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The Value of Pre-Screening in the Alzheimer's Prevention Initiative (API) Autosomal Dominant Alzheimer's Disease Trial

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Abstract

The Alzheimer's Prevention Initiative (API) Autosomal Dominant Alzheimer's Disease (ADAD) trial evaluates the anti-amyloid-β antibody crenezumab in cognitively unimpaired persons who, based on genetic background and age, are at high imminent risk of clinical progression, and provides a powerful test of the amyloid hypothesis. The Neurosciences Group of Antioquia implemented a pre-screening process with the goals of decreasing screen failures and identifying

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Ethical standards: The entire pre-screening process was approved by the local Ethic Committee (Comité de Investigaciones y Ética en Investigaciones del Hospital Pablo Tobon Uribe).

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participants most likely to adhere to trial requirements of the API ADAD trial in cognitively unimpaired members of Presenilin1 E280A mutation kindreds. The pre-screening failure rate was 48.2%: the primary reason was expected inability to comply with the protocol, chiefly due to work requirements. More carriers compared to non-carriers, and more males compared to females, failed pre-screening. Carriers with illiteracy or learning/comprehension difficulties failed pre-screening more than non-carriers. With the Colombian API Registry and our prescreening efforts, we randomized 169 30–60 year-old cognitively unimpaired carriers and 83 non-carriers who agreed to participate in the trial for at least 60 months. Our findings suggest multiple benefits of implementing a pre-screening process for enrolling prevention trials in ADAD.

Keywords

Autosomal dominant Alzheimer's disease; Alzheimer's prevention initiative; registry; pre-screening

Introduction

Clinical trials for Alzheimer's disease (AD) have been shifting toward preclinical and prodromal stages of the disease (1, 2). The evolving understanding of the earliest stages in the AD continuum have generated preclinical trials in both genetic-at-risk and amyloid-at-risk cohorts, defined by an absence of clinically detectable impairment but the presence of either a genetic mutation that confers near certainty of developing symptomatic AD, or biomarker evidence of AD-related pathology (3, 4). Finding individuals in these categories, who are in either the prodromal or unimpaired phases of disease, has thus become a major challenge for such trials (2, 5, 6). Trial candidates are typically unaware of their risk and may not be seeking evaluation or treatment. Given the hypothesis that disease-modifying treatments might be most effective when initiated early, prevention trials are likely to proliferate in the near future (7). There is thus an urgent need for novel recruitment strategies in AD prevention trials (3, 7, 8) that efficiently identify participants most likely to meet clinical trial requirements.

The Colombian Alzheimer's Prevention Initiative (API) Autosomal Dominant AD (ADAD) trial is a collaborative project involving the Neurosciences Group of Antioquia (GNA), the Banner Alzheimer's Institute, Genentech/Roche, and the National Institute on Aging. The trial evaluates the anti-Aβ antibody crenezumab in cognitively unimpaired 30–60 year-old members of the Colombian PSEN1 E280A kindred (NCT01998841 for trial design), the world's largest ADAD kindred, including carriers randomized to active treatment or placebo and non-carriers assigned to placebo only (this eliminates the need for genetic disclosure and provides a nested cohort study of placebo-treated carriers and non-carriers). The study capitalizes on the unusual size of this ADAD kindred, including 5806 cognitively and genetically assessed kindred members and 1117 living mutation carriers, and on the well-established ages of onset for cognitive impairment (44±5 years) and for dementia (49±5 years) in the carriers (10).

To recruit eligible candidates, the sponsor team and GNA created a pre-enrollment registry (9) and devised a pre-screening process with three goals: to decrease screen failures, to

permit recruitment to the trial in a manner that maintained the correct ratio of mutation carriers to non-carriers, and to optimize compliance and adherence. We describe here the Colombian API ADAD trial pre-screening process, and report the main reasons for pre-screen failures, information that may be useful for other preclinical trials.

