0 (17.9)
Baseline NPI	17	9.71 (12.1)	8	18.4 (22.1)
Visit 7 MMSE	5	19.2 (4.44)	5	19.6 (7.30)
EOS ADAS-cog	14	24.1 (10.1)	6	28.9 (20.6)
Visit 10 MMSE	10	19.0 (3.83)	6	19.5 (9.81)
EOS CDR-sb	14	6.82 (2.49)	7	9.21 (6.22)
EOS ADCS-ADL	14	52.4 (10.9)	7	46.6 (19.0)
EOS NPI	14	14.3 (14.0)	7	14.0 (23.2)

Abbreviations: ADAS-cog= Alzheimer's Disease Assessment Scale-cognitive, ADCS-ADL=Alzheimer's Disease Cooperative Study Activities of Daily Living Scale; CDR-sb=Clinical Dementia Rating-sum of boxes; MMSE=Mini-Mental State Examination; NPI=Neuropsychiatric Inventory; EOS = End of Study. Values are Mean (SD)

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Table 2

Number of subjects with treatment-emergent adverse events by primary system organ class

System/Organ	N (All AEs)	Treatment	Control	Early Term	Totals
1 Gastrointestinal	5				9.1%
• Indigestion	1	1		0	
• Diarrhea	1		1	0	
• Constipation	1	1		1	
• Bowel Inflammation	1	1		1	
• Upper GI hemorrhage	1	1		1	
2 Skin	5				9.1%
• Rash (NS, morbilliform)	3	3		3	
• Sores (arms/buttocks)	1	1		1	
• Itching	1	1		1	
3 Urinary /Renal	8				14.5%
• UTI	6	6		3	
• Urine values out of range	1	1		1	
• Renal insufficiency (new onset)	1		1	1	
4 Infections	4				7.3%
• Flu symptoms	1	1		0	
• GI/Viral gastroenteritis?	2	1	1	1/0	
• Nonspecific	1	1		1	
5 Neurological	18				32.7%

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System/Organ	N (All AEs)	Treatment	Control	Early Term	Totals
• Tremor	2	1	1	0/1	
• Increased tremor	2	2		0	
• HA	3	3		0	
• Tingling in extremities (right)	1	1		0	
• Dizziness	3	3		1	
• Somnolence/sleepiness	2	2		2	
• Sedation	1	1		0	
• Fatigue/Malaise	1	1		0	
• Unsteady gait	1	1		0	
• Pain – burning/bottom of feet	2	2		2	
7 Respiratory	1				1.8%
• Pneumonia-B/L lung involvement	1	1		1	
8 Other	4				7.3%
• Edema					
-weight gain	1	1		0	
-swelling extremities (ankles, feet)	2	2		1	
-swelling extremities (hands)	1	1		1	
9 Injury	4				7.3%
• Bumped head	1	1		0	
• Falls	3	3		1	
10 Cognitive	1				1.8%
• Confusion	1	1		0	

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System/Organ	N (All AEs)	Treatment	Control	Early Term	Totals
11 Cardiovascular	2				3.6%
• Bradycardia	1	1		1	
• Venous thromboembolism	1		1	0	
13 Expired	1				1.8%
• Death		1		1	
14 Procedure	1				1.8%
• Backache after LP	1		1	0	
15 Hematological	1				1.8%
• Anemia (new onset)	1		1	1	
TOTAL AEs		48	7		100 %
	55			28	

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Table 3

Severity by organ system for treatment group

Organ System	Maximum Intensity	n	Percent
Neurological	*Mild*	*12*	*75%*
	Moderate	*4*	*25%*
Urinary/Renal	*Mild*	*6*	*100%*
Gastrointestinal	*Mild*	*1*	*25%*
	Moderate	*1*	*25%*
	Severe	*2*	*50%*
Skin	*Mild*	*4*	*100%*
Infections	*Mild*	*2*	*67%*
	Moderate	*1*	*33%*
Respiratory	*Moderate*	*1*	*100%*
Edema	*Mild*	*4*	*100%*
Injury	*Mild*	*4*	*100%*
Cognitive	*Mild*	*1*	*100%*
Cardiovascular	*Mild*	*1*	*100%*
Death	*Severe*	*1*	*100%*

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Table 4

Changes in cognitive and functional measures between baseline and termination of study

	N	Thalidomide Group	N	Placebo Group	P
ADAS-cog	14	2.14 (4.66)	6	0.22 (1.81)	0.346
CDR-sb	14	2.21 (1.07)	7	1.50 (1.04)	0.162
ADCS-ADL	14	-6.64 (6.32)	7	-5.57 (8.22)	0.744
NPI	14	4.21 (13.6)	7	-4.71 (9.79)	0.141
MMSE (Visit 1, Visit 10)	10	-2.90 (2.73)	6	-2.17 (4.67)	0.694

Abbreviations: ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive, ADCS-ADL=Alzheimer's Disease Cooperative Study Activities of Daily Living Scale; CDR-sb=Clinical Dementia Rating-sum of boxes; MMSE=Mini-Mental State Examination; NPI=Neuropsychiatric Inventory.

*Values = Mean difference (SD)

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