

Short Report

Adherence/Retention Alzheimer's Prevention Initiative Colombia Plan

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Abstract

Introduction: The Alzheimer's Prevention Initiative Colombia Trial is a collaborative project involving the Neurosciences Group of Antioquia, Genentech/Roche, and the Banner Alzheimer's Institute, studying whether crenezumab can delay or prevent the clinical onset of Alzheimer's disease in cognitively unimpaired individuals who carry the *PSEN1 E280A* mutation. In an effort to optimize participant compliance and adherence and maintain interest in the trial for its duration, the Neurosciences Group of Antioquia developed an "Adherence/Retention Plan." This plan identifies potential barriers to trial adherence related to characteristics of the participants and study partners, protocol design, sponsors, investigators, environmental factors, and characteristics of this population in general and identifies potential solutions to these barriers.

Methods: Neurosciences Group of Antioquia designed and implemented a number of strategies including a) a prescreening process that emphasized detailed and staged informed consent involving the participant and family and/or friends, b) a schedule of visits and assessments designed to minimize burden while achieving the trial's aims, c) appointment reminders, d) reimbursement for transportation and missed work, e) meals during study visits, f) birthday cards, g) quarterly newsletters, h) annual in-person feedback meetings, i) a supplemental health plan to participants, and j) a social plan to support family members. All the methods used in this plan were approved by local ethics committees.

Results: By the end of the fourth year of the trial, participant retention was 94.0%, with most participants reporting that they felt "very satisfied" with their participation in the trial.

Discussion: The Adherence/Retention Plan plays a crucial role in maintaining adherence and compliance needed to achieve the ambitious goals of the Alzheimer's Prevention Initiative-Colombia Autosomal Dominant Alzheimer's Disease Trial and may offer guideposts for other prevention trials.

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Conflicts of interest: S.R.-R., N.A.-B., L.M.-Z., F.L., and L.L. report participation in other projects financed by the National Institutes of Health, Comité para el Desarrollo de la Investigación, and Colciencias. W.C. is a full-time employee of Genentech, Inc. and a member of the Roche Group. He also owns stock in Roche and is one of inventors on a crenezumab patent. H.S. and L.J. report no conflicts. J.B.L. has received consulting fees from Biogen and Lilly. E.M.R. has received consulting fees from Alkahest, Alzheon, Biogen, Denali, Pfizer, United Neuroscience, and Zinfandel Pharma. He received research support from Avid/Lilly, Genentech/Roche, and Novartis/Amgen, the National Institute on Aging, the National Institute of Neurological Disorders, Banner Alzheimer's Foundation, Alzheimer's Association, GHR Foundation, FBRI, NOMIS Foundation, Flinn Foundation, and the State of Arizona. P.N.T. has received consulting fees from Acadia,

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1. Background

Clinical trials in Alzheimer's disease (AD) face difficulties in recruitment and retention similar to those faced by other clinical trials of interventions with potential risks and uncertain benefits [1]. Furthermore, AD clinical trials have unique challenges [1], including the potential for impaired decision-making capabilities as a result of progressive cognitive decline and the requirement of study partners [2]. Recruitment and retention of a sufficient number of participants in trials are critical, particularly for randomized clinical trials and cohort studies. Failure to recruit and retain participants in a study may lead to invalid or inconclusive results, extend the clinical trial, or result in premature trial termination for operational futility [2-4].

In the current AD clinical trials era, there has been a significant shift toward preclinical and prodromal stages of the disease. Several secondary prevention clinical trials are underway, targeting cognitively unimpaired individuals with genetic predisposition to the disease or with biomarker findings indicating increased risk of cognitive decline and AD pathology [5-8], as well as studies of tertiary prevention in individuals with mild cognitive impairment and early treatment of people with mild AD dementia [9]. There is hope for primary prevention trials in the future, which will require novel strategies for outreach, recruitment, enrollment, adherence, and retention.

The Alzheimer's Prevention Initiative is a collaborative international project among the Neurosciences Group of Antioquia (GNA), Genentech/Roche, the Banner Alzheimer's Institute (BAI), and other key partners, studying whether crenezumab, a monoclonal antibody directed against toxic amyloid β species [10,11], can delay or prevent the clinical onset of AD in cognitively unimpaired individuals who carry the *PSEN1 E280A* mutation. The "API Colombian Autosomal Dominant AD (ADAD) trial" is described elsewhere [12] (NCT01998841). This trial requires people without cognitive impairment, with and without the *PSEN1 E280A* mutation, to commit to a trial lasting at least 5 years. Extensive evaluations and experimental treatment are required in a community with little research experience. To optimize chances for operational success, GNA developed and implemented a trial-specific Adherence/Retention Plan that we describe here.

2. Methods

2.1. Identification of influential factors and barriers

GNA identified possible factors, positive and negative, that could affect adherence and retention (Fig. 1). Consideration was given to socioeconomic, demographic, cultural, and

regional characteristics of the study population in Colombia, relying on GNA's experience working with families with the *PSEN1 E280A* mutation for more than 3 decades. Potential factors and barriers included participant and study partner circumstances, aspects of protocol design, sponsor and investigator characteristics, and cultural, political, and social factors.