Methods

Step 1: Generation of lists of eligible candidates from the Colombian API Registry

The pre-screening process started with the generation of lists of potentially eligible candidates from the Colombian API Registry (9). Persons with early onset, potentially familial AD, as well as their healthy relatives, age 8 years and older, are eligible for the Colombian API Registry. Registrants undergo at least one general medical and neurological evaluation, cognitive assessment, and genetic testing, after which they are identified as being part of a new or existing pedigree. Registrants remain blind to their genetic status, except for those with symptomatic AD. The only GNA staff unblinded to genotype were those responsible for balancing genotype of participants referred to the trial; these staff members had no role in trial operations. GNA, through SISNE2 (a secure and closed enterprise database system), manages extensive information including demographics, medical, neurological, and neuropsychological evaluations, in order to support various research projects involving PSEN1 E280A families. In addition, GNA created a database of pedigrees, using the Cyrillic pedigree drawing software (Cherwell Scientific, Acton, MA) and Progeny genetic pedigree software (Ambry Genetics, Aliso Viejo, CA), of all registered families including those affected by the PSEN1 E280A mutation. Demographic and medical information was captured using a WEB application and Postgresql Data base while the pedigree information was collected using progeny genetics. Lists of registrants potentially eligible for the trial were created from SISNE2. The unblinded data analyst filtered all potentially eligible candidates according to their PSEN1 E280A carrier status (in a 2:1 carrier/non-carrier ratio to match the randomization ratio of carriers/non-carriers in the API Colombia clinical trial), some of the key inclusion/exclusion (I/E) criteria for the trial (30–60 years of age, not known to be cognitively unimpaired or to have significant medical conditions) and marked all eligible candidates as “active” for pre-screening.

Step 2: Detailed review of Inclusion/Exclusion data available from the Colombian API Registry

The clinical history of each active candidate was reviewed by a trial investigator, who evaluated health status and whether I/E criteria were potentially met (blinded to genetic status). Eligibility was classified as “probable” (appeared to meet all protocol I/E criteria), “possible” (appeared to meet nearly all I/E criteria but full eligibility remained to be confirmed during screening) and “ineligible” (definitely or probably excluded). When the candidates were considered ineligible for further pre-screening, they were designated as “inactive.”

Step 3: Informed Consent meetings

All probably and possibly eligible candidates were contacted by telephone and invited, with their intended study partners, to group meetings at which the principal investigator described

the trial, possible risks and benefits of participation, trial procedures, and reimbursement for transportation, missed work, and meals as a result of attending study visits. Participants and study partners had opportunities to ask questions during and after the meeting. They were given the Informed Consent Form (ICF), a companion illustrated study brochure, and diagrams of the study visits to review at home with their families. The companion study brochure was created by GNA, using clear language and pictures explaining in detail the main goals of the trial, its duration, the schedule of visits, all procedures including lumbar puncture, MRI and PET scans, potential risks and benefits, information about the investigational product and method of study drug administration, the requirement for double contraception, and the role of the study partner. In addition, it provided information about the availability of a health plan for participants to ensure timely evaluation, treatment and follow up of possible adverse events, conduct additional testing if needed, offer contraception, and provide gynecological and other specialist evaluations for participants in instances where their standard medical care could not address health concerns in a timely way or at all. Participants were given the opportunity to have a letter sent to their place of work noting that they are participating in a research study and explaining why they would need to miss work periodically. They were provided telephone numbers of key study personnel as well as the Ethics Committee (EC) and an independent attorney in the event they desired legal consultation.

Step 4: Pre-screening questionnaire and reconfirmation of eligibility

At the end of the IC meeting, each candidate filled out a pre-screening questionnaire assessing current health status, past medical history, past and concurrent medications, substance use, plans regarding conception, and availability of a reliable study partner. A qualified study team member reviewed this information, clarified ambiguous information, and updated the information in SISNE2. One of the investigators then rendered a clinical judgment regarding likelihood of eligibility of each candidate; those who remained “probably” eligible and remained interested were scheduled for a screening visit. An investigator assessed the capacity to provide informed consent and the candidate’s/partner’s understanding of the potential risks and benefits of trial participation. Before signing the ICF, each candidate had the opportunity to ask questions. The entire pre-screening process was approved by the local Ethics Committee.

