



Winter 2019

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Pathways to a Cure

The CAA Newsletter

MESSAGE FROM THE DIRECTOR

The overarching objective of all our CAA research is to bring us closer to disease modifying treatments. The goal is not just to improve the symptoms associated with CAA, though we hope to do this as well, but to slow or completely stop the underlying process that degenerates the brain. If you think about other neurodegenerative brain diseases, such as Alzheimer's or Parkinson's, none yet has a treatment that can do this. This is the "Holy Grail" of neurodegenerative brain disease.

In this issue we review the results of an early phase study of a candidate for disease modifying treatment in CAA, Ponezumab. Unfortunately, Ponezumab did not show evidence of being a promising successful treatment. This of course is disappointing for all the study participants who generously donated their time and themselves to the study. It is equally disappointing to those of us who designed and conducted the study. We have learned from experience that identifying a successful disease modifying treatment is difficult and requires multiple tries before the goal is met.

We learn a tremendous amount even from the trials that do not give positive results and Ponezumab is no exception. One piece of encouraging news from the study is that we were able to successfully use a new marker of treatment effect: the reactivity of the blood vessels to activation of the visual part of the brain. This marker, which appears to be an early step in CAA, is likely to be useful in future trials for new candidate treatments.

For all the different kinds of research that we do, we are only as strong as the community of CAA patients and supporters who make our studies possible. We are happy to highlight the participation of different members of the community in our newsletter. In this issue we are delighted to share the work of Mr. Mark Cragle in building support and understanding for CAA research.

Sincerely,
Steve Greenberg, MD, PhD



Ponezumab: What We Learned

In this edition of Pathways to a Cure, we wanted to share with our readers a summary of results from the Ponezumab trial, a novel drug trial for Cerebral Amyloid Angiopathy (CAA). Ponezumab was a Phase II, Double Blind, Placebo Controlled, Randomized trial conducted at several centers across the country, with 24 CAA patients participating at the MGH Stroke Research Center. The aim of the trial was to test the efficacy of the experimental drug Ponezumab (a specific type of antibody against amyloid) in reducing amyloid protein in the brain's blood vessels and improving brain function. Although data from the trial ultimately showed that the drug did not produce the improvement in blood vessel function that researchers had hoped to find, it did result in an increased understanding of how to measure this effect for future trials.

In Double Blind, Placebo Controlled, Randomized trials, study participants ("subjects") are randomized (randomly assigned by a computer) across two study "arms": subjects in one arm receive the study drug, and subjects in the other arm receive a placebo drug (a non-active product meant to look identical to the experimental medicine but with no effect).

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— Ponezumab: What We Learned

Neither the study physicians nor the research subjects themselves know which arm of the trial each subject has been assigned to. Thirty-six subjects were enrolled into the Ponezumab trial and were randomized 2-to-1: 24 subjects received the experimental drug and 12 subjects received a placebo. All subjects were monitored for 90 days for changes in brain vascular blood flow, using an innovative measurement method that involved functional MRI (or fMRI). This fMRI technique measured whether blood flow to the brain improved in CAA patients treated with Ponezumab.

In CAA, amyloid protein accumulates in the walls of the brain's small blood vessels. This protein accumulation makes the vessels brittle and less able to respond to changes in blood flow that are normal in our daily lives. As a result, patients with CAA can develop bleeding in the brain as well as other, non-bleeding forms of brain injury, such as white matter lesions and microinfarcts.

The expectation of CAA researchers is that a drug shown to effectively remove amyloid buildup within the vessel walls will

decrease the risk of the resulting brain injuries and improve brain function in areas like cognition and memory. While the findings from the study showed that Ponezumab did not improve cerebral blood flow in patients with CAA, key insights gained from this study will help CAA researchers move forward as we actively continue our search for an effective treatment for this devastating disease. In future studies, we hope to employ other cutting-edge brain imaging techniques to better understand the relationship between amyloid build-up in the blood vessels and both brain lesions and clinical impairments in the disease.

Clinical trials like these are not possible without the time and willingness of dedicated research subjects. We would like to thank the CAA patients and families who participated in this important trial – you are the most essential component in finding a cure for the disease, and we are grateful for your partnership in this cause. Planning of new treatment trials is actively underway and the MGH CAA Research Program will share developments as they occur.

