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Latest Data Publication on Quantifying the Link Between TTR Response and Mortality Reduction

Announcer:
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Dr. Judge:
Let's review a recent publication from JACC regarding the evidence for a direct association between a prompt and sustained increase in serum TTR upon initiation of treatment with acoramidis and improved survival in patients with ATTR-CM. This is ReachMD, and I'm Dr. Dan Judge.

In our study, we looked at serum TTR levels and asked the question, does the change in TTR level correlate with improved outcomes? By way of background, we know that TTR amyloid is associated with destabilization of the TTR tetramer, which results in monomers that misfold and deposit in diseased tissues. We know that the serum TTR level correlates with the degree of instability of the TTR tetramer. And prior studies have shown that the lower your level, the worse your outcomes. Well, no one to date has shown that changes in serum TTR level correlate with improved survival. And so that was our hypothesis going into this study.

As a little bit of background, we have several ways of treating TTR amyloid these days, and TTR stabilizers are something that are certainly proven as effective for this disease. Unfortunately, there's no good way of measuring the stabilization in some of the tests that are done in the basic laboratories, like western blots and fluorescent probe exchange assays; they're not clinically available. Well, I'm excited that the serum TTR level, or the change in the serum TTR level, can reflect the stabilization effect of a medication like acoramidis.

We used the phase 3 ATTRibute-CM clinical trial, where we did have data on most participants for the change in serum TTR level at 28 days.

We divided patients on both treatment and placebo into analyses, looking at their serum TTR level or their change in TTR level.

We used 4 separate quartiles for patients in terms of their change in serum TTR level in response to acoramidis versus placebo. Of course, in placebo, many patients had either no change or a decline in their serum TTR level, whereas nearly all the patients treated with acoramidis had an increase in their serum TTR level. But the degree of stabilization and the degree of change in serum TTR level was something that we were able to measure in terms of how it affected outcomes.

There are lots of things that we know affect outcomes with patients with ATTR-CM. Some of it is baseline demographic, some of it is regarding whether they have a hereditary or wild-type form of TTR. Often, it's the stage of their disease at the baseline.

Well, we took all of those parameters into account and did our analysis separately, to say, putting those univariate measures aside and

doing a multivariate analysis, we were able to show, in fact, that the change in serum TTR level correlated with improved outcomes, including improved survival.

And the first analysis, of course, looked at patients treated with placebo, and compared to those treated with acoramidis. And we know already that there's going to be an improved amount of serum TTR level in response to stabilization.

And we showed with P value less than 0.0001, that survival was better in patients with improved acoramidis-mediated TTR stabilization, measured by their serum TTR level or their change in serum TTR level.

We next looked at quartiles of responsiveness of the change in serum TTR level from as low as 6 mg/dL to as high as 26 mg/dL in the highest arm of TTR stabilization. In that analysis, we once again looked out to 28 days in change in TTR level and looked over the course of the 30-month study for improvements in survival. And we showed, again with statistical significance, that those with the greatest degree of increase in their serum TTR level, or change in serum TTR level in response to treatment with acoramidis, had the best survival.

Well, what does that mean for clinical practice? In the past, there's been only 1 therapy FDA-approved for TTR amyloid, particularly the wild-type form of TTR amyloid. And clinicians would sometimes not necessarily look for other mechanisms of how well is the drug working. As more therapies have become available in clinical practice, the burden is on us to decide, well, what's the right treatment? And how is my patient doing on the treatment that I'm giving them? We use cardiac biomarkers, of course, to assess how someone's doing or their prognosis, and those have been established in multiple measures of prognosis.

But in our analysis of the ATTRibute-CM study, we were able to show separately that this is a univariate measure of improved survival, and it's additive to the other things that we know associate with outcomes in ATTR-CM.

So I see it personally as a responsibility for us as clinicians to check not only cardiac biomarkers but also change in serum TTR levels. Start with a prealbumin level prior to therapy. Remember, prealbumin and serum TTR levels are the same thing. In response to treatment, look for a change. And if the change is not robust, in response to treatment with the stabilizer, look for other better therapies.

We know already from analyses that have been done, including in the ATTRibute-CM study, that patients who were initially treated with tafamidis after 1 year—everyone after 1 year was allowed to take tafamidis if it was available—and those who were on placebo and then added tafamidis at 1 year had a fairly nominal increase in their serum TTR level.

If they extended into the open-label portion of the study and then were switched over from tafamidis to acoramidis, we saw greater increases in their serum TTR level. And that's led to the conclusion by many that acoramidis is a more effective stabilizer at clinically approved doses.

What's the take-home message? Well, once again, in clinical practice, it's a responsibility to measure things like serum TTR levels, and know that the degree of change in the serum TTR level correlates with improved survival. Acoramidis, which is a near-complete TTR stabilizer, is the best of the therapies on the market today at improving TTR stabilization. And serum TTR level is one marker of TTR stabilization that we can use in clinical practice to determine how our patients are doing.

That's all the time we have today. So I want to thank the audience for listening and keeping up with the evidence suggesting a clinically protective role for stabilizing TTR.

Announcer:
This is ReachMD. Be part of the knowledge.