

Aficamten: A New Cardiac Myosin Inhibitor for Obstructive Hypertrophic Cardiomyopathy

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Interview Summary

Cardiac myosin inhibitors (CMI) are set to change the treatment landscape for patients with obstructive hypertrophic cardiomyopathy (oHCM). The newest entrant into this class of drugs is aficamten (CK-274). Safety and efficacy data from the Phase II REDWOOD-HCM trial were announced in July,¹ and additional findings were presented in a late-breaking clinical trial session at the Heart Failure Society of America (HFSA) Annual Scientific Meeting 2021 in Denver, Colorado, USA, and online.²

In this interview with the EMJ, Iacopo Olivotto, Head of the Cardiomyopathies Unit at Careggi University Hospital, Florence, Italy, provided his insights into the data and highlighted the aspects he believes are the most relevant for patients and physicians.

EFFICACY

REDWOOD-HCM was a multicentre, randomised, placebo-controlled, double-blind, dose-finding clinical trial of aficamten in patients with symptomatic oHCM on background medical therapy. Two cohorts were randomly allocated 2:1 to aficamten or placebo. Patients allocated to aficamten received up to three escalating doses once daily: 5, 10, and 15 mg in cohort one (n=21) and 10, 20, and 30 mg in cohort two (n=20). Echocardiography was performed after 2 weeks of treatment at each dose to assess eligibility to up-titrate to the next dose. Dose titration was performed at Weeks 2, 4, and 6. The overall treatment duration was 10 weeks with a 4-week

follow-up period after the final dose. The baseline characteristics of patients in the trial were consistent with a symptomatic population with high resting and Valsalva gradients, reflecting a substantial burden of disease.

Regarding efficacy, the trial demonstrated consistent and clinically meaningful reductions in left ventricular outflow tract (LVOT) gradients within 2 weeks. For patients receiving aficamten in cohort one (n=14), the average Valsalva LVOT gradient changed from 74.4 mmHg at baseline to 38.1 mmHg at 10 weeks, while the corresponding reduction for those in cohort 2 (n=14) was from 82.3 mmHg at baseline to 29.8 mmHg at 10 weeks. For patients in the combined

placebo group (n=13), the average Valsalva LVOT gradient changed from 84.6 mmHg at baseline to 76.0 mmHg at 10 weeks ($p=0.001$; $p<0.0001$ in cohorts one and two, respectively, versus placebo). Significant changes in resting LVOT gradient were also observed in the aficamten groups.

The target goal of treatment, resting gradient <30 mmHg and post-Valsalva gradient <50 mmHg at Week 10, was achieved by the majority of patients receiving aficamten (78.6% and 92.9% of cohorts one and two, respectively) compared to just 7.7% of those in the placebo group.

“These gradient results would not have been achieved with any other drug regime in current practice, so that is what’s most striking,” said Olivotto. “The effect on the gradient and on the overall obstruction in patients with both dosing regimens was notable.”

RAPID ONSET OF ACTION

A distinct feature was that the treatment effect was observed after just 2 weeks, highlighted by Olivotto: “That’s because of the 3.4-day half-life of aficamten, which allows for rapid titration.”

Reductions in LVOT gradient were maximised within 2–6 weeks and were sustained until Week 10. Reversibility of the pharmacodynamic effect was seen after a 2-week washout, with resting LVOT gradients, N-terminal pro-B type natriuretic peptide and left ventricular ejection fraction (LVEF) returning to baseline values. “It’s good to have a drug that responds fairly quickly,” said Olivotto, “and the effect will revert fast if patients drop their ejection fraction too much, which is important for safety.”

SAFETY

Treatment with aficamten was generally well tolerated and the incidence of adverse events was similar between treatment arms. No patients receiving aficamten in cohort one had an LVEF $<50\%$. In cohort two, one patient with an LVEF at baseline of 58% was up-titrated to 20 mg of aficamten and experienced transient LVEF reduction to $<50\%$ (remaining above 40%) requiring down-titration. Another patient had an LVEF $<50\%$ (49.3%) at Week 10 (end of treatment). The patient was on 20 mg of

aficamten. No dose change was required per protocol and LVEF returned to baseline at Week 12. No interruptions or discontinuations of treatment with aficamten occurred in any patient.

Olivotto observed that the safety profile was “extremely favourable.” He added: “There were only two patients with transient reduction of ejection fraction below 50%, which was totally reversible.” Overall, the most remarkable findings, he said, were “the consistent and sustained reduction in gradient with only a very small reduction in ejection fraction”. LVEF returned to baseline in all patients within 2 weeks after the end of treatment in both cohorts, which was consistent with the reversibility of effect observed in healthy participants in the Phase I study of aficamten.

SYMPTOMS AND QUALITY OF LIFE

Treatment with aficamten was associated with changes in New York Heart Association (NYHA) class. Improvement by at least one class was achieved by 31% of the placebo group, 43% of patients on aficamten in cohort one ($p>0.1$), and 64% of patients on aficamten in cohort two ($p=0.08$).

Olivotto noted that during treatment with aficamten, patients found that their symptoms gradually got better and better. “The sheer benefit in quality of life is what matters most to patients. They not only regain the ability to do things that they have not done for a long time but occasionally are even able to do things that they have never done before.”

