COMMENTARY

Considerations for managed care pharmacy in evaluating mavacamten, a novel agent for obstructive hypertrophic cardiomyopathy

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It is estimated that between 1 in 200 and 1 in 500 individuals in the United States are with a heart muscle disorder called hypertrophic cardiomyopathy (HCM).¹ Hypertrophic obstructive cardiomyopathy (HOCM), a subtype of HCM, occurs in patients who have a narrowing and obstruction of the left ventricular outflow tract (LVOT), which can occur with either exertion or at rest. Patients with HCM exhibit other diverse exertional symptoms, including diastolic dysfunction and microvascular angina.² In addition to the exertional symptoms that can occur at random, there is a small yet real risk of sudden cardiac death.

Patients with HOCM are typically treated with β -blockers (BBs) and calcium channel blockers (CCBs) as first-line therapy to mitigate symptoms. Disopyramide, when available and not subject to supply chain issues, is also used with some benefit in patients who need more control BBs and CCBs. Patients may be eligible for surgical procedures that alleviate the occurrence of symptoms. However, the surgeries themselves carry a small risk of death and are only recommended to be completed at centers of excellence (COEs), of which there are only 42 around the continental United States. There are dozens of states that have no HCM COE, and patients

hoping for the best outcome of surgery must travel to a nearby center.³

Currently, there are no medications specifically indicated for treatment of HOCM. Mavacamten, a novel agent that targets the sarcomeres, has been studied in patients to help improve outcomes. Recently, the Institute for Clinical and Economic Review (ICER) published a final evidence report on the effectiveness and value of mavacamten for patients with hypertrophic cardiomyopathy.²

ICER determined that, when added to usual care vs usual care alone, mavacamten rated promising but inconclusive (“P/I”).² When compared with disopyramide, ICER rated the clinical effectiveness of mavacamten as “P/I,” mostly due to weak evidence supporting the use of disopyramide. ICER did not clinically compare mavacamten with surgical procedures because, although it is thought that the outcomes with surgery may be more effective than with mavacamten, there are small but real significant adverse outcomes, including death.²

Managed care pharmacists will need to consider the unique patient-specific factors when determining clinically appropriate pharmacy coverage policies. In addition, a review of existing medical policies for patients with HOCM is warranted to limit

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unintentional consequences due to HOCM's heterogeneous nature.

Patient Factors and Perspectives

“The current treatments just aren't enough. As patients, we've become accustomed to the thought of only ever being able to get treatment for symptoms...but we're tired of that. We want more than just symptom relief.”

—Wendy⁴

HOCM is a heterogeneous disease in that patients exhibit a wide spectrum of disease activity both

compared with other patients, as well as to themselves. This presents many challenges for patients and their families. Patients have reported being able to go up a flight of stairs with no exertional symptoms one day yet have significant symptoms the next, with apparently no rhyme or reason.⁴

According to the Hypertrophic Cardiomyopathy Association, approximately 90% of the patient population take BBs and CCBs, 30% of the population have implantable cardioverter defibrillators, and nearly 25% have had a myectomy, whereas 5% have had the alcohol septal reduction to treat the LVOT obstruction. With these limited treatment options, patients like Wendy, quoted at the start of this section, are hoping for treatments that treat the disease itself rather than only symptoms.⁴

Just like how HOCM is a heterogeneous disease, patients have reported vastly different treatments and expertise of providers with HOCM. Medical management today involves the use of medications and devices that were not designed, studied, or intended for HOCM. This results in challenges to providers who may not be well versed in the differences on how these treatments affect patients with HOCM vs those with other disease states.⁴

Patients with HOCM have a vastly affected quality of life. Approximately 10% of patients make the difficult decision to leave the workforce and go on disability. Many patients have comorbid conditions of depression and anxiety due to the constant fear of possibly experiencing sudden cardiac arrest and possible death. Activities that one takes for granted, such as walking from the car to the store or going up a flight of steps, can be daunting and overwhelming for patients.⁴

Value of Patient-Reported Outcomes

Patients with HOCM have reported challenges with finding the right combination of medical management for them and subsequent success of these measures on quality of life. About 53% of patients reported that treatments “helped somewhat” and 37% reported that the treatments “helped a lot” or had “significant benefit.”⁴

