Future of Clinical Trials for Pulmonary Hypertension

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“It is better to lose the battle and win the war.”
—Sun Tzu (circa 6th century BCE Chinese General and military strategist)

In 1995, the first successful randomized controlled trial (RCT) for pulmonary arterial hypertension (PAH) led to the approval of the pulmonary vasodilator epoprostenol. Under the assumption that PAH was a disease of inappropriate pulmonary vasoconstriction, testing a drug that had vasodilator properties seemed reasonable. The 6-minute walk test was the primary end point in the trial because it was in keeping with the Food and Drug Administration precedent that an outcome assessment in a patient with cardiopulmonary disease needs to reflect how the patient feels, functions, or survives.

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There are now 7 vasodilator therapies for PAH, all approved because they improved exercise capacity for 3 to 4 months. Whether they affect long-term survival remains a valid question. Recently, a sobering report from a highly respected referral center in France noted that the current 3-year survival for patients with pulmonary hypertension managed with state-of-the-art multiple drug therapy was only 58%, marginally better than in 1980s when there were no treatments at all. In addition, it appears that these drugs do not protect patients from developing severe pulmonary vascular disease.

Our knowledge of the pathobiology of PAH today is quite different from what it was 20 years ago. Scientific studies have demonstrated that cellular proliferation, inflammation, and thrombosis are the dominant underlying pathobiological processes and that chronic pulmonary vasoconstriction appears to play a relatively minor role. It is therefore understandable why the RCT by Kawut et al in this issue of Circulation chose to study the safety and efficacy of simvastatin and/or aspirin, therapies directed at normalizing endothelial cell function and platelet activation, as a treatment for PAH. Following a traditional clinical trial design, it represents a first-rate academic attempt to evaluate a new approach to treating PAH. In keeping with previous PAH trials, a 6-minute walk test was selected as the primary end point, and patients from 5 different subgroups of PAH were randomized to one or the other drug or a combination. Unfortunately, the treatments failed. What we do not know is whether they failed because they were ineffective or because the beneficial effects of these treatments could not be reflected in a 6-minute walk test. If we discover a drug that halts the progression or induces the regression of the underlying pulmonary vascular disease, how long would it take for one to be able to see this manifest as improved exercise capacity? How would it affect survival? Could we detect if it works on only a small subgroup of PAH? Although the study on aspirin and simvastatin in PAH failed to meet its goal, it succeeded in opening our eyes to the complexities of conducting clinical trials for pulmonary hypertension in the future.

I believe the era of the traditional RCT for PAH is probably over. PAH combines the challenges inherent to treating an orphan disease with a disease in which the knowledge of the molecular biology is complex and in advance of current medical therapies. Some of the challenges include the unknown effects of newer treatments on clinical symptoms, the unknown duration of trials necessary to demonstrate efficacy, the possible need for multiple therapies, and the unknown potential toxicities, including adverse effects on right ventricular function. With few patients and the high cost of drug development, we have to find ways to identify promising drugs more quickly, with smaller numbers of patients and shortened times to approval if we expect the pharmaceutical industry to continue to invest in treatments for this disease. Fortunately, along with advances in our understanding of the science of PAH have been important advances in the science of clinical trials. But meeting this challenge will require the bringing together of all the stakeholders: the academics, the regulatory agencies, and the pharmaceutical industry.

Academic investigators need to test new treatments of PAH based on animal models of pulmonary vascular disease that better mimic human disease. Human PAH is a complex heterogeneous disorder, and a continued investment in translational science to support these efforts is essential. Recent National Institutes of Health funding is aligned with this priority. Defining the molecular and genetic lesions that underlie pulmonary hypertension should allow phase 1 trials to target those pathways and to identify patient subgroups that will have a high response rate. Clinical scientists must develop methods that confirm the mechanism of drug action in the study patients, something that is not currently required, and include the early evaluation and validation of companion biomarkers. Classes of drugs and alternative therapies are going to be evaluated that have never been tested in RCTs for PAH and will likely include multitarget inhibitors, serotonergic inhibitors, metabolic modulators, and endothelial progenitor cells. Clinicians should also explore the repurposing of existing drugs that have therapeutic potential in PAH.
are available to researchers. Although the study done by Kawut et al was not successful in its attempt to repurpose aspirin and simvastatin for PAH, sildenafil is one example of a marketed drug that was repurposed for PAH with great success. Thus, it is better to lose a battle and win the war.

