The Practicability of New Endpoint Measures in Pulmonary Hypertension Trials

Dear Editor,

I read with interest the thoughtful article by Hassoun et al.[1] titled "Updating clinical endpoint definitions." One of the primary tasks in my role as a pulmonary hypertension (PH) research nurse coordinator is to identify PH patients in our clinic who are eligible and willing to participate in research studies. This is not always an easy task.

As Hassoun et al. point out in their article, PH studies historically have run 12 weeks, requiring several hundred patients, based on a primary endpoint of 6-minute walk distance (6-MWD) test, an endpoint which has fallen out of vogue in the PH community. More recent studies have used morbidity/mortality as primary endpoint. These types of studies require very large numbers of patients (some 1,000 or more) and take many years, some five or more years, to complete. At the recent American Thoracic Society meeting in Philadelphia, vocal PH experts declared this endpoint the be-all-end-all solution to future PH studies. The worrisome scenario that comes to my mind is that in the near future, when a truly novel and potentially curative agent comes to phase II/III testing, there will be no eligible, willing, and available PH patients left to enroll because most will be committed to years-long morbidity/mortality trials. Given the rarity of PH, requiring morbidity/mortality outcomes for all clinical trials may have the unintended consequence of suppressing innovation of novel therapies in the field, thereby reducing any progress in this disease. Progress will come to a slow crawl.

While I do not claim to have the answer for what should be the best endpoint of study, I suggest that there could be a compromise between a historic 12-week outcome measure like the 6-MWD test and a multiyear outcome measure like morbidity/mortality. Practicability ought to be taken into account. I can only hope that regulatory agencies, along with the PH physician community and pharmaceutical companies, consider recruitment implications and keep the best interest of the PH patient in mind when determining the future of drug trial design in this patient population.

Deborah H. McCollister, *Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado, Anschutz Medical Campus, Aurora, Colorado (deb.mccollister@ucdenver.edu)*

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Updating clinical endpoints in pulmonary arterial hypertension: when challenges are welcome

We thank Ms. Deborah McCollister for her feedback on our recent article titled "Updating clinical endpoint definitions." McCollister judiciously points out some of the challenges raised with the recent trend among investigators and pharmaceutical companies involved in pulmonary arterial hypertension (PAH) clinical trials to move away from the 6-minute walk distance (6MWD) as a primary outcome in favor of a more composite endpoint, such as time to clinical worsening (TTCW), which includes elements of morbidity (such as hospitalization, clinical worsening, and need for additional therapy) and mortality.

While there is no doubt that the 6MWD has served its purpose for almost two decades of PAH clinical trials, allowing several important PAH-specific drugs to be approved, it is clear to many if not most of the members of the greater PAH community that it is now time to move beyond a test that (1) has many limitations (as detailed in our review), (2) may not be applicable to all forms of PAH (an example includes patients with connective tissue disease with multiple comorbid conditions, where functional status may be limited for reasons other than cardiovascular ones), and (3) may be less sensitive to treatment effects in patients receiving background therapy (now the norm considering the availability of effective therapy).

It is, however, also clear that with new endpoints such as TTCW, clinical trials for PAH will no longer be limited to just 12 weeks. Such trials take years to complete (e.g., the SERAPHIN,[1] GRIPHON,[2] and AMBITION[3] trials) and involve hundreds of patients, akin to most pivotal cardiovascular trials of the past several decades. Indeed, these trials are becoming increasingly difficult to enroll, and such trial designs represent significant challenges for a relatively rare disease such as PAH, as pointed out by McCollister.

One of the goals of our review of PAH clinical trial endpoints was to continue engaging and energizing the PAH community in its search for novel and highly relevant parameters that might be used as surrogate endpoints in clinical trials. Examples include imaging and characterization of the right ventricle, an important protagonist in PAH that to date has neither been used as an outcome nor targeted by current therapies despite the fact that it is the main determinant of survival.

While a higher bar for trial design (both in the endpoint used and in the study duration chosen) may indeed limit trial recruitment, we do not believe that there will be significant suppression of therapeutic innovation. The field of PAH research has never been as vibrant as it is today, despite new and perhaps radical modifications in clinical trial design. We believe that these changes (both in endpoints and in trial design) represent major improvements that will likely lead to increased scrutiny, a more objective assessment of drug efficacy, and, ultimately, improved patient care.

In the meantime, we agree that novel agents that show promise in treating PAH can and should be tested with surrogate endpoints in intermediate duration trials—a sentiment shared by the Pulmonary Hypertension Academic Research Consortium, from which our endpoint review was chartered.

Paul M. Hassoun, *Johns Hopkins University School of Medicine, Baltimore, Maryland, USA (phassou1@jhmi.edu)*
Sylvia Nikkho, *Bayer Pharma AG, Berlin, Germany*
Ronald J. Oudiz, *David Geffen School of Medicine, University of California, Los Angeles, California, USA*

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