The value of approved therapies for pulmonary arterial hypertension

Stuart Rich, MD Chicago, IL

Price is what you pay. Value is what you get.

Warren Buffett

In this issue of the Journal, Macchia et al present the first meta-analysis of trials for pulmonary arterial hypertension (PAH). Their findings are startling, yet not surprising at the same time.

Meta-analyses can be very helpful in strengthening the power of small intervention effects and in providing guidance for future clinical trials with respect to the population enrolled, appropriate end points, and length of follow-up. One should also remember that meta-analyses taken from studies published in the literature potentially suffer from a negative publication bias because negative trials are often not published, and thus the meta-analyses oftentimes represent “the best of the best.” In addition, if the clinical trials are widely heterogeneous with respect to the patient population under study, or by design, the conclusions may need to be tempered.

This article is particularly timely, given the recent approval of several medications for PAH, which is widely considered as a seriously disabling and fatal disease. Currently, there are 7 medications approved for PAH worldwide, which are estimated to generate >1600 million dollars in revenue in 2007 (personal communication). Because PAH has now become among the most expensive diseases to treat in the world, it is certainly fair to ask if we are getting a fair “bang for our buck.”

This meta-analysis included data from 16 randomized clinical trials extracted from the published literature, representing 3 different classes of approved therapies (prostacyclins, endothelin receptor blockers, and phosphodiesterase 5 inhibitors). One of the observations was the remarkable homogeneity among the studies. All but 1 of the trials included patients who had World Health Organization Category 1 PAH, and 70% of the patients were World Health Organization Functional Class 3. These studies were very homogeneous in design as well. Only 1 of the trials was >16 weeks in duration, all but 1 compared the active therapy against placebo, and half used a change in 6-minute walk distance (6MW) as the primary end point. A close look into the trials reveals that it was often the same centers, and same investigators, who enrolled patients into the studies.

The authors confirmed that a statistically significant increase in 6MW of 42.8 m occurred from active therapy. They also found a statistically significant improvement in functional class (33% on active therapy improved vs 15% of those receiving control). Whether these small intervention effects are clinically meaningful has been the subject of debate. However, I think we can conclude from this analysis that the use of a vasodilator as therapy for PAH will predictably result in a small change in 6MW over a 12- to 16-week period irrespective of the drug used. Because patients who show marked vasoreactivity at the time of diagnosis are excluded from these trials, this response likely reflects that there exists a small pulmonary vasoconstrictive component in patients with PAH, which, when reversed, translates into a modest improvement in exercise tolerance. Because it appears that this phenomenon has now been firmly proven, there seems to be little need for any more vasodilator trials of this sort.

More importantly, there was no survival benefit realized from these therapies. In addition, although patients with worse 6MW tests at baseline had worse survival, the authors were unable to show any association between the change in 6MW and improved survival. In fact, the CIs revealed a mortality effect ranging from a 30% reduction to a 22% increase. Their startling conclusion is that the approved therapies of PAH have yet to demonstrate an impact on survival in this highly fatal illness and that the data fail to validate that the widely accepted 6MW is an adequate surrogate end point for this disease.

The treatment of PAH has had an interesting history. The use of calcium-channel blockers as first-line therapy in a subset of patients found to be highly vasoreactive at the time of diagnosis is widely accepted by expert opinion and evidence-based guidelines as an important treatment of this disease. There has never been a long-term randomized clinical trial using calcium blockers for PAH, but the prospective observational reports that used...
survival as an end point have shown a dramatically improved survival over historical controls and published registries.\textsuperscript{10,11} Of note is that the report of the long-term benefits of calcium-channel blockers was not published until 5-year follow-up was available, citing a concern that it remains unknown whether this response will persist indefinitely.\textsuperscript{10} Fortunately, calcium blockers are widely available and inexpensive.

Compare that with the approved medications, which in trials have consistently shown small changes in 6MW with therapy, an end point that has never been validated, and one that can more improve with an exercise rehabilitation program.\textsuperscript{12} They also produce trivial changes in hemodynamics and no effect on survival with the sole exception of intravenous epoprostenol in critically ill patients over 12 weeks.\textsuperscript{13} In addition, for some reason we continue to ignore the prodigious results from the Beraprost Study Group,\textsuperscript{14} which conducted the only randomized clinical trial evaluating a treatment of pulmonary hypertension for 1 year. That study showed a 3-month improvement in 6MW comparable to what has been achieved with all the other approved therapies, which then vanished by the end of a year.

The possibility that therapies for PAH may have no beneficial long-term efficacy may seem incredulous to some. However, those of us with gray hair vividly remember the observations mentioned by Macchia et al\textsuperscript{1} about the disconnect between improving ejection fraction and mortality in patients with heart failure and between the reduction of ventricular arrhythmias and arrhythmic deaths in patients with coronary artery disease. This could be déjà vu all over again.

To me, the message from this meta-analysis is that the time has come for a major change in the design of clinical trials evaluating the treatment of PAH. I believe that any future trial of therapies seeking approval for PAH should be at least 1 year in duration and should use survival as the primary end point. It is unlikely that the pharmaceutical industry will voluntarily propose this, and it is unlikely that the physicians who sit on the steering committees of the trials will insist on it. This leaves me then to appeal to the regulatory authorities who can and should demand that our approach toward developing new therapies for PAH undergo a major overhaul.

There are currently 10 new therapies for PAH in various stages of clinical development, promising to be as expensive as their predecessors. For many of these therapies, the same clinical trial design appears to have been adopted, making it unlikely that we will learn anything new about the treatment of this devastating disease. All of this makes me wonder that when it comes to the treatment of PAH with the many approved and expensive therapies, we may have “bought the farm.”

**References**