One important participant factor is that the age range (30-60 years) represents a time of life during which there may be interest, likely to vary over time, in having children, as well as reluctance to comply with strict contraception requirements: both could have a marked impact on compliance and retention during a lengthy trial. Low education level and low income [3] may predispose to instability at work, more frequent job changes, and changes in work locations, relationships with employers, and responsibilities, factors that, in the aggregate, may be associated with high withdrawal rates. Young adults and single mothers are more likely to withdraw from clinical trials [3]. Physical and psychological characteristics, such as chronic illness, fatigue, substance use, and lack of interest/motivation can also lead to study withdrawal [3]. Depression, a common manifestation of AD, is one of the strongest predictors of nonadherence to treatment, possibly resulting from associated pessimism, cognitive disturbance, social, and impaired motivation [13]. Impaired language skills, difficulty understanding risks, benefits, and requirements of the protocol, as well as cognitive deterioration related to AD, may also contribute to attrition [13]. The fact that the trial requires being blinded to one's own genetic risk for AD and the fact that a proportion of participants do not carry this risk may influence adherence and/or retention. Progression to a symptomatic stage of AD will likely impact motivation of participants and/or family members to continue in the trial.

A reliable study partner is an important factor for adherence and/or retention of the primary participant. Study partners provide information about cognitive, psychological, and functional status, compliance, and physical well-being of participants: this represents a significant time commitment. If symptoms of AD emerge in the participant, the study partner may become the participant's legal representative and caregiver, which would entail even more commitment and responsibility [1].

Protocol complexity and burden [3], including long treatment duration (5-8 years), biweekly visits for study drug administration, lengthy research visits every 6 months at the main site in Medellin, and repeated blood tests, lumbar punctures, and neuroimaging (magnetic resonance imaging and positron emission tomography scans), can threaten adherence and retention [12]. Protocol complexities can also lead to frustrating scheduling challenges, especially if rescheduling is required due to technical or operational problems at the site



Fig. 1. Factors/barriers and strategies of Adherence/Retention Alzheimer's Prevention Initiative Colombia Plan.

(e.g., radioligand synthesis failure). Obligatory dual contraception methods for females and use of condoms for males can be associated with emotional distress or discomfort during sex for some participants and their partners.

Potential sponsor-related factors include protocol amendments to change study drug dose [14], mode of administration, and/or addition of more assessments, all potentially contributing to discomfort (e.g., higher volume subcutaneous injections) or burden and possibly attrition.

Investigator-related factors include the experience and training as well as adoption of processes to predict and detect threats to compliance, using communication tailored to the education and cultural characteristics of participants and partners, promptly detecting and managing adverse events, and making efforts to create visit schedules that optimize the time and effort of the participants and partners [1,14].

Cultural, social, and political factors may influence the adherence/retention of participants [1,3,13]. These include changes in lifestyle and/or social support, social stigma related to AD and/or the familial nature of the disease, "machismo", religious affiliation, mysticism, superstition, altruism, skepticism, employer willingness to support research participation, media influence, violence and safety concerns resulting from political changes during the study, and accessible transportation in rural areas.

2.2. Strategies

The Adherence/Retention Plan started with our prescreening process [15], which was designed and implemented by GNA to decrease screen failures and optimize compliance/adherence (Fig. 1). This process included the following: confirmation of eligibility via prescreening according to the trial inclusion and exclusion criteria and providing detailed and multistage informed consent (IC) to optimize the likelihood that candidates had a good understanding of the trial risks, benefits, and requirements and were thus prepared to start the

screening process. The IC process consisted of group meetings involving the principal investigator, eligible candidates, and their study partners, using a slide presentation along with an illustrated study brochure (as a companion to the informed consent form) to explain the goals of the study, its duration, the visit schedule, procedures, mode of study drug administration, possible adverse events, potential risks associated with pregnancy, and the role of the study partner. After this, a prescreening questionnaire was reviewed by a subinvestigator. Participants and study partners brought the informed consent form and study brochure home to review with their families and, in some cases, physicians. Those who wished to proceed attended an IC meeting to discuss any questions and concerns with a subinvestigator. IC was obtained for all participants and study partners. Provisions are in place to assess possible eventual loss of capacity in individuals who develop cognitive impairment, in which case assent procedures will be used. Consent and assent procedures were and are conducted in accordance with local ethics committee standards. The trial was approved by the Colombian Health Authority, Instituto Nacional de Vigilancia de Medicamento y Alimentos (INVIMA).

The study team developed a number of strategies to address possible barriers that could affect adherence and retention, including developing a schedule of visits and assessments designed to optimize the time required of participants and study partners; using appointment reminders; making staff available by telephone 24 hours a day; providing reimbursement for transportation, missed work, meals and hotels during study visits; sending birthday cards; educational brochures, and annual newsletters; and offering in-person feedback meetings. In addition to the main site located in Medellin, three satellite sites were activated in Yarumal, Bogota, and Armenia to provide study drug administration and safety visits closer to the homes of some participants.