The weakness and fatigue experienced by patients with oHCM, particularly in hot weather, is often a side effect of β -blockers. However, Olivotto noted: “There are hopes that CMIIs may not only be decisive as add-on therapy, but may emerge as ideal in monotherapy and therefore avoid the side effects of β -blockers.”

SELECTION OF MEDICINES IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

The standard first-line treatment for oHCM is β -blockers. Olivotto said: “ β -blockers are effective for provokable obstruction, in

other words related to effort, but less so for resting obstruction. Disopyramide is usually added, which is more potent for resting obstruction.” Calcium channel blockers are rarely used at his institution unless the patient is intolerant to β -blockers.

“The point is that β -blockers alone may provide some symptom relief but almost never provide relief of severe obstruction,” explained Olivotto. “Disopyramide provides complete resolution of symptoms in only one-quarter of patients. It also has side effects, particularly very dry mouth, constipation, and prostatic problems in males. In addition, disopyramide tends to lose efficacy over time because of tachyphylaxis so we use it a lot as a bridge to myectomy.”

Overall, Olivotto estimated that 70–75% of patients with oHCM have some response to standard medications, at least for a period of time. “But if we’re talking about optimal response, meaning normal quality of life and exercise performance, in my experience less than 10% of patients achieve that with current drug therapies. Considering that the average age of these patients is about 45 years, this is not a trivial matter,” outlined Olivotto.

EVALUATING THERAPEUTIC RESPONSE IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

Routine assessment in oHCM includes echocardiography. Responders in clinical trials are defined as patients in whom treatment reduces resting gradient to <30 mmHg and exercise gradient to <50 mmHg or ideally <30 mmHg. Reductions in gradient are usually accompanied by symptom relief. According to Olivotto, clinicians typically rely on patients’ report of symptoms, particularly angina, shortness of breath, presyncope, palpitations, and fatigue, to evaluate the efficacy of pharmacological treatment. “The other thing that is very peculiar to oHCM is postprandial symptoms,” he added. “We have patients with obstruction consistently telling us that they cannot eat normal meals at night because they get angina or shortness of breath, and socially that’s a disaster.”

NYHA class is routinely evaluated. In addition, more precise quality of life endpoints are

entering the research arena, such as the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Olivotto said: “In chronic, slowly progressive conditions such as genetic cardiomyopathies, in general, patient-reported outcomes are really the future and patients will be the pioneers advancing the field.” Initiatives are underway to monitor sports participation, leisure activities, and lifestyle. “Wearables are probably the way to go,” he commented. “This is a disease that changes day-to-day so tracking activities, side effects, and symptoms on a smartwatch or smartphone would be a more accurate representation of patient experience than periodic measurements.”

HOW CARDIAC MYOSIN INHIBITORS FIT INTO THE TREATMENT LANDSCAPE

Initially, candidates for CMI treatment will be patients with symptomatic oHCM who are not responding well or optimally to medical treatment and are not immediate candidates for surgery. “The debate here is whether to use CMIs as an add-on to β -blockers, for example, or simply as a monotherapy thereby avoiding, for example, chronotropic incompetence and fatigue due to β -blockers,” said Olivotto. “In the short term, I would see CMIs as an intermediate step between first-line pharmacological treatment and surgical options; hopefully, however, indications may broaden with time.”

While REDWOOD-HCM was conducted in oHCM, which is a relatively homogenous population, Olivotto envisages CMI usage expanding to other conditions. “These are drugs that are aimed at treating the myocardium, not just the obstruction, so I think this is a pipeline of agents that will help us treat the whole spectrum of patients with HCM,” he said.

Olivotto’s hope for the future is that CMIs will be used to stop oHCM even before symptoms develop: “Ideally, we would identify mutation carriers with a very early propensity to develop the phenotype and treat them with a CMI to halt the progression of disease, as we observed in experimental models.”

FUTURE DIRECTIONS FOR CARDIAC MYOSIN INHIBITORS

An update of the European cardiomyopathy guidelines is expected and for the first time will have randomised trial evidence to support recommendations on CMIs for relief of symptoms in oHCM. Olivotto would like to see an outcome study in approximately 500 patients performed in the next 5 years, to complement the “feel and function” trials performed so far. “Such a trial would need a composite endpoint to keep the required duration of follow-up manageable; for example, hospitalisations, implantable

cardioverter-defibrillator shocks, transplant, and new-onset atrial fibrillation. Such trial design may ultimately allow accrual of evidence that CMIs improve outcome in patients with HCM, as well as resolve potential doubts regarding their long-term safety.”

The Phase II REDWOOD-HCM open-label extension trial is ongoing and includes a cardiac MRI sub-study to evaluate changes in cardiac morphology, function, and fibrosis. The results of REDWOOD-HCM have informed dose selection and a Phase III registrational clinical trial is expected to start in 2021.

References

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2. Cytokinetics. Full results from REDWOOD-HCM demonstrate improvements in biomarkers and heart failure symptoms in patients with obstructive hypertrophic cardiomyopathy treated with aficamten supporting progression to phase III clinical trial. 2021. Available at: <https://ir.cytokinetics.com/news-releases/news-release-details/cytokinetics-announces-results-redwood-hcm-and-galactic-hf>. Last accessed: September 2021.

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