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Managing patients with HCM and HF: what's new in the therapeutic landscape?

Hello, my name is Iacopo Olivotto. I'm a clinical cardiologist working in Florence, Italy, and together with you, I would like to revisit the old and new treatment options for heart failure in patients with hypertrophic cardiomyopathy. These are my disclosures.

Hypertrophic cardiomyopathy is a very peculiar disease. As you know, genetic cardiomyopathy is the most common genetic cardiomyopathy, and heart failure in this disease occurs in two opposite contexts. The first one is in the early phase of disease when the phenotype is hypercontractile, characterized by left ventricular outflow obstruction, which is a dynamic process caused by systolic anterior movement of the mitral valve causing impedance of flow, and hence heart failure symptoms. This is fully reversible and has been, as you know, addressed in many ways, including surgery and alcohol septal ablation. At the other opposite of the spectrum, there is advanced LV systolic and diastolic dysfunction. This is the so-called end stage or burnt out phase of disease. It is usually defined as hypokinetic dilated, but it's most often hypokinetic restrictive phase of disease where the dysfunction is caused by extensive fibrosis. It is quite difficult to treat because symptoms are refractory and the myocardium is so altered in its structure that response to standard treatment is often unsatisfactory.

We are now on the verge of a big revolution in this context due to the recent introduction of cardiac myosin inhibitors which have been designed specifically to counter the excessive myosin activation seen in patients with hypertrophic cardiomyopathy and restore a normal energetic and metabolic state by lowering the affinity of myosin for actin. There are two molecules developed for clinical use. The first one is mavacamten, which is already approved for clinical use in US, Switzerland, Brazil and soon to come to the rest of the European Union, and aficamten, which is still undergoing clinical experimentation. These two drugs work with very similar mechanisms and, as you will see, have similar efficacy.

Again, what these drugs do in hypertrophic cardiomyopathy, at least what we know from beta-myosin mutation model, which is the best studied model, there are too many myosin heads involved in contraction at any given cycle. What myosin inhibitors do is they reduce affinity of myosin for actin, and therefore reduce the number of heads involved in contraction at any given cycle. Therefore, this sort of, if you want, hyper-consuming and unaffordable Lamborghini, which is the HCM heart, now becomes a diesel truck which is more sustainable over a lifetime. By doing so, we know at least in the short term that these drugs are effective in improving functional capacity, reducing the gradient in obstructive patients, and restoring quality of life.

This is EXPLORER-HCM, the first phase three trial which was successfully completed with mavacamten and led to registration of the drug. In this trial, the primary endpoint, which was a combination of functional capacity and improvement in NYHA functional class, was achieved by 37% of patients as opposed to 17% in placebo. Not too many patients reached the primary endpoint here, because peak VO2, as you know, is very much dependent on heart rate and most of the patients were on beta-blockers, but as you will see in a later slide, functional capacity in fact improved in most of the patients. If you look at the secondary endpoints, the reduction in the gradient and improvement in symptoms and improvement in quality of life was quite impressive.

These are the main results. As you can see here, the reduction in exercise gradient in blue below a threshold of 50 in majority of patients, no change in placebo, so very striking reduction in the gradient in the mean of almost 50 millimeters of mercury. This was achieved at the cost of a very small reduction in ejection fraction. This being a negative inotrope, it's nice to know that the safety profile

of the drug was overall quite satisfying and only a handful of patients had to temporarily suspend the drug due to excessive falling ejection fraction, but were later able to resume the drug and complete the study and enroll into the long-term extension.

Quality of life improvement, as measured by the Kansas City Questionnaire, striking improvement, nine points, which is quite impressive for a drug in the content of a heart failure model. This is just to show you one of the example.

This is a patient from Florence enrolled in EXPLORER. You can see the SAM hypercontractile phenotype, the high gradient, the very relevant ECG abnormalities, which you would expect in the hypertrophic cardiomyopathy patients, but after 30 weeks of treatment, you can see the same patient has preserved but less hypercontractile systolic function, no SAM, the gradient has gone and quite unexpectedly, the ECG abnormalities have gone as well. We don't know what these ECG changes mean, but, obviously, it's nice to speculate maybe that we are actually acting at the profound level, at the molecular level and energetic level in HCM cardiomyocytes.

This is a recent sub-analysis of EXPLORER looking at other CPET, cardiopulmonary testing parameters, which are not heart-rate dependent, so different from peak VO2 including V2- VCO2 ratio, and you can see here that the improvement in functional capacity is quite consistent in patients on mavacamten as opposed to patients on placebo.

Furthermore, in a different sub-analysis of EXPLORER, there is preliminary evidence that treatment with mavacamten leads to favorable remodeling of HCM hearts. Of course, we still lack very long-term data, but at least in the 30 weeks of treatment, and now the data has extended up to 120 weeks, there is a small but significant reduction in LV mass index, a reduction in the left atrial dimension, and also some reduction in maximal LV wall thickness.

This is, for example, one of our patients who has now been on the drug for three years, and you can see that the cavity size, as well as the septal shape, and to some extent, the extent of the hypertrophy has reduced. We don't know yet whether this is real loss of mass or just a remodeling, a better relaxation of the heart, which leads to this different geometry, but there is definitely some action on the myocardial that is quite intriguing to see, and we hope that this will amount to the demonstration that mavacamten is a disease-modifying drug for patients with hypertrophic cardiomyopathy.

