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# The Shifting ATTR-CM Landscape: Early Diagnosis, Emerging Therapies & Personalized Care

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## Chapter 1

**Dr. Garcia-Pavia:**
Achieving optimal outcomes in patients with transthyretin amyloid cardiomyopathy, TTR cardiomyopathy, remains a challenge as diagnosis is often delayed. Patients have a reduced life expectancy and experience debilitating pain and poor quality of life. Join us as we review the latest information on new and emerging treatment options regarding transthyretin amyloidosis and the potential role that it has in patients with cardiomyopathy.

This is CME on ReachMD, and I am Pablo Garcia-Pavia from Madrid, Spain.

**Dr. Cappelli:**
And I'm Dr. Francesco Cappelli. I work in Florence, Italy, in the Tuscan Referral Center for Cardiac Amyloidosis.

So let's begin. Pablo, here is our most basic question of the day: What is ATTR cardiomyopathy?

**Dr. Garcia-Pavia:**
Thank you, Francesco. So TTR cardiomyopathy is a challenging disease that we thought it was super rare, and nowadays we recognize that it’s a frequent cause of several clinical scenarios and diseases that we encounter very frequently in cardiac clinics, like heart failure with preserved ejection fraction, also concomitant with aortic stenosis, or in patients with increased wall thickness that might have been diagnosed with hypertensive heart disease or hypertrophic cardiomyopathy.

In this disease, the body has a protein, a circulating protein, which is named transthyretin which is a transporter of retinol and vitamin A and thyrosine as well. And this transporter protein, which is a tetramer, gets fragmented and deposited in the forms of amyloid fibrils in the heart.

It is important to know that there are two forms of this disease. One is the hereditary form caused by mutations in the transthyretin gene, and this is called ATTRv or hereditary or variant. And the other form is the wild-type form where there aren't mutations, but by a process that we don't really know entirely, the transthyretin, with aging, gets fragmented, and those deposits in the form of monomers get folded and lead to the formation of the transthyretin fibrils at the heart level.

This is a devastating disease, progressive, that ultimately leads to a restrictive cardiomyopathy phenotype and heart failure with grim prognosis if left untreated.

So now that we know better the pathophysiology of this disease, it is important to know how this process of formation of the transthyretin

fibrils can be understood in the sense to have different therapeutic options that we can use in this disease. Can you talk about those different options that we have nowadays or are in development, Francesco?

**Dr. Cappelli:**
Thanks, Pablo. TTR is produced, as you have already said, by the liver. TTR is a tetramer; it is stable. So a first approach is to stabilize this tetramer. And now we can stabilize this tetramer in two different way. The first one is using tafamidis that reduce the instabilization in according to the pouch of thyroxine.

The other way to stabilize TTR is using the same way in which a protective variant, T119, stabilized the tetramer. Acoramidis is able to stabilize with the hydrogen bond between the 4 tetramer. So stabilize the protein, reduce the misfolding of the monomers, and then the deposition.

And the two ways to reduce the deposition of TTR are reducing the production from the liver, and we can reduce the production from the liver with the antisense oligonucleotide or interferon RNA or with CRISPR-Cas9. Now we are able to reduce the production of TTR from the liver till 85%-90% of the normal production. The third way to reduce the amount of amyloid in tissues is to convince some macrophages to remove amyloidosis inside the tissues. And we can do this with monoclonal antibody that can identify TTR in heart or other organs and induce reabsorption of the, already deposited in tissues, amyloid.

**Dr. Garcia-Pavia:**
And what about liver transplantation, Francesco? Because it is known that in the past, this was an available therapy that was used for some patients with TTR cardiomyopathy. Is it still being used?

**Dr. Cappelli:**
Exactly. It was historically used and would get good results, especially in V30M patients. In other kind of mutated patient, the result was not very good. Now this kind of treatment is no more utilized, because now we can reduce the production or stabilize. Probably the drugs that we are going to use are better than the liver transplantation with far less problems related to immune-modulating drugs that are requested during and after transplantation. So probably the drug treatment that we have, and we will have in the future, probably will be better for outcome and reducing all the problems related to the transplantation. So I don't think that liver transplantation will be an option in the next years.

**Dr. Garcia-Pavia:**
In fact, it is more than 6, 7 years since we last performed in our center a liver transplant because of TTR hereditary cardiomyopathy. Probably this will completely disappear with the emergence of the new therapies.

**Chapter 2**

**Dr. Cappelli:**
Now that we understand the pathophysiology of ATTR cardiomyopathy, Pablo, what recent clinical trial results should our audience know about?

**Dr. Garcia-Pavia:**
Thank you very much. So far, there have been 4 different trials in TTR cardiomyopathy that have some positive results.

The first one was published in 2018, and it was the ATTR-ACT trial with tafamidis. In this important study that was conducted for over 30 months, 441 patients were randomized to receive either tafamidis 20 mg in 20% of participants, tafamidis 80 mg in 40% of participants, or placebo in the remaining 40% of participants. Patients were followed during 30 months.