The EXPLORER randomized controlled trial (RCT), which compared patients on mavacamten vs placebo while on first-line treatments, included patient-reported outcomes (PROs) as secondary endpoints. These include Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath subscore (HCMSQ-SoB).⁵

The KCCQ-CSS combines both physical limitation and symptom and frequency domains that reflect the main ideas of the New York Heart Association (NYHA) functional class. Scores for the KCCQ-CSS are represented on a scale from 0 to 100, in which lower scores represent more severe limitations/symptoms and a score of 100 signifies no symptoms or limitations.⁶ Studies demonstrate that every 5-point improvement in KCCQ-CSS score is associated with a 10% reduction in risks of hospitalizations and mortality, 100-m improvement in a 6-min walk test, and an increase of 2.5 ml/kg/min in peak oxygen consumption.⁶ The HCMSQ-SoB is a novel PRO that was developed by the sponsor of EXPLORER trial specifically to help assess symptoms patients with HOCM exhibit, particularly dyspnea, fatigue, arrhythmia, chest pain, dizziness, and loss of consciousness.⁷

Patients receiving mavacamten in the EXPLORER trial demonstrated improvements in KCCQ-CSS of 9.1 (5.5 to 12.7) and -1.8 for HCMSQ-SoB (-2.4 to -1.2), both at $P < 0.0001$. In addition, the scores for KCCQ-CSS reverted to baseline within 8 weeks for patients in the study during the wash-out period who were previously receiving mavacamten.² These results demonstrate not only significant but also meaningful improvements in PROs for HOCM patients and mavacamten's effect on patients' lives.

ICER does not use either of these PROs, but rather the NYHA functional class, in determining the quality-adjusted life-year (QALY) values associated with the use of the medications. Although NYHA functional class is used in managing patients with HOCM, there is variability both daily and throughout the lifespan of patients with HOCM.⁸

Other PROs that may help better manage patients with HOCM include those that help assess depression or anxiety, like the Patient Health Questionnaire-9. Patients with HOCM are uncertain if, and to what degree, their disease state will progress. Many patients report challenges with anxiety, depression, isolation, relationships, and job opportunities. Patients recommend that future clinical trials also include mental health secondary endpoints to highlight these additional issues associated with the disease that are not directly tied to the disease state.⁴

Conclusions

Managed care pharmacists should review the ICER study and understand the difficulty in assessing not only an inter-heterogeneous but also intraheterogeneous disease. This heterogeneity should be considered when developing coverage policies not only for mavacamten but also for other treatment-related policies. For example, although the ICER report showed that surgical options dominated the QALY

assessments, it is not clinically appropriate to mandate surgery prior to coverage of mavacamten because of patient-specific factors. The decision to have a surgical procedure, which carries inherent risk, is not something that can be applied to patient populations as a generality.

When developing coverage criteria, it is clinically reasonable to place mavacamten as second-line after BBs and CCBs but not necessarily to also require the use of disopyramide. Not only is there a lack of high-quality RCTs for the use of disopyramide in patients with HOCM, but there is also a substantial long-term supply chain issue with its availability.

Another major coverage policy concern for patients is access to COE. Managed care policies should be reviewed to ensure that there are no unintentional barriers for patients to receive access to care, such as limiting telehealth for patients or limiting interprofessional consults between providers at the specialized centers and community cardiologists.

The QALY assessments and values assigned were based on NYHA functional class, which ICER stated was the best evidence-based method for assessment. However, NYHA functional class is not specific to HOCM and may not provide the most accurate impact of the disease on patients' quality of life. Additional research into PROs that may be less variable than NYHA for patients with HOCM is warranted, with possible incorporation into the QALY assessments in the future.

Unintentional consequences that inadvertently limit access to both pharmaceutical and medical care for HOCM patients can occur because of the heterogeneity and complexity of the disease. Managed care pharmacists should consider these elements when determining medical and pharmacy coverage policies. Patients

with HOCM are on the verge of adding another arrow in their quiver in managing their disease state that has demonstrated not only clinical benefits but also improvements in quality of life.

DISCLOSURES

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