Broadening the Treatment Horizon for Heart Failure Patients

Through its issuance of recommendations and regulatory decisions concerning medical products, the US Food and Drug Administration (FDA) typically considers the "unmet medical need" surrounding a particular disease or condition. In the most extreme circumstances, as with many rare diseases, FDA-approved therapies may not be available. There are also numerous contexts, however, in which treatments are approved, but a need still exists for refinement to better target the patient population—such is the case for heart failure (HF) drugs.

The FDA notes that, despite the availability of HF therapies in multiple drug classes, mortality remains high, and treatment options for a broader range of patients are needed. HF occurs when the heart is unable to pump sufficient blood and oxygen to support other organs. Because HF patients tend to accumulate excess fluid in the body, they can experience particularly debilitating symptoms that include shortness of breath, fatigue, and difficulty with physical movement.

HF can also take a toll on mental health. The authors of a literature review published in 2018 reported that "depression and anxiety disorders are associated with the development and progression of HF, including increased rates of mortality, likely mediated through both physiologic and behavioural mechanisms."[1] The article noted that antidepressants – in particular, selective serotonin re-uptake inhibitors (SSRIs), which are first-line treatment for major depression, generalised anxiety disorder, post-traumatic stress disorder, and panic disorder – are effective in patients lacking heart disease but have "mixed" evidence for their use in HF.

That the incidence of HF is increasing further supports the urgency to address this condition. The American Heart Association (AHA) 2021 annual report, produced in conjunction with the US National Institutes of Health (NIH), noted that the prevalence of HF continues to rise over time with aging of the population.[2] According to data from 2015 to 2018, an estimated 6 million adults in the US aged 20 years and older had HF. Prevalence of HF is higher in women than men aged 80 years and above, and overall prevalence is particularly high in both Black females and Black males. Of incident hospitalised HF events, approximately half are characterised by reduced ejection fraction and the other half by preserved ejection fraction.

Treatment Alternatives for HF

As part of a wider commitment to reducing the impact of heart and vascular diseases, the NIH's National Heart, Lung, and Blood Institute (NHLBI) funds many studies related to HF, including basic research, clinical trials, and large longitudinal studies. The NHLBI notes that not everyone responds to existing treatments, which include medicines, implanted devices, and surgery; thus, research is ongoing to discover alternative treatments. In collaboration with the NHLBI and Yale University, Duke University is conducting TRANSFORM-HF (ToRsemide compArisoN with furoSemide FOR Management of HF), a large-scale, pragmatic, randomised, unblinded phase 3 study comparing torsemide versus furosemide as a treatment for HF.

The NIH webpage description for TRANSFORM-HF notes that loop diuretics such as torsemide and furosemide are a "cornerstone" of therapy for HF patients.[3] Relative to furosemide, torsemide "advantageously alters pathophysiological mechanisms associated with progression, has a favourable pharmacodynamic profile, and may decrease HF morbidity and mortality," the description states. However, it adds, furosemide "is overwhelmingly" used daily in the clinic, "which highlights clinical equipoise and an unmet need for an adequately powered study to definitively determine whether torsemide compared to furosemide improves outcomes to guide clinical practice."

TRANSFORM-HF will enrol approximately 6,000 patients with HF at more than 50 US hospital sites, with the primary objective to compare the treatment strategy of torsemide versus furosemide on clinical outcomes over 12 months in patients with HF who are hospitalised. The trial is targeting enrolment of racial and ethnic minorities and women and is randomizing participants 1:1 to either oral torsemide or furosemide prior to hospital discharge. As of May 12, 2022 the trial status at ClinicalTrials.gov was listed as "active, not recruiting."[4]

Modernised Therapeutics, New Indications

The FDA's efforts to widen the breadth of treatments for HF patients has included the approval of new formulations. In June 2021, the agency approved an updated version of torsemide under the trade name Soaanz, from Sarfez Pharmaceuticals, Inc (Sarfez), for the treatment of edema associated with HF or renal disease in adults. The product label notes that the initial US approval of torsemide was in 1993. According to the sponsor, Soaanz is an improved once-daily formulation of torsemide that provides a new treatment option for HF patients who experience persistent edema and swelling in the lower limbs and/or abdomen, despite a loop diuretic therapy. The drug is intended to provide a longer duration of peak effects without causing excessive urination. Thus, it gives a therapeutic option to HF patients who choose to skip loop diuretic treatment due to concerns with increased urination, as well as patients with chronic kidney disease, Sarfez stated.

More recently, in February 2022, the FDA approved a new indication for Jardiance (empagliflozin), an inhibitor of sodium-glucose co-transporter 2 (SGLT2), from Boehringer Ingelheim Pharmaceuticals, Inc, (Boehringer), to reduce the risk of cardiovascular death and hospitalisation for HF in adults with HF. The FDA originally approved Jardiance in 2014 as an adjunct to diet and exercise to improve glucose control in adults with type 2 diabetes. It is also indicated to reduce the risk of 1) cardiovascular death in adults with type 2 diabetes and established cardiovascular disease and 2) cardiovascular death and hospitalisation for HF in adults with HF and reduced ejection fraction.

"While Jardiance may not be effective in all patients with heart failure, this approval is a significant step forward for patients and our understanding of heart failure," stated Norman Stockbridge, MD, PhD, director of the Division of Cardiology and Nephrology, FDA's Center for Drug Evaluation and Research (CDER), in the FDA press announcement of the approval.[5]

For this latest indication, Jardiance was granted priority review designation, one of the FDA's programs intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition. Under this designation, the agency's goal is to take action on an application within 6 months (compared to 10 months under standard review). The agency anticipates that drugs under priority review, if approved, "would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications."[6]

The February label update for Jardiance coincided with the annual observance of American Heart Month, which is hosted by the NHLBI and its health education program, The Heart Truth. American Heart Month is "a reminder for individuals to focus on cardiovascular health," Stockbridge said, adding that Jardiance, through the latest approval, "will provide physicians another tool to address heart disease."

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