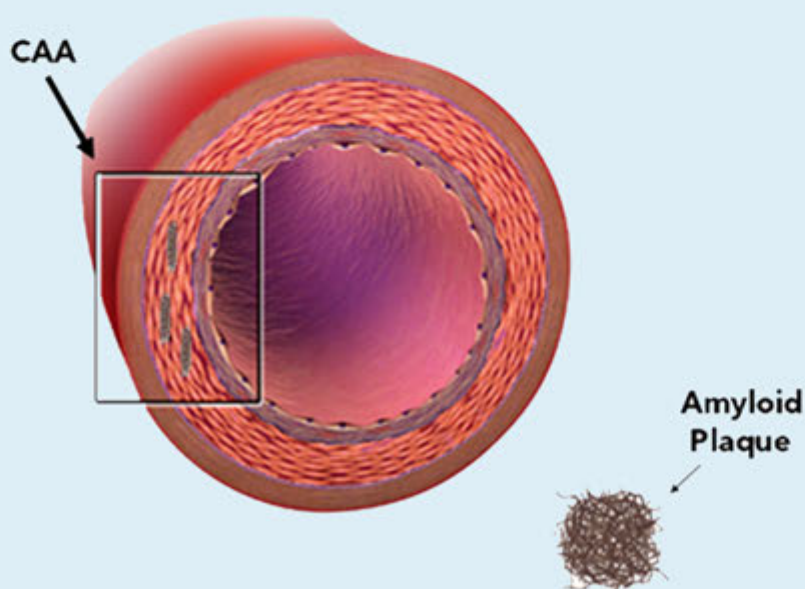


Figure 1: Amyloid plaque in CAA. This illustrates amyloid protein accumulating in the walls of the brain's small blood vessels.



PATIENT SPOTLIGHT: MARK CRAGLE

In this edition of Pathways to a Cure we highlight Mr. Mark Cragle, one of the many members of the CAA community who has inspired us. Motivated by his wife Mrs. Teri Cragle, his two sons, and his two beloved grandchildren, Mr. Cragle has been dedicated to raising funds for CAA research and spreading knowledge since his own CAA diagnosis.

Tell us more about your background:

"I was born and raised in Rochester, NY and received my mechanical engineering degree from RIT. I currently live in Texas. I'm married to the love of my life, Teri, and we have two boys and two awesome grandsons. They really motivate me to do all I can to battle CAA. About nine years ago I had a life-threatening concussion. I had slurring of words and headaches. The slurring went away but the headaches did not improve. About once a year I would get an MRI. Every year they would say there had been no change. Then on June 1st, 2018 I went in for what I thought was a routine evaluation and that's when I was told I had CAA."

How did you hear about the MGH CAA Research Program?

"I spent hundreds of hours researching and found a lot of things on Dr. Greenberg. For example, how he developed the Boston Criteria to help diagnose CAA. I watched a lot of his videos and really liked his demeanor and his intelligence. There is great respect from my local neurologists for Dr. Greenberg as well. I realized that I really had to go and see him. Most of my career I have sold technology including software to hospitals. So, when I stepped into MGH and saw how busy but efficient the hospital was I was very impressed. It was unlike any other hospital I've seen. MGH is always at the top in clinical research and Neurology. In my opinion Dr. Greenberg is the best doctor in the world for this disease."



What drives your passion for CAA research?

"I try to live my life with compassion. I work with special needs children at our church and that really keeps things in perspective. I wish I could do more and be a participant in the research studies at MGH, but my case is unique. The next best thing I could do is to be an advocate for CAA as well as help fundraise."

My intention was to find some miracle drug from a clinical study, but it has just worked out with all the information I have learned that I pay it forward and help to continue to learn more information. CAA is not like cancer where you can do radiation and chemotherapy. The hardest thing to wrap your head around is that there is no treatment. I understand I am on the younger side of people with CAA and have some internet savviness to help organize efforts like this."

Can you tell us a little more about your fundraising?

"You can say this about a lot of diseases but there truly is not enough research or funding for CAA. Quite frankly many doctors don't know enough about CAA. I want to find out as much information as I can and share this information with as many people as possible. My fundraising page has been up since June of 2019. MGH is the best place to raise funds because of the value of the researchers there. I know that some people can't donate or even get on a plane to go to MGH. I am really hoping that some big donation will come in from someone who has been affected by CAA and is blessed to donate a large amount to CAA research. In the meantime, every dollar will help to chip away at a cure."

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What would you like to say to those with CAA and their families?

“This really touches my heart. I have a medical band that says, “keep fighting”. I would tell them to fight this battle with everything you can, don’t give up. No one is promised tomorrow so we should look for joy in each day. Set short-term and long-term goals. My goal is to go to Israel in 2020. Even though this past year has been the hardest time of my life, I still see the beauty that can be found. Also control what you can control, monitor your diet and blood pressure, exercise. Listen to your body and rest when you are tired. If you can get out and socialize that can make all the difference. Let your loved ones know how much they mean to you. Each day is a gift.

To join Mr. Cragle in his fundraising efforts to support CAA research, visit his fundraising page at:

<https://because.massgeneral.org/fundraiser/2174061>

The MGH CAA Research Team wants to thank Mr. Cragle and others in the CAA community for the continued support, dedication and encouragement.

Looking to support CAA Research?

Many patients and families have lent their time and heartfelt dedication to finding a cure for CAA by helping raise funds for our clinical research program. The CAA Research Team at MGH encourages your interest in hosting a charity event or fundraising among friends, family and colleagues, and appreciate the efforts you have already made to this end!

If you would like to learn more about how to support CAA research at MGH, please visit this link:

<https://giving.massgeneral.org/crowdfunding-community-fundraising/>

Individual donations can also be mailed to:

MGH Development Office c/o Shawn Fitzgibbons
125 Nashua Street, Suite 540 Boston, MA 02114

*Please make checks payable to Mass General Hospital,
memo: #1200-028184