Of course, aficamten is also very interesting drug. The main difference from mavacamten is the shorter half-life and maybe less interaction with the concomitant medications, as well as a shallow dose-response curve.

The phase two study shown here was quite successful and the data in terms of reduction of the gradient and symptomatic response is quite similar to that shown by mavacamten in a similar phase two trial. Aficamten is now undergoing a large phase three trial in hypertrophic obstructive cardiomyopathy patients.

Based on what we have just seen, they're very exciting. It's the first time that a drug has been specifically developed, or a class of drugs have been specifically developed for a genetic cardiac disease. What are we going to expect in patients with obstructive hypertrophic cardiomyopathy? First of all, patients will need to still be tested on the standard drugs that we use for obstruction, including beta-blockers, calcium antagonists, and disopyramide before moving to invasive options such as alcohol ablation or surgical myectomy if symptoms are refractory, and this is the standard of care as advocated by international guidelines. It's quite likely that myosin inhibitors will position themselves here, so in patients who have not responded fully to first-line therapy, but are not yet or would be candidates for invasive options but may be treated with myosin inhibitors instead.

Whether this will actually lead to reduction or the avoidance of invasive treatment altogether, is the object of another study called VALOR, which is another study performed with mavacamten in patients with obstructive hypertrophic cardiomyopathy who were already candidates for surgery, either listed or fulfilled the guideline criteria for surgical myectomy or alcohol ablation eligibility. These patients were enrolled and started randomized placebo to mavacamten one to one and re-evaluated at the end of the study in terms of whether they were still eligible for surgery or whether they still wanted to be operated or not. As you can see on the slide on the left, 82% of the patients enrolled on mavacamten, at the end of the study were not eligible for invasive options as according to international guidelines, as opposed to only 23% of the patients on placebo. Most of the patients on placebo remained eligible and, in fact, most of them were operated. The reason for this shift is that patients on mavacamten, of course, they had a fantastic response in terms of symptomatic improvement and full in outflow gradient.

Ultimately, this is definitely a drug that is very useful to treat heart failure in the context of obstruction, but let's remember that these drugs were not developed for obstruction specifically. They were developed in order to improve the myocardial abnormalities associated with HCM, and in animal models, this is shown to be the case.

Hopefully, we will soon, or maybe not so soon, it will take some time to show that these drugs, in fact, are disease-modifying and may prevent disease progression, which leads us to the second scenario of heart failure in this disease. The disease that's burnt out where fibrosis has set in and where, as in this very young patient who we have followed over time, he was diagnosed as a teenager, you can

see, if you move across these images, over a span of 18 years, you can see that the phenotype is progressively less hypercontractile. The hypertrophy is progressively less evident, and what is happening here is this, the fibrosis is setting in, is becoming extensive. This is a patient that represents a minority of about 5% to 10% of our patients, so it's not the most common scenario in this disease, fortunately, but it is extremely challenging to treat, extremely challenging. Of course, as you can expect, response of these kinds of standard heart failure treatment for left ventricular dysfunction is not the best.

Maybe myosin inhibitors may have a role here as well in the context of heart failure in non-obstructive disease. There's a very large phase three study ongoing right now called ODYSSEY-HCM. This will take another couple of years before we have the data.

At this very meeting, some data on aficamten in patients with non-obstructive disease will also be presented by Dr. Masri.

Of course, we now are looking at other molecules. For example, there is a lot of hype, interest in the effects of SGLT2 inhibitors because of the potential effects at various levels on different models of heart failure. Unfortunately, all of the studies on HFpEF have failed to enroll patients with hypertrophic cardiomyopathy.

We still don't have any specific data, but some of the direct effect, including inhibition of CAM kinase and improvement of mitophagy and autophagy are definitely very interesting because they are part of what we desire to achieve in hypertrophic cardiomyopathy hearts.

There is one little small study ongoing with empagliflozin, and that's still in the early days, but hopefully, some results will come from this.

Also, another effort is now being pursued with a mitotrope, with an agent called ninerafaxstat, which is aiming to shift myocardial metabolism from fatty acid oxidation to glycolysis. This has already been done in HCM with a molecule called perhexiline, which showed encouraging results several years ago. However, the drug is challenging to use and may be hepatotoxic. This is a new attempt to improve metabolism and cardiac efficiency in order to improve the energetic status and possibly ameliorate heart failure in the context of non-obstructive disease mostly.

There is a phase two study which is now ongoing and enrolling, and as you see can here, the key efficacy endpoints again will be peak VO2 and phosphocreatine to ATP ratio as a measure of energetic efficiency and energetic homeostasis. This is, again, early days.

These are just initial efforts. We still don't have the magic wand to treat the myopathic process when this is too advanced, but still, there is a lot of investment, there's a lot of energy, there's a lot of ongoing research in the field. I think something is changing in the field of hypertrophic cardiomyopathy, particularly in the early phase model with the hypercontractile phase model, which is often associated with obstruction and heart failure due to obstruction. Cardiac myosin inhibitors are the new kids on the block which show promise to not only reduce the need for surgery or interventional procedures, but also in the long-term modify, reduce the adverse consequences of sarcoma gene mutations on the myocardium and possibly reduce the need for progression of disease towards the late end-stage phase of disease and refractory heart failure. Although we still don't have an answer to that. Hopefully, we'll have more and more data as further studies are being performed. Thank you very much.