Clinically Important Endpoints to Measure Heart Failure

How treatments affect aspects of life that are most important to patients is a priority for the US Food and Drug Administration (FDA) as it seeks ways to facilitate and accelerate drug development programmes.

This topic was the basis of a public workshop held in July during which the FDA sought stakeholder input on clinical endpoints for trials in heart failure that could be used to support FDA approval of drugs. The meeting focused on endpoints related to symptoms (e.g., dyspnea, fatigue) and physical function (e.g., walking, exercising, other activities of daily living). The need to assess mortality effects of drugs under development for heart failure was also discussed.

"There's something beautiful about an endpoint that involves symptoms – and that is, that the patient can figure out if they feel better," said Ellis Unger, MD, director, Office of Drug Evaluation-I, Office of New Drugs, Center for Drug Evaluation and Research (CDER), FDA. The "benefit-risk calculus" is affected greatly by whether patients can tell if they are deriving a treatment benefit, he said. They can notice such benefit for symptomatic endpoints (e.g., dyspnea, fatigue), but not for "hard" endpoints such as hospitalisation prevention or death.

According to Eldrin Lewis, MD, MPH, FAHA, associate professor of medicine at Harvard Medical School, despite the FDA's issuance of its December 2009 final *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, which he called a "very comprehensive" document, the use of patient-reported outcomes (PROs) for regulatory requirements and to measure changes in outcomes has not occurred on a regular basis.

Lewis explained that often a considerable amount of emphasis is placed on mortality. As patients progress through their natural history, however, they become more symptom-sensitive instead of survival-sensitive. PROs or health status encompass "the entire spectrum between symptom status and overall quality of life," Lewis said. "Sometimes we get caught up in the terms when we really should just focus on how to do best for our patients," he added.

New FDA Guidance on Heart Failure Drugs

The recent meeting in July was prompted by the FDA's issuance of the *Draft Guidance for Industry: Treatment for Heart Failure: Endpoints for Drug Development* in June. In particular, the agency was interested in soliciting feedback regarding four high-priority topics:

- Identify endpoints related to symptoms or physical function of clinical importance, including an approach to quantifying hospitalisation.
- Understand when the nature, magnitude, and clinical importance of an endpoint may justify deferral or omission of outcomes studies.
- Identify the risk of mortality that should be ruled out in outcome studies and whether the acceptable upper bound should be influenced by a drug's demonstrated benefit and risk.
- Discuss the pros and cons of capturing all-cause events versus cause-specific events, and the need for adjudication of events.

This guidance has two purposes: 1) to make it clear that an effect on symptoms or physical function, without a favourable effect on survival or risk of hospitalisation, can be a basis for approving drugs to treat heart failure; and 2) to provide recommendations to sponsors on the need to assess mortality effects of drugs under development to treat heart failure.

Functional/wellbeing outcomes of interest could be more important to the patient than the traditional hospitalisation/mortality outcomes, said Scott Solomon, MD, the Edward D. Frohlich Distinguished Chair, professor of medicine at Harvard Medical School, and senior physician at Brigham and Women's Hospital. For example, at the end stage of disease, a patient may forego duration of life for quality of life (QOL). It would be easy if mortality was the only measure in clinical trials, Solomon said, but there are many aspects that patients care about besides the hard outcomes. How to better incorporate those aspects into trials and how to convince payers that these kinds of benefits are worth paying for need consideration, he said.

One of the patient representatives speaking at the July meeting was Rhonda Monroe, who overcame numerous challenges relating to heart disease with considerable hard work (e.g., cardiac rehab, surgery). Monroe, who is African American, commented that this demographic is disproportionately affected by heart disease/heart failure and its members often do not recognise the symptoms. For example, patients do not perceive fluid retention as related to heart disease; instead, they think it is due to standing too long or eating too much salt. She advised that, if clinical trials are to be based on symptoms, clear education is needed about what symptoms are, so that patients are relating those symptoms to their disease state.

Monroe said she is grateful for all the work being done in the heart failure field, including to establish guidelines. "But if [a therapy] never comes to market because of litigation or I can't ever access it because my payer won't cover it, then it's fruitless," she said.

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