Pulmonary Arterial Hypertension (PAH) is a devastating disease that, until recently, had no effective medical therapy. In 1996, a prostacyclin, epoprostenol, was approved; since then, several therapies, including prostacyclin analogues and agents that modulate other vasoactive pathways—endothelin receptor antagonists and phosphodiesterase inhibitors—have received approval. In this issue of *Circulation*, Galiè et al report the results of the 2 pivotal trials of the endothelin receptor antagonist, ambrisentan, that lead the US Food and Drug Administration to approve this agent in June 2007.1

**The Status of Treatment for PAH**

Although we “pulmonary hypertensionologists” think we have made a significant impact on this disease, is this really true? We believe that we have improved the clinical status of our patients and their survival, but do we have data to support our “gestalt” or has the recognition of the disease and its background treatment changed to such a degree that the pulmonary-specific medications have not really had much of an impact? A recent meta-analysis of randomized clinical trials in PAH suggests that we may have overestimated our success.2

This meta-analysis reviewed 16 randomized clinical trials of the 3 approved classes of therapies through December 2005. A statistically significant increase in 6-minute walk (6MW) of 42.8 meters was observed, as well as a statistically significant improvement in functional class with active therapy; whether these effects, although statistically significant, are clinically important is not clear and much disputed. More importantly, the meta-analysis did not demonstrate a survival benefit with active therapy nor an association between change in the standard measure of exercise tolerance, the 6MW, and improved survival. Thus, the major conclusion, certainly not what we had hoped for, was that currently approved therapies, as a group, have not increased survival. In fact, only 1 study, the pivotal epoprostenol trial, has ever demonstrated improved survival against placebo.3 A second disconcerting conclusion of the meta-analysis was that the most commonly used end point in almost all clinical trials, the 6MW, was not an adequate surrogate end point in this disease. Even if this were not the case (if the 6MW were an adequate surrogate), it is interesting that the most impressive improvement in 6WM has been achieved in a study of the effect of a structured exercise program in patients with PAH,4 an improvement in 6MW much greater than that achieved by any of the approved pharmaceutical therapies.

In sum, although patients and physicians both feel we have had a positive impact on PAH, it is clear from the compendium of studies of various pulmonary-specific therapies that half of the patients treated with active therapy are still unable to walk more than 400 to 450 meters, approximately half of the patients are still New York Heart Association/World Health Organization functional class III to IV, mean pulmonary artery pressure is still 50 to 55 mm Hg, the minority of patients in these trials have significant clinical improvement, quality of life is suboptimal, and survival is reduced. Obviously, we prefer to cure PAH, but short of that, we would like to improve the patients’ status to as near normal as possible. Given this situation, what do we need to move forward?

**Why Haven’t We Achieved More?**

The major reason we have not had a greater impact on PAH is that we do not know the initial molecule(s) that leads to this vasoconstrictive, proliferative, occlusive phenotype.5 Although we have identified 3 potential vasoactive molecules that are important in this disease, it is clear that none of them are “the silver bullet”; each of them likely represents the end point of vascular endothelial cell dysfunction rather than the initiating event. For this reason, the vasodilator therapies currently approved or nearing approval have likely achieved the most that they can. Thus, we are unlikely to have further or greater impact on PAH until we determine the molecule(s) that initiate the disease; it is thus encouraging that several of the therapies in development target other potentially important pathways, such as proliferation.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Editorial

The Status of Pulmonary Arterial Hypertension in 2008

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What Else Can Be Done to Achieve Our Goals?

Aside from finding the initiating molecule(s) and developing therapies that target different potentially important pathways, it seems that at least 6 other issues are of importance.

End Points

Foremost, we need more objective and believable end points in our trials. Functional class, Borg dyspnea score, and 6MWT are too subjective, are affected by many other variables and have not been well standardized. To change or improve clinical trial end points, we will need input and cooperation of "pulmonary hypertensionologists," pharmaceutical companies, and regulatory agencies. What can we substitute? In a recent editorial, Stuart Rich advocated survival as the primary end point. Survival is certainly the most objective end point; however, this is likely impossible unless specifically mandated by regulatory agencies. Most patients will not enroll in nor will most physicians refer patients to long-term survival studies. Perhaps, some form of time to clinical worsening is a starting point; however, the criteria must be made stricter and less subjective (eg, include emergency room visits, early clinic visits, or outpatient uptitration of therapies).

In addition to improving end points, the length of trials must be changed; previous and current trials are too short (most commonly only 12 to 16 weeks) and provide little to no data on durability of response. The perfect example of the problem with short trials is the trial of the oral prostanoid, beraprost. If the study had been run the "PAH standard" trial length, the drug would have been approved; however, at 1 year, the initial significant clinical effects observed at 12 weeks had waned and were no longer significant.

Head-to-Head Trials

It would be of great clinical benefit to compare agents within the same class and among the different classes; however, because of cost, time, number of patients needed, and corporate risk, this is not likely to occur initiated by the National Institutes of Health.

Different Treatment Paradigms

Most physicians in the field believe that parenteral therapy (prostanoids) is superior; however, because of inconvenience and toxicities, they prefer to start oral therapy in most patients. Would we do better if initial therapy were more aggressive, similar to treatment paradigms in diseases such as malignancy or congestive heart failure? This should definitely be explored.

World Health Organization Group I

Although all patients with PAH (World Health Organization Group I) have similar histology, it is clear that they are not the same. First, marked differences in mortality with treatment can be observed depending on the subtype; for example, patients with idiopathic PAH have a better outcome than patients with scleroderma but do have as good an outcome as patients with congenital heart disease. Second, the response to calcium channel blockers is markedly different; only a small number of patients with idiopathic PAH are likely to benefit from this treatment; other subtypes do not respond. Third, a marked difference can be found in an identified genetic mutation; BMPR2 mutations really only occur routinely idiopathic PAH and familial PAH. Thus, we should continue to explore differences among subtypes of PAH and likely will need different treatment strategies in many of these to optimize clinical outcome.

Biomarkers and Noninvasive Testing

It would be a huge step forward if we had reliable noninvasive mechanisms to predict and to follow PAH, but this has not been achieved thus far. Given the complexity and the different pathways that are seemingly important in PAH, it is unlikely that a single biomarker will be sufficiently sensitive to achieve this goal. Moreover, noninvasive testing, such as echocardiography, has not proved adequate; perhaps other noninvasive methods, such as magnetic resonance imaging, will be more beneficial. This is an area of active investigation and should be expanded.

The Right Ventricle

It is clear that clinical demise in patients with PAH is related to the function and integrity of the right ventricle; at the same time, it is even clearer that we know very little about the physiology and the pathophysiology of the right ventricle. We definitely need more knowledge in this area and, likely, more specific treatment directed toward this chamber to make a significant impact on PAH.

Conclusions

In sum, please don't interpret this editorial as pessimistic; it is more a realistic evaluation of the field and a call to do better. I do believe we have made significant clinical and scientific inroads into this disease. I do believe, however, that we have less to show than we have accomplished, because our clinical trials have not been designed appropriately, have essentially been "me too" trials and have suffered from a "we do not have enough patients so let's not do adequate science" attitude.

So, let's change this: design better trials, continue the increasing research into this disease, develop new therapies and, ultimately, we will achieve our common goal of improving the outcome of PAH patients.

Disclosures

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