Recent Reports

The Clinical Trials Update highlights new and ongoing research trials that are evaluating therapies for PAH. In this issue, Dr Torres examines a study on the RELAX trial and a study on a revision to the Lung Allocation Score.


Diastolic dysfunction, or heart failure with preserved ejection fraction (HFpEF), is commonly encountered in pulmonary hypertension (PH) programs and carries significant morbidity and mortality. There are no specific medications to treat diastolic dysfunction, and patient management can be challenging, with morbidity and mortality that is as high as that of patients with heart failure with reduced ejection fraction. The study of this disease in the PH community has been difficult, as the definition of this disease continues to evolve. A specific task force from the 2013 World Symposium on Pulmonary Hypertension (WHO) which was held in Nice, France, was assigned to provide a more uniform definition to aid in improving developments of therapies and design clinical trials.

The RELAX trial was initiated to evaluate patients with HFpEF. Enrollment began in October 2008, and finished in February 2012. During this period, 216 stable outpatients with HFpEF were enrolled in a multicenter clinical trial across North America. Twenty-six centers participated. The inclusion criteria consisted of patients with heart failure with ejection fraction ≥50%, elevated NT-proBNP, or elevated invasively measured filling pressures and reduced exercise capacity. The study was designed to capture all types of diastolic dysfunction, not just the patients with pulmonary venous hypertension. The median age in the study was 69 and 48% of participants were female. The median peak oxygen consumption was 11.7 mL/kg/min and mean 6-minute walk distance (6MWD) was 308 meters. The patients were randomized 1:1 to receive either placebo or 20 mg tid of sildenafil for 12 weeks, and then the dose was increased to 60 mg tid for the remaining 12 weeks. At 24 weeks when the patients were reevaluated at the end of the study, the results were disappointing.

The primary endpoint of peak oxygen consumption in patients receiving placebo or sildenafil was not met as there were not significant differences (P=0.90) between the groups. The secondary endpoints of 6MWD and hierarchical composite clinical status score were also not statistically different. Subgroup analysis looking at creatinine, NT-proBNP, endothelin-1, and uric acid levels increased more in patients treated with sildenafil. There were more patients in the sildenafil group who withdrew consent, died, or were too ill to perform the cardiopulmonary exercise test. Furthermore, patients treated with sildenafil had a higher incidence of adverse events and serious adverse events. The investigators also performed multiple subgroup analyses in this population that did not show any trend toward improvement of peak oxygen consumption.

The investigators measured levels of sildenafil in the subjects and were able to show that the serum levels achieved were consistent with other clinical trials that have shown efficacy in other disease states. It is still possible that a higher dose of sildenafil could have a positive effect in this population, though possibly with an increase in adverse events. This study did not include patients with severe pulmonary arterial hypertension (PAH). This is important, as the Guazzi et al study showed a positive result using sildenafil for the treatment of diastolic dysfunction and included patients with more severe PAH than was noted in the RELAX study. Thus, the potential that sildenafil may only be effective in patients with severe PH remains a possibility. See full results of the RELAX trial.

It is possible that the negative results of this sildenafil study in HFpEF may not be a class effect of all PDE-5 inhibitors. Studies evaluating the efficacy of tadalafil in this population are being developed.


During the ISHLT 2013 conference in Montreal, Dr Gomberg presented data supporting a change of the Lung Allocation Score (LAS) for patients with PAH. Historically, the patients with PAH were placed on the waiting list to undergo lung transplantation as soon as they were diagnosed with the disease. Thus, it was common for PAH patients to be on the waiting list for bilateral lung transplantation for 2 or 3 years. At that time, the donor organs were allocated to recipients solely based on time on the wait list.

In May of 2005, United Network for Organ Sharing (UNOS) introduced the LAS. The new system ranks patients on the waiting list according to the severity of illness and probability of surviving a lung transplant 1 year later. This system significantly benefited the patients with interstitial lung disease (ILD) in time to
transplantation, and over the past 8 years there has been a steady increase in patients with ILD undergoing lung transplantation. Similar changes were noted in patients with cystic fibrosis. Unfortunately, such changes were not seen in the PH population.

While the numbers of transplants has remained stable, the percentage of PH patients undergoing lung transplantation has decreased. Dr Gomberg and colleagues presented data to support changing the score allocated to PH patients on the waiting list for lung transplantation. After the introduction of the LAS system, patients with PH had a worse survival than predicted by the current LAS equation. Gomberg et al created a new equation that will help predict the survival of PH patients on the waiting list. This equation uses 3 variables to predict survival in the waiting list: cardiac output, 6MWD, and oxygen requirement at rest. If this new equation is adopted by UNOS, the way in which organs are allocated should improve for PH patients awaiting lung transplantation.

Hearing Hoof Beats:
The Latest on the Sometimes it’s PH Campaign

The Power of PR in Spurring Earlier PH Diagnosis
by Lynn Brown, MD, campaign chair

An online article published April 8, 2013, in JAMA Internal Medicine called for a reevaluation of educational efforts to deepen awareness of pulmonary hypertension (PH) among medical professionals and to improve PH patient care and outcomes. The article, Referral of Patients With Pulmonary Hypertension Diagnoses to Tertiary Pulmonary Hypertension Centers, by Roderick et al raised concerns about late referrals, misdiagnoses, and inappropriately prescribed medications at PH clinics at academic medical centers. (See it online at http://bit.ly/100JZKR.)

PHA’s 5-year Sometimes it’s PH early diagnosis campaign is an important way we are moving toward wider knowledge of PH in medical circles. Direct educational efforts are now being organized through the campaign, and in the meantime a companion PR initiative has already generated several well-placed articles on PH and early diagnosis.

Sometimes it’s PH teaches more professionals in the medical community that PH is a “medical zebra,” or unexpected diagnosis, of common symptoms such as chest pain, shortness of breath, and fainting. The campaign plays off this medical school adage: “When you hear hoofbeats, think horses not zebras.” It reminds practitioners that although sometimes it’s asthma or COPD or sleep apnea, sometimes it’s PH.

In April, the American College of Physicians published an article on diagnosing and treating PH in its monthly membership publication, ACP Internist. The article, available online at www.acpinternist.org, was the cover story of that monthly issue sent to more than 130,000 primary care doctors. The piece covered how to screen for PH, when to refer to a specialist, and how to blend primary and specialty care.

A second article introduced PH awareness to respiratory therapists (RRTs). Appearing in the online news magazine ADVANCE for Respiratory and Sleep Medicine, it explained how RRTs may suspect PH if patients are following their treatment regimens but not feeling better. Author Gerilynn Connors, a respiratory therapist and the Pulmonary Hypertension Professional Network (PHPN) Practice Committee chair, wrote the article, also introducing Sometimes it’s PH and the professional education and growth opportunities available through PHA. The article can be found online at http://owl.li/k9nTS.

Future PR plans also call for publishing review articles and editorials in medical journals, generating coverage in news publications for other allied health professionals, inviting key professional associations to communicate our message to their members, and producing coverage in the mass media.

PHA’s campaign is gaining traction and momentum through careful networking in the health community and by proactively seeking opportunities to bring this rare disease to wider attention. Your ideas and talents to advance early diagnosis are important to the campaign. I welcome the opportunity to hear from you about ways to continue to work toward early and accurate diagnosis of PH. Please send your thoughts to me at Lynn.M.Brown@imail.org. I also encourage you to visit the campaign’s website, www.SometimesItsPH.org, for the latest campaign information.