Data analysis

Using SISNE2, data from all eligible candidates were filtered using an algorithm based on PSEN1 E280A status (using a 2:1 carrier/non-carrier ratio), clinical records, and selected trial inclusion/exclusion criteria. Weightings were assigned to each I/E criterion according, in part, to its variability over time. For example, “planning to conceive” received a low weight because this could change from one evaluation to another; conversely, “having suffered severe head trauma” received a high weight because of its relative stability. Failures in criteria with low weightings did not affect the candidate’s likelihood of being selected for a pre-screening list. Descriptive anonymized statistics were calculated for the demographic data (age, gender, schooling, marital status and geographic location) and genetic status of the population considered during the pre-screening process in order to determine their impact on

failures. Fisher's exact tests were used for inferential testing of categorical variables; percentages of pre-screening failures in carriers vs. non-carriers were used only if blinding to genotype could be protected.

Results

Pre-screening for the trial occurred from November, 2013, to December, 2016, at the Sede de Investigaciones Universitaria, Medellin. Overall, 1782 persons from the Colombian API Registry failed to qualify for pre-screening. A total of 50 pre-screening lists (blinded to E280A status, and preserving a 2:1 carrier/non-carrier ratio) were reviewed for a total of 623 eligible candidates. Of those, 201 (32.3%) did not attend an IC meeting because they either clearly did not meet I/E criteria or they decided not to come. Among the candidates who attended an IC meeting: 99/422 (23.5 %) failed pre-screening after review of the pre-screening questionnaire. A total of 8/422 (1.9%) did not come to a screening visit after passing all pre-screening requirements. Overall, 54 (18%) probably eligible and 246 (82%) possibly eligible candidates failed pre-screening.

The total pre-screening failure rate was 48.2% (300 candidates); demographic characteristics are described in Table 1. There were no significant differences between pre-screening failures versus non-failures in marital status or geographic location; nevertheless, a higher pre-screening failure rate was seen in participants age 50–54 years (12.3% vs 5.8%, p=0.004) and in participants age 60 (6.7% vs 1.6%, p=0.0016). Carriers failed more than non-carriers (77.7% vs. 66.3%, p=0.0018); men failed more than women (62.2 % vs. 54%, p=0.042), and candidates with no formal education failed more than those with any schooling (5.7% vs. 1.2%, p=0.003).

The most frequent causes for pre-screening failures were: 118/300 (39.3%) expected inability to comply with the protocol, 39/300 (13.0%) mild cognitive impairment due to AD based on investigator judgment, 39/300 (13.0%) not in good health, 25/300 (8.3%) substance dependence, 22/300 (7.3%) learning/comprehension difficulties or illiteracy, 19/300 (6.3%) planning to conceive, 18/300 (6.0%) dementia due to AD based on investigator judgment, 8/300 (2.7%) contraindication to MRI, and 12/300 (4.1%) other reasons.

Looking further at barriers to protocol compliance, almost half 55/118 (46.6 %) were due to work; 31/118 (26.3 %) were averse to required testing and/or potential adverse effects of study drug; 16/118 (13.6%) lived outside the country (6/16) or far from trial sites (10/16); 4/118 (3.4%) could not participate because of time constraints related to child care or care of family members with AD dementia, and 12/118 (10.2 %) due to a combination of reasons.