In the context of health-care options in Colombia and due to the fact that most of the E280A population did not have

routine access to healthcare, GNA and the sponsors determined that a study-related complementary health plan was needed to ensure timely evaluation, treatment, and follow-up of 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 study-related health concerns in a timely way, or at all.

In view of the fact that the evolution of AD is associated with a range of personal and social challenges affecting the entire family, GNA in collaboration with sponsors created the "Social Plan" for participants' families, consisting of programs and workshops for affected patients, caregivers, and family members including children and incorporating home visits as needed to assist affected patients and families, offer coping strategies, support their participation in relevant research, and try to improve the quality of their lives. The Social Plan does not benefit trial participants directly, and all services are provided whether or not the family members participate in any research studies with GNA [16].

2.3. Evaluation and monitoring of strategies

- For monitoring attrition, the team established indicators that include depressive or other behavioral symptoms, emerging cognitive decline, family/work difficulties, visit and procedure cancellations or tardiness, and reported noncompliance with double contraception methods.
- GNA implemented an annual participant survey that seeks detailed feedback regarding participant/partner concerns related to the protocol, investigators, coordinators, sites, as well as information about personal issues relevant to the welfare of participants and study partners, such as the status of family, work, and health.
- The team reviews concern or discomfort identified at visits, or resulting from the survey, with each participant and/or study partner to clarify and address the cause(s) of barriers/factors and find appropriate solutions/support.

The adherence/retention strategies are reevaluated periodically by GNA and are adjusted according to the needs of participants and based on experience gained during the study. GNA staff are trained to maintain an attentive and supportive attitude toward participants, study partners, and families, with emphasis on respecting their opinions and privacy. This plan was endorsed by the trial's independent Ethics and Cultural Sensitivities Committee [12] and the independent Ethics Committee (Comité de Investigación y Ética del Hospital Pablo Tobón Uribe) and funded by the sponsors.

3. Progress/results

Two hundred fifty-two participants were recruited between December 2013 and February 2017 [12]. As of December 2017, 237 participants remain on treatment, 10 are followed off treatment but per protocol, and five have withdrawn

from the study, the Adherence/Retention is (237/252) 94.0%. Based on preliminary analysis of the data, the most frequent cause of study medication discontinuation or study withdrawal was "personal decision" (due to work-related issues). According to the survey performed in August-September, 2017, of all (236/238) 99.1% participants remain on treatment have been feeling: (210) 88.9% very satisfied, (21) 8.9% satisfied, (4) 1.7% neutral, and (2) 0.8% unsatisfied with their participation in the trial. The (7) 2.9% participants remain on treatment did not respond this question.

4. Discussion/next steps

AD prevention trials are typically complex and long, consequently requiring effective adherence and retention strategies [9]. There are no easy answers about how to retain cognitively unimpaired participants or participants with emerging cognitive/behavioral signs in such trials.

We believe that our Adherence/Retention Plan plays a crucial role in maintaining study adherence and retention. GNA has adopted a proactive and dynamic approach, based on all of the factors and barriers described here, starting with prescreening processes and developing new strategies as new issues arise during the study, recognizing above all that participants want and need to feel special and valued. We note that retention strategies need to be used without being coercive. Thus far, adherence/retention has been high, and most participants feel very satisfied with taking part of this clinical trial. Many participants report feeling highly motivated, despite not knowing their genetic status, hoping that they can help find an effective preclinical treatment for ADAD. Most participants understand the historical importance of this trial and feel that they are trying to help their families as well as the population affected by AD elsewhere in the world. The GNA continues to evaluate the impact of the retention strategies through the study. Sharing our experience and results may help other current and future prevention clinical trials in AD and ADAD in Colombia and worldwide.

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RESEARCH IN CONTEXT

1. Systematic review: The Alzheimer's Prevention Initiative Colombia Trial is a collaborative project involving the Neurosciences Group of Antioquia, Genentech/Roche, the Banner Alzheimer's Institute, and other key partners, studying whether crenezumab can delay or prevent the clinical onset of Alzheimer's disease in cognitively unimpaired individuals who carry the *PSEN1 E280A* mutation. In an effort to optimize participant compliance and adherence and maintain interest in the trial for its duration, the Neurosciences Group of Antioquia developed an "Adherence/Retention Plan."
2. Interpretation: The Adherence/Retention Plan identifies potential barriers to trial adherence related to characteristics of the participants and study partners, protocol design, sponsors, investigators, environmental factors, and characteristics of this population in general and identifies potential solutions to these barriers.
3. Future directions: The Adherence/Retention Plan plays a crucial role in maintaining adherence and compliance needed to achieve the ambitious goals of the Alzheimer's Prevention Initiative-Colombia ADAD Trial.

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