Monoclonal Antibody Studies

An Interview with Rachelle S. Doody, MD, PhD

What monoclonal antibodies are you researching for Alzheimer's disease?

We have 2 late-stage programs with 2 monoclonal antibodies. Crenezumab and gantenerumab are both antibodies against amyloid-β (Aβ) protein in the brain. So, we have 2 late-stage molecules, each of them with large double-blind multicenter controlled trials, where we are trying to show an impact on Alzheimer's disease (AD). You might ask why we have 2, and it's because each of those monoclonal antibodies is different. Antibodies have to be directed against something. Crenezumab, delivered intravenously, is directed against oligomeric forms of amyloid-beta: soluble and small aggregates, which we think are probably the most toxic form of amyloid. Gantenerumab, delivered subcutaneously, is directed against oligomers but also against aggregated, deposited Aβ in plaques. The 2 antibodies target Aβ differently, and both have the potential to be efficacious. We hope someday we may be using them to tailor our treatments for patients with AD.

We are also working on phase 2 trials with monoclonal antibodies against tau, another important target in AD pathology. We have a PET tracer allowing us to measure amounts of tau in the brain and are studying monoclonal antibodies to aggregate forms of tau.

Why does targeting Amyloid-β makes sense?

Amyloid is present in every cell in the body, and in typical amyloid metabolism, is cut by enzymes into alpha and gamma forms. In AD, the enzymes cleave amyloid differently—into beta and gamma forms. The beta form is what accumulates in AD and is a small protein that is highly prone to aggregation and has no known function in the body. When aggregates are formed into amyloid plaques, there is a dynamic equilibrium between the plaques, oligomers, and soluble Aβ.

What results do you see with each antibody?

When there are Aβ plaques, around the plaques there are Aβ oligomers, so there's a dynamic equilibrium between the plaques and the smaller species of Aβ. Both plaques and oligomers are good targets for therapy and we've seen signals of efficacy for antibodies against either.

In early trials with crenezumab, we learned that even with lower doses in patients with advanced AD, there was a signal of benefit on cognition, so our current trials are using 4-times-higher doses in patients with prodromal to mild AD. We're hoping it will have an impact on the global abilities of patients, including cognition and function.

With gantenerumab, our early studies were in patients with prodromal or mild AD. Using a fifth of the dose we are planning to use in our next trials, we saw positive effects on not only cognition and function, but also on removal of Aβ in the brains of treated patients.

In an open-label extension substudy, 40 patients were given 1200 mg per month of gantenerumab subcutaneously, with dose titration occurring over 2 to 6 months. Subjects' amyloid level on PET imaging after 52 weeks was compared to their amyloid level on PET imaging at the beginning of the open-label extension. This study showed significantly higher reductions of amyloid plaque with the 1200-mg gantenerumab dosing regimen and showed that within a 6- to 9-month higher-dose treatment period, approximately a third of subjects achieved below-threshold Aβ levels.

How are you measuring effects of the antibodies?

We are using a number of different standardized scales to measure potential treatment effects in our clinical trials. In particular, we use the clinical dementia rating scale sum of the boxes scoring methodology. Many groups including task forces that I've been a part of have selected this tool because it has good properties for measuring cognitive changes over time. Scores on this measure are affected by any benefits we see on cognition or function, so it gives us a combined rating scale. We are also using secondary outcome measures to look at executive function, working memory, and functional tasks. We are using amyloid imaging and tau imaging biomarkers to measure disease progression.

How can clinicians diagnose prodromal Alzheimer disease?

Prodromal AD or mild cognitive impairment (MCI) can be diagnosed with a number of tools and scales--neuropsychiatric testing can be useful but is not necessary. If you can determine that somebody has a true episodic memory disorder with or without other minor cognitive difficulties but hasn't yet begun to decline functionally, then you can identify prodromal AD. Currently, only imaging biomarkers are available, but there is much research on measuring Aβ, total tau, and phosphorylated tau in the cerebrospinal fluid (CSF). We would like to be able to advance other fluid biomarkers and are targeting 18 different potential biomarkers. We hope eventually to help clinicians and researchers not only identify the right subjects for clinical trials, but also to have a biomarker that measure impact on disease activity. ■

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