And after that period, it was found that patients receiving tafamidis, the pooled aggregate of both 20 mg and 80 mg, had a 30% relative risk reduction in mortality compared with those receiving placebo. This difference resulted in a number needed to treat of around 8 patients to avoid 1 death, which actually is one of the lowest numbers needed to treat that we have had in clinical trials in cardiology so far.

Regarding key secondary endpoints, they were 6-minute walking test and KCCQ, quality of life assessed by the Kansas City Questionnaire. And it was found that those patients who received tafamidis, the rate of decline on deterioration in these two parameters was much smaller than the rate observed in those receiving placebo. It is important to realize that patients did not improve, but the slope of the deterioration in these parameters was less pronounced in those receiving placebo.

Since that trial was published, there have been additional subanalyses showing that the higher dose of tafamidis had better results than those who received the lower dose. And that is the reason why nowadays in clinic, we use tafamidis 61 mg free acid, which is equivalent to tafamidis 80 mg meglumine used in the trial.

Also, it is important to realize that in this trial, patients who were in NYHA class III had higher degree of hospitalizations, higher number of hospitalizations compared to those who received placebo. And this has been explained by the fact that those patients who received placebo eventually died. And obviously, if you die, you won't be hospitalized.

This was further confirmed by a recent study that analyzed specifically what were the outcomes in patients who were NYHA class III before entering the study. And it was found that in the long term, analyzing these patients, they saw positive outcomes. Regarding mortality, for example, those who received tafamidis from the beginning did better than those who initially received placebo and then, in the long-term extension, they transitioned it to receive tafamidis.

The second study that has been published showing positive results for patients with TTR cardiomyopathy is the study of acoramidis, another TTR stabilizer that

was tested in the ATTRibute-CM trial. In this trial, 632 patients were randomized to receive in a 2:1 fashion, they were randomized to receive acoramidis 800 mg twice a day or placebo. Patients were followed during 30 months, and the primary endpoint was hierarchical analysis consisting of all-cause mortality, cumulative frequency of cardiovascular hospitalization, change from baseline in NT-proBNP, and change from baseline in 6-minute walking test.

Well, the primary endpoint was in favor to patients receiving acoramidis, and 58% of ties in the primary outcome were broken by the two first components of the primary outcome, which were mortality and cardiovascular hospitalization. Of note, the all-cause mortality was not significant in favor to patients with acoramidis after 30 months, despite those treated with acoramidis exhibited a reduction in the risk of mortality of around 25%.

In this trial, the frequency of cardiovascular hospitalization were highly in favor to patients receiving acoramidis with a reduction of almost 50% in the number of cardiovascular hospitalization in this group compared to those on placebo. Finally, it is important to highlight that additional analysis like a time to first event using a composite of all-cause mortality and cardiovascular hospitalization, which is an analysis that is very frequently used in heart failure trials, showed positive effect of acoramidis in those treated compared to those who received placebo in patients included in the trial, with differences observed after only 3 months, which is really, really early. And a number needed to treat to avoid death or first cardiovascular hospitalization of only 7 patients over 30 months.

And lastly, it is important to highlight that we have the opportunity already to know results about the use of genetic silencers for patients with TTR cardiomyopathy. In this regard, the APOLLO-B trial was published last year at *The New England Journal of Medicine*. And in this trial, patients were randomized to receive patisiran or placebo. Patisiran is a genetic silencer, which is given IV every 3 weeks, and after 1 year of therapy, it was found that those patients who received patisiran had better outcomes in the 2 primary endpoints of the study, which were 6-minute walking test distance and quality of life assessed by the KCCQ questionnaire. It is true that the difference between both arms was not great, because obviously it was only 1 year of follow-up. And the difference in the 6-minute walking test distance between the arms was only 14 meters. The difference in the KCCQ also it was around 3.5 points. And both differences in 6-minute walking test and KCCQ were thought to be below the thresholds considered usually clinically significant, which are around a difference of almost 30 meters and a difference in the KCCQ of 5 points. Because of this, patisiran was not approved by FDA for the therapy of patients with TTR cardiomyopathy.

**Chapter 3**

**Dr. Garcia-Pavia:**
We had the pleasure to participate in a new trial that was published this summer and presented simultaneously at the European Society of Cardiology Meeting in London, where the results of a new generation of genetic silencer, vutrisiran, was represented. In this trial, the HELIOS-B trial, patients were randomized to receive either vutrisiran or placebo. And patients were followed for more than 36 months in this study.

After that period, patients who received vutrisiran showed a statistically significant reduction in the composite of all-cause mortality and recurrent cardiovascular events with a reduction of 28% in the overall population. Moreover, also the components of the primary endpoint, both all-cause mortality and recurrent cardiovascular hospitalization, were in favor of those receiving vutrisiran during the double-blind period, which was 33 to 36 months. Regarding all-cause mortality through 42 months, those who received vutrisiran achieved a 36% reduction compared to those receiving placebo. And the subgroup analysis was consistent with these results in all patients.