Fortunately, the regulatory agencies are already leading the way to adopting changes in the drug approval process. A key example is the Food and Drug Administration Critical Path Initiative that was created to allow an innovative approach to clinical trial design for diseases like PAH and to facilitate more effective drug testing from the exploratory phase to the confirmatory phase. Central to this approach are novel tools such as adaptive design trials. An adaptive design clinical study is one that includes a prospectively planned opportunity to modify 1 or more specified aspects of the study design and hypotheses based on the analysis of data from subjects in the study. The analyses are performed at prespecified time points within the study, can be performed in a blinded or unblinded manner, and can occur with or without statistical hypothesis testing. When used properly in the exploratory phase, adaptive designs can ensure the judicious use of limited patient resources, reduce patient exposure to ineffective or poorly tolerated drug doses, and lead to the recruitment of patients who, on the basis of biomarker analysis, are most likely to respond.

In the confirmatory phase of development, simulation can help clarify how different study designs will affect the outcome and likelihood of success, thereby guiding the development strategy. An adaptive trial design could allow interim data to be used to modify and improve the study design in a preplanned manner without undermining its validity or integrity. It can facilitate the early identification of efficacious treatments or, conversely, allow one to drop a poorly performing trial arm. Sample size re-estimation methods would provide flexibility to increase or decrease the sample size at an interim point in the trial to ensure that the trial is adequately powered. This will be important in instances where there is uncertainty about subject variance in response or about the size of a clinically meaningful effect at which to power the trial.

We also need to include industry as an equal partner to provide input into PAH drug development and to address how to make new drugs economically viable for them. In return, our industry partners must be willing to embrace a paradigm that will require data sharing and collaboration. All would benefit if placebo data from prior PAH studies were shared across companies to enhance the power of modeling in the exploratory phase of new drug development. Their active support and participation in the Biomarker Consortium will be essential because I believe that validated biomarkers for PAH will be critical to accelerate drug development and to allow better patient management. There is also reason to believe that treatments for PAH that will have the most dramatic impact will require novel combination therapies such as tested in the study by Kawut et al. Multiple molecular pathways appear to be active, and multiple pathways will likely need to be targeted for a treatment regimen to be truly effective. The Food and Drug Administration has provided a framework for this. The establishment of a pulmonary hypertension consortium among academia, regulatory agencies, and industry would be a mechanism for facilitating the discussion of innovative clinical strategies and to address concerns or objections that may inhibit the adoption of modern tools and adaptive study designs. The battles should be against the disease, not among ourselves.

It is ironic that the most effective treatment of PAH to date has been the use of calcium channel blockers (drugs that have never been approved for this indication) for the subset of vasoreactive patients. If we were given a mandate to test this class of drugs in an RCT today, we could apply adaptive design methodology and use acute vasoreactivity during cardiac catheterization as a biomarker of potential drug success. By randomizing only vasoreactive patients with a marked response, we could conduct an inexpensive RCT to evaluate the effectiveness of calcium channel blockers and to determine drug efficacy with a follow-up catheterization after 3 months. If necessary, the number of patients enrolled could be adjusted after a prespecified interim analysis to ensure a statistically significant and clinically meaningful result. Safety data would be easy to obtain because we would be repurposing a drug with years of accumulated safety information. If we could also establish hemodynamics as a surrogate end point that is predictive of long-term survival by pooling data from other PAH trials, we could use these data to claim a new life-saving treatment for PAH. Fortunately, we already won that battle.

Disclosures

None.

References


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