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Current Alzheimer's disease clinical trials: Methods and placebo outcomes

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Abstract

Background: Eighteen-month-long randomized, placebo-controlled clinical trials are common for phase II and phase III drug development for Alzheimer's disease (AD). Yet, no 18-month trial has shown statistically significant outcomes favoring the test drug. We examined characteristics and underlying assumptions of these trials by assessing the placebo groups.

Methods: We searched the clinicaltrials.gov registry for randomized, placebo-controlled clinical trials for AD of at least 18-month duration and extracted demographic, clinical, and trials characteristics, and change in main outcomes from the placebo groups. We obtained additional information from presentations, abstracts, publications, and sponsors.

Results: Of 23 trials identified, 11 were completed and had baseline data available; nine had follow-up data available; 17 were phase III. General inclusion criteria were very similar except that minimum Mini-Mental State Examination (MMSE) scores varied from 12 to 20. Sample sizes ranged from 402 to 1,684 for phase III trials and 80 to 400 for phase II. Cholinesterase inhibitor use was from 53% to 100%, and memantine use was from 13.5% to 78%. The AD Assessment Scale-cognitive (ADAS-cog) was the co-primary outcome in all trials; and activities of daily living, global severity, or global change ratings were the other co-primaries. *APOE* ε4 genotype carriers ranged from 58% to 67%; mean baseline ADAS-cog was 17.8 to 24.2. ADAS-cog worsening in the placebo groups during 18 months ranged from 4.34 to 9.10, with standard deviations from 8.17 to 9.39, increasing during 18 months.

Conclusions: Inclusion criteria are essentially similar to earlier 6-month and 12-month trials in which cholinesterase inhibitors were not allowed, as were mean ADAS-cog rates of change. Yet increasing variability and relatively little change overall in the ADAS-cog placebo groups, eg, about 25% of patients do not worsen by more than 1 point, might make it more unlikely than previously assumed that a modestly effective drug can be reliably recognized, especially when the drug might work only to attenuate decline in function and not to improve function. These observations would be strengthened by pooling individual trials data, and pharmaceutical sponsors should participate in such efforts.

Keywords: Alzheimer's disease; Clinical trials; Clinical trials methods; Alzheimer's Disease Assessment Scale (ADAS); Clinical Dementia Rating scale; Clinical global impression of change; Activities of daily living; Amyloid-beta protein; Cholinesterase inhibitors; Memantine

1. Introduction

Although 6-month trials are still standard regulatory guidelines [1,2], 18-month-long randomized, placebo-controlled clinical trials are very common for phase II and phase III drug development for Alzheimer's disease (AD). Many 18-month trials have been launched during the past 8 years, but there has been no completed trial with statistically significant outcomes in favor of the test drug. Although this is most likely due to the inefficacy of the drugs tested and underpowered trials, other possibilities include the insensitivity of the cognitive, global, and activities of daily living outcome measures and incorrect assumptions regarding underlying pathology and clinical course.

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Despite some concerns about increasingly longer durations of clinical trials [3–5], an ad hoc group has formally suggested longer trials for disease modification coupled with slope analyses and biomarkers, specifically recommending that 18-month-long trials be used [6]. We systematically compared and examined the methodology and some underlying assumptions of these trials with regard to outcomes.

2. Methods

We searched the clinicaltrials.gov registry to identify randomized, double-blinded, placebo-controlled clinical trials for AD of 18-month duration or longer. We separated the trials into completed and ongoing trials and extracted summary sociodemographic and clinical data characterizing patients and methodologic characteristics of the trials. The former included mean ages, gender, educational level, *APOE* genotype, cholinesterase inhibitor and memantine use, and clinical rating scales scores at baseline. Methodologic characteristics extracted included inclusion criteria, sample size, randomization allocation ratio, and clinical outcomes scores. Because the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [7] is frequently used and recommended [6] as the primary cognitive outcome and the Clinical Dementia Rating scale (CDR) [8], clinician's global impression of change [9], and activities of daily living scales [10,11] as co-primary outcomes, we retrieved those change scores from the placebo groups over the durations of the completed trials.