Medical exclusions were due to: 10/39 (25.6%) cardiovascular diseases, 9/39 (23.1%) metabolic/endocrine disorders, 6/39 (15.4%) autoimmune disorders, 5/39 (12.8%) severe traumatic brain injury, 3/39 (7.7 %) psychiatric diseases, 2/39 (5.1%) cerebrovascular disease, 2/39 (5.1%) movement disorders, 1/39 (2.5%) tuberculosis, and 1/39 (2.5%) complications of meningitis. The most common pre-screen failure for substance dependence included combined dependence on marijuana and cocaine 21/25 (84%), marijuana

dependence 3/25 (12.0%); and alcohol dependence 1/25 (4.0%). Twenty-two individuals who were fully functional and independent failed due to illiteracy or learning/comprehension difficulties: 7/22 (31.8%) were illiterate and had no formal education; another 12/22 (55%) had one to two years of education but could not read and write, and 3/22 (13.6%) could read and write but could not understand conversation.

Non-carriers failed significantly more than carriers due to inability to comply with protocol requirements (53.7 % vs 35.0%, p=0.007), and carriers failed significantly more than non-carriers due to illiteracy or learning/comprehension difficulties (9.0% vs. 1.5 %, p= 0.035). Males were more likely than females to fail due to substance dependence (15.9% vs. 1.9%, p<0.0001) (Table 2).

Discussion

With the Colombian API Registry and our pre-screening efforts, we enrolled 169 30–60 year-old cognitively unimpaired carriers and 83 non-carriers from the PSEN1 E280A kindred who met all eligibility criteria, agreed to comply with the time commitments and contraception requirements involved in a trial of at least 60 months' duration. The pre-screening failure rate was high 300/623 (48.2%); the primary reason being expected inability to comply with the protocol, chiefly due to work requirements. More carriers compared to non-carriers, and more males compared to females, failed pre-screening. Carriers were more likely to fail pre-screening because of illiteracy or learning/comprehension difficulties. There were more pre-screen failures age 50–54 and 60 years, presumably because the median age of onset of dementia in PSEN1 E280A is about age 50 (10) and because 60 years was the maximum age to for trial eligibility.

Among those who failed pre-screening due to work issues, the main factors were anticipated absences from work due to drug administration schedule, time required for major procedures, and the duration of the trial (at least 60 months). Most eligible subjects were young (30–39 years), where conception was a life priority. A substantial minority (about 26.3%) of candidates expressed fears about the required testing and/or potential adverse effects of study drug (11).

Males failed pre-screening more than females: the majority of candidates who failed due to substance dependence were male (88%), similar to rates reported elsewhere (12). Of note, most substance-dependent males (84%) were cocaine-dependent concurrent with marijuana-dependence, in contrast to other studies in the general population, which described up to 23% of concomitant dependence to both substances (13).

Carriers failed significantly more during pre-screening than non-carriers. This may be due in part to the fact that they were more likely to meet criteria for dementia due AD, as expected in this population. On the other hand, failure due to meeting criteria for MCI did not differ between carriers vs. non-carriers, possibly because MCI can occur for a variety of reasons (14). Notably, we observed that almost all candidates (21/22) who failed due to illiteracy were carriers. All of them were functional and independent in daily activities, and we could not determine if these difficulties were related to lower/borderline IQ, specific learning

disabilities undiagnosed in childhood, or environmental factors (e.g., limited access to schooling, poverty). Given evidence that children at genetic risk for ADAD have functional and structural brain changes and abnormal levels of plasma Aβ1-42 (15), it is possible that there are neurodevelopmental changes associated with preclinical AD. Further studies in children from PSEN1 E280A and other ADAD families may help identify specific preclinical or neurodevelopmental differences in carriers.

Using the Colombian API Registry (9) as a source for the API ADAD clinical trial and using a structured pre-screening process helped identify eligible candidates efficiently before formal screening, and allowed trial recruitment ensuring a 2:1 carrier/non-carrier ratio. Providing a detailed IC helped identify candidates at risk of poor compliance. We believe our pre-screening process prevented high rates of screen failure, saving cost and participant burden by quickly and efficiently eliminating possible participants who were not likely to make it through the screening process, and identified candidates most likely to adhere to the demands of this trial. By the end of the third year of the trial retention of participants was 96.6%.