So certainly, fantastic results across 4 different therapies. And nowadays we have different alternatives that we might be able to use very soon in our patients with transthyretin cardiomyopathy.

**Dr. Cappelli:**

Were there any difference in the HELIOS-B trial between patient that were taking tafamidis and vutrisiran compared to those that was taking tafamidis in the placebo arm?

**Dr. Garcia-Pavia:**
Yeah, that's a very good question. I mean, in this trial, in the HELIOS-B, there was a 40% of patients who received concomitant tafamidis, and this was balanced across those patients who were treated with vutrisiran and those who received placebo. When these were compared regarding the primary endpoint, which were first cardiovascular event and all-cause mortality, there were several trends in baseline tafamidis subgroup on both primary composite and all-cause mortality, but this difference was not statistically significant. This means that it seemed that those patients who received vutrisiran combined with underlying tafamidis had better outcomes than those who received placebo on top of underlying tafamidis. But again, the number of patients who were treated with tafamidis at baseline in this study was limited; only 40% of participants, and therefore, we cannot extract definite conclusions from this analysis.

For those just tuning in, you are listening to CME on ReachMD. I am Dr. Pablo Garcia-Pavia, and here with me today is Dr. Francesco Cappelli. We are reviewing the latest information on new and emerging treatment options regarding transthyretin amyloid and specifically the potential role that modifier therapies have in TTR cardiomyopathy.

**Dr. Cappelli:**
Thanks, Pablo. May I ask you, in ATTRibute trial, all-cause mortality was slightly not significant at 30 months, while the HELIOS-B trial decided to postpone the analysis of all-cause mortality at 42 months, probably using the results of ATTRibute trial, understanding that they had, in the ATTRibute, not enough endpoint of all-cause mortality to reach the significance. Can you comment on this point?

**Dr. Garcia-Pavia:**
Yeah, and you're right. The population of patients with this disease is changing. Nowadays, we realize that the patients have better outcomes than they used to have. And the patients enrolled in these trials are slightly better than the ones that were enrolled in the past, so it took a longer time in order to show differences in mortality across groups of patients. So when the steering committee of the HELIOS-B trial saw the results of the ATTRibute trial, obviously there were concerns about the possibility of not reaching a statistically significant outcome regarding mortality. And they decided, actually, we decided to extend the trial a little bit in order to capture additional events in these patients.

Well, so now that we have several trials where we have demonstrated the efficacy of several drugs, how can we compare the results of these trials? How are we going to decide which drug are we going to use for each patient? Do you have any clue that you would like to share with us, Francesco?

**Dr. Cappelli:**
Thanks, Pablo, for this question. It's really difficult to compare these trials. We have to keep in mind that ATTR-ACT trial enrolled patients in 2015, and patient populations changed vastly from 2015 to nowadays. Now we are diagnosing patients that are older but less advanced disease, more often in NYHA class I and II and not in NYHA class III, with a better profile of NT-proBNP and stage. So these populations are really different to be compared.

In the ATTR-ACT trial, 1/4 of the population was of patients with the ATTR variant. In the ATTRibute and in the HELIOS-B, only 10% of patients were affected by TTR variant. And now our real-life population, at least in my experience, is more or less that; now we have 10% of patients with ATTR variant because we have more patients with wild-type.

So I think it's really difficult to compare these three trials. We can say that these 3 trials were really positive, that these 3 drugs work well, but I think we cannot really say that one drug is better than another until we will have a direct comparison at least between the 2 categories of drugs that we are going to use. I mean, silencer versus stabilizer.

**Dr. Garcia-Pavia:**
Yeah, that’s true because the number of patients that had concomitant tafamidis, because there is no head-to-head comparison trial in this space yet, and the number of patients who had concomitant therapy with a stabilizer in the HELIOS-B trial was limited. It’s very difficult to compare that. I think we will have probably the opportunity to compare stabilizers against combined therapy or even stabilizers against a genetic silencer in the ongoing CARDIO-TTRansform trial, which has enrolled more than 1,400 individuals and probably is large enough to do such comparison between different therapies of drugs.

Well, this has been a really fascinating conversation, but before we wrap up, let's each provide a final take-home message for our audience. Francesco, what do you hope our listeners will leave with today?

**Dr. Cappelli:**
I think the main message should be TTR amyloidosis is more common than expected. It is definitely a treatable disease, so now we

need to think about it and try to diagnose the TTR cardiomyopathy at the earliest stage as possible, and to treat that disease as soon as possible, because the best results of all the drugs that we are using are in patients that are diagnosed at the earlier stage of the disease.

**Dr. Garcia-Pavia:**
I agree completely. But also would like to add that this is a fascinating area with new advances that will come in upcoming years that will not be only about preserving deterioration and limiting deterioration of our patients. We have new therapies on the horizon that might help us also in improving our patients.

So it has been great discussing with you today. I want to thank our audience for listening, and thank you, Francesco, for joining me and for sharing all your valuable insights and experience. It was great speaking with you today.

**Dr. Cappelli:**
Thank you very much, Pablo. It was my pleasure.

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