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Understanding the etiology of HCM and pathways for intervention

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Hello, I am Dr. Roberto Barriales-Villa, a cardiologist at the Coruna Hospital at the University Hospital Complex in Spain, and in this brief presentation I'm going to discuss the etiology of ACM and pathways for intervention.

These are my disclosures.

As you know, hypertrophic cardiomyopathy is a disease of sarcomeric proteins. If we make a genetic study in a patient with hypertrophic cardiomyopathy in up to 40% to 60%, depending of course on the course, we're going to find a mutation in the sarcomeric protein genes, mainly beta myosin and myosin-binding protein C. This is going to be a monogenic disease with a pattern of inheritance, autosomal dominant, and the probability of final mutation is higher in young patients and in patients with familial disease.

In 5% to 10% of the cases, we are going to find genocopies, inherited metabolic and neurologic neuromuscular diseases. And in 25% to 30% the genetic study is going to be negative. No monogenic variant found, older patients, no family history, sporadic presentation with hypertension, and with less cardiovascular events than the previous cohort.

That does not really mean that there is not a genetic course in these patients, realize a complacent etiology. We know that there is polygenic inheritance where non-Mendelian factors and non-genetic factors are required to reach the threshold for development of disease. But the precise mechanism by which the pathogenic variants result in the clinical phenotype has not been fully elucidated. We know that the chains of amino acids and mutant variants, because of the negative dominant effect or the deficiency of the protein because of a HER2 category, for example, because of the upload insufficiency mechanism instigate a series of functional changes in the sarcomere.

It has been previously published that the mutations in beta myosin induce sarcomere hypercontractility. And this is very interesting because if we look at the echocardiogram of a patient with hypertrophic cardiomyopathy, we can see that the myocardium is hypercontractile, particularly in the earlier stages of the disease, which raises the possibility that the increased activity of the sarcomere is at the basis of HCM development.

Let's focus on the sarcomere. The contractile unit of the cardiomyocyte composed by thick and thin filaments. The thick filament, mainly composed by beta myosin and myosin binding protein C. Remember, the 2 main affected genes when we make a genetic study in a patient with HCM. And the thin filament, mainly composed by f-actin and troponin. But the real motor or molecular engine of the contraction is the cardiac myosin with different domains, 2 heads, 2 tails, and in the head an enzyme and ATP-ase that relies ATP to ADP that generate the energy required for the contraction.

And how does contraction occur? Well, according to the slide and filament theory, or the swinging cross bridge model, muscular contraction is defined as the propelling of the thin filament over the thick filament, forming actin-myosin cross bridges, and all these pathways are regulated by calcium. As you can see in the video, when calcium increase, binds troponin C, that cause to move tropomyosin exposing the acting myosin binding sites. It’s very important to take into account that the force generated by the muscle is proportional to the number of actin-myosin cross bridge that form when calcium goes down, the thin filament is activated and the

realization occurs.

Nowadays this theory is better to call as swinging lever arm model because further evidence that shows that myosin not only is important in the 4th generation, but also in the regulation of the contraction with 3 different myosin configurations. The first one, the active one with a strong actin/myosin cross bridge occurs during contraction. The other 2 occurs during relaxation. The super related state where the heads of the myosin are bounded to the backbone of the thick filament, and the disorder-related state where the 2 heads of the myosin are freed from the backbone.

The ATP hydrolysis rate is totally different, maximum in the active form and minimum in the super relaxed state. Using a sports simile because of the recent Olympics, we can say that in the super relaxed state, the cyclists of our sarcomeres are resting at the Olympic Village. In the disorder related state, they are on the bike at the start, but without pedaling. And in the active form, the cyclists are pedaling at full power.

In healthy humans in resting condition, at least 50% of the myosin are in the super relaxed state. But if we need to do an exercise, some of these myosin heads that are in the super relaxed state are required back to being axiom.

It has been demonstrated that mutation in beta myosin and myosin binding protein C can cause the same effect. So, it looks like in hypertrophic cardiomyopathy patient there is an excess of actin/myosin acting myosin cross bridge activation that leads to hypercontractility, impaired relaxation and stiff ventricles. The good news is that today, we can reverse the situation. There is a, for the first time in HCM treatment, disease-modifying treatments as the myosin inhibitors. We can say that we can send our cyclists to rest. Mavacamten is the first in class allosteric inhibitor of cardiac myosin ATP-ase that reduced the affinity of a thin myosin regulating the number of HEF that are in the super relaxed states.

In a previous feline model of obstructive hypertrophic cardiomyopathy, the mavacamten demonstrated to reduce to reduce hypercontractility, some and left ventricular outflow tract obstruction. Mavacamten has finished three phase 3 clinical trials with very good results. And for the first time in European guidelines, mavacamten is a recommendation to aid in the treatment of symptomatic obstructive hypertrophic cardiomyopathy.

There is next-in-class myosin inhibitor, aficamten, also designed to treat hypercontractility with a shorter half-life and acting in a different myosin domain. Aficamten has a concluded a phase 3 clinical trial in obstructive hypertrophic cardiomyopathy, the SEQUOIA-HCM, also with very good results, and is waiting for the approval from the FDA and the EMA.

Future. We cannot forget the nonobstructive hypertrophic cardiomyopathy with two phase 3 clinical trials, 2 big phase 3 clinical trials, the ACACIA-HCM and ODYSSEY-HCM that they are ongoing. We need to wait for the results, as I said.

What happens if we give mavacamten or aficamten to pediatric patients? Well, there are also two phase 3 clinical trials ongoing, CEDAR-HCM and SCOUT-HCM. But previously, mavacamten and aficamten have demonstrated to restore the function of cells affected with mutations in beta-myosin, myosin binding protein C, and even troponin I.

A very interesting aspect is that mavacamten had demonstrated in a mouse-model carrier of pathogenic mutation in beta-myosin that the early initiation with treatment can prevent the left ventricular hypertrophic development disarray and fibrosis. That is very interesting because we don't know if we can stop the disease progression in human healthy carriers. We need more trials.

Other drugs, targeting other sarcomeric proteins. There is a drug, the EDG 7,500, that regulates a number of actin/myosin cross bridges without affecting the motor and conserving the function of the heart. It’s a phase 2 ongoing, very promising.

There are 2 drugs, ninerafaxstat and sotagliflozin, that have two phase 3 trials ongoing. This drug shift the metabolites from fatty acids oxidation to glucose oxidation, improving myocardial energetics. And we cannot forget gene therapy. There is one Phase 1 trial ongoing in carriers of myosin binding protein C mutations, and the main concern of these studies are the safety and the durability of the effect.

To conclude, we can say that the future of hypertrophic cardiomyopathy is bright and very promising. Thank you very much for your attention.