Limitations of our pre-screening process should be noted. The duration of pre-screening was almost three years: unimpaired carriers may have developed AD symptoms during this time. However, the lengthy process meant that some candidates who initially failed were eventually able to be reconsidered: those with transient health issues or who were pregnant, or those who initially declined for personal reasons and changed their minds. It is our impression that those who changed their minds about trial participation may have done so in part because of an extensive media campaign developed by GNA about the importance of the Colombian API Registry and the trial. Second, pre-screening failure was categorized by one main criterion, but it is likely that some candidates failed more than one criterion. Third, there was lack of detailed information about some recent Registrants. Finally, although analytical approaches such as logistic regression to examine determinants of screen failure might afford more insights, we chose approaches that would not unblind genetic status. The results are descriptive and exploratory, and conclusions based on genetic status and gender should be interpreted cautiously.

In conclusion, our findings suggest multiple benefits of creating a registry of people potentially interested in research of this nature and implementing a pre-screening process as an effective strategy for enrolling prevention clinical trials in ADAD. They provide a detailed picture of the population at risk for ADAD in Colombia that may be relevant to other prevention trials. In addition, future prevention clinical trials might benefit from less burdensome protocol designs, including reduced frequency of study drug administration, and more flexible I/E criteria.

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Table 1

Demographic characteristic and geographic locations of pre-screening failures vs. non-failures

Characteristic	Number of Failures (n =300)	%	Number of Non-failures (n=323)	%	p-value
Age distribution (years)					
30–34	60	20.0	73	22.6	0.43
35–39	54	18.0	79	24.5	0.05
40–44	51	17.0	63	19.5	0.46
45–49	51	17.0	64	19.8	0.40
50–54	37	12.3	18	5.8	**0.004**
55–59	27	9.0	21	6.5	0.29
60	20	6.7	5	1.6	**0.0016**
Carriers	233	77.7	214	66.3	**0.0018**
Women	162	54	201	62.2	**0.042**
Years of education					
0	17	5.7	4	1.2	**0.003**
1–8	160	53.3	166	51.4	0.63
9+	123	41	153	47.4	0.12
Marital status					
Single	67	22.3	72	22.3	1.00
Married	124	41.3	128	39.6	0.68
Separated	21	7	24	7.4	0.87
Widowed	4	1.3	5	1.6	1.00
Divorced	2	0.7	2	0.6	1.00
Living common law	82	27.3	92	28.5	0.78
Geographic location					
Metropolitan Medellin	176	58.7	174	53.9	0.26
Yarumal	55	18.3	59	18.3	1.00
Santafe de Antioquia	17	5.7	31	9.6	0.07
Santafé de Bogotá	7	2.3	7	2.2	1.00
Cali	9	3.0	10	3.1	1.00

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Characteristic	Number of Failures (n =300)	%	Number of Non-failures (n=323)	%	p-value
Armenia	2	0.7	6	1.9	0.29
Other locations	34	11.3	36	11.2	1.00

Bold values are considered significant (p-value <0.05)

Table 2

Pre-screening failures according to genetic status and gender

Criteria	Main reason	Carriers (n=233)	Non-carriers (n=67)	p-value	Female (n=162)	Male (n=138)	p-value
I19	Expected inability to comply with visit schedule, n, %	82(35.0%)	36(53.7%)	**0.007**	65(40.1%)	53(38.4%)	0.81
I8	Criterion MCI, n, %	34(14.6%)	5 (7.5%)	0.15	22(13.5%)	17(12.3%)	0.86
E1	Not in good health, n, %	28(12.0%)	11(16.4%)	0.40	21(12.9%)	18(13.0%)	1.00
E18	Substance dependence, n, %	20 (8.6%)	5 (7.5%)	1.0	3 (1.9%)	22(15.9%)	**p<0.0001**
I14	Learning/comprehension difficulties or illiteracy, n, %	21 (9%)	1 (1.5%)	**0.035**	11 (6.8%)	11 (7.9%)	0.82

Note. n = number, I-inclusion, E-exclusion; Comparisons performed with Fisher's exact test; Bold values denote p-value <0.05