We obtained information from the clinicaltrials.gov registry, presentations at meetings, published abstracts, and publications on the trials. We searched Google and Google News and queried sponsors to seek additional information on the unpublished trials identified on clinicaltrials.gov. We summarized data into text and tables describing characteristics of the completed trials and ongoing trials and the changes on main outcomes scales of the placebo groups from the completed trials in order to facilitate review.

3. Results

From 243 AD trials citations on clinicaltrials.gov (accessed January 15, 2009), we identified twenty-three 18-month trials. Eleven trials were completed as of May 2009; 12 were ongoing and recruiting. Ten of the 11 completed trials and seven of 12 ongoing trials were classified by their sponsors as phase III and the others as phase II. We obtained screening or baseline demographic and clinical information from 10 of the 11 completed trials, and we obtained clinical outcomes follow-up data from the placebo groups from nine trials. Two of the 11 completed trials were discontinued by their sponsors prematurely, after enrollment was complete but before the last patient completed the 18-month follow-up, because a previous trial with the same drug did not show statistically significant results, and the development programs were terminated.

3.1. Completed trials

3.1.1. Trials characteristics

Data were obtained and summarized from the 11 completed trials (Table 1). The sponsors of the trials were Pfizer (one trial), Sanofi-Aventis (two trials), Bellus (previously Neurochem, two trials), Myriad (two trials), Elan and Wyeth (one trial), and the National Institutes for Health Alzheimer's Disease Cooperative Study (NIH ADCS; three trials).

Inclusion criteria were very similar. All required participants to have probable AD diagnoses [21]. Mini-Mental State Examination (MMSE) [22] inclusion scores ranged from 12 to 26 (1 trial), 13 to 26 (1 trial), 14 to 26 (2 trials), 16 to 26 (5 trials), and 20 to 26 (2 trials). Differences among trials were mainly in certain trial-specific exclusion criteria in which a medical condition or concomitant use of a medication might confound effects of the test drug, eg, vitamin use, abnormal lipid profiles, excess fatty acid dietary intake, and diabetes were each an exclusion criterion in one trial but not others.

Sample sizes ranged from 402 to 1,684 for the phase III trials; sample size was 234 for the phase II. The three NIH ADCS–sponsored trials used sample sizes of 402, 406, and 409. Sample sizes for the pharmaceutical company–sponsored phase III trials of drugs under development ranged from 841 to 1,684. The numbers of clinical sites per trial ranged from 40 to 133; thus the average number of patients enrolled per site per trial ranged from 7.4 to 15.7. Five trials were conducted exclusively in the United States; two in the U.S. and Canada; two in North America and Europe; one exclusively in Europe; and one across the U.S., Europe, South Africa, Asia, Australia, and New Zealand.

Eight trials randomized patients to one dose of test medication or placebo; two randomized to two doses or placebo. The phase II trial was unique in that its methodology involved randomizing four cohorts of 60 patients to ascending doses of an amyloid-beta monoclonal antibody, bapineuzumab, or placebo and staggering the starts of each cohort. Therefore, the placebo group is the sum of the placebo groups from the four sequentially conducted comparisons [18].

3.1.2. Patient demographic and clinical characteristics

Mean age per trial ranged from 73.6 to 76.3 years for the phase III trials and was 69.0 for the phase II trial. Gender distribution ranged from 50.1% to 59.4% female, and mean years of education were from 13.9 to 14.3, with 26% to 62% of patients per trial having some university education. The mean proportion of patients per trial that carried one or two *APOE* ε4 alleles ranged from 58.1% to 66.9%.

All trials allowed patients to use cholinesterase inhibitors; three required their use, and one required donepezil specifically. In seven of 11 trials, more than 91% of the participants used cholinesterase inhibitors. In the remaining four, cholinesterase inhibitor use was 82%, 75%, 68%, and 53%. All allowed memantine use, and the baseline prevalence for use ranged from 13.5% to 78% in the nine trials from which information was available.