MEDCO FORUM®

PRESENTING INNOVATIVE PRODUCTS & SERVICES TO HEALTHCARE PROFESSIONALS

VOLUME 14 NUMBER 21 MAY 2007

REPRINT

OPTIMIZING PAH PATIENT CARE:

Employing a Patient-Based Multidisciplinary Approach

The past decade realized significant advances in the disease area and course of treatment for Pulmonary Arterial Hypertension (PAH). A chronic, life-threatening cardiovascular syndrome, involving lung and heart functioning (including hemodynamics), PAH presents as elevated pulmonary artery pressure and pulmonary vasoconstriction.[1,2] Optimal treatment requires synchronizing therapeutic options with patient needs and relies on dialogue with patients and multidisciplinary teams regarding balancing treatment risks and benefits with quality of life considerations.

Evolution of Therapy for PAH: Improved Patient Outcomes and Better Quality of Life

The course of the disease has changed because treatment options have changed "quite considerably," says Terence Trow, MD, Pulmonologist, Director of the Pulmonary Hypertension Center and Assistant Professor of Medicine at Yale University School of Medicine. Dr. Trow adds, "We didn't have the number of effective therapies to offer ten years ago that are available today, and there has been an explosion in basic science and pharmaceutical research in the field. As a result, we have new oral therapies and one inhaled therapy option to choose from. New measures are also emerging to assess benefits of these treatments that may guide our selection."

Vallerie McLaughlin, MD, Cardiologist, Director of the Pulmonary Hypertension Program and Associate Professor of Medicine, University of Michigan, says, "Over the past ten years, we have learned more about the evaluation of prognostic factors." Dr. McLaughlin explains, "Physicians now think of PAH as a diagnosis. They consider it earlier, look for it earlier, and diagnose it earlier. We are finding patients earlier, treating earlier, and obtaining better outcomes."

Components of Optimal Therapy: A Patient-Based, Multidisciplinary Approach

A major shift in PAH management is a patient-based approach. At Yale, patients are an integral part of the treatment decision process. Dr. Trow notes that "as soon as a true diagnosis of PAH is established, patients spend 1½ hours with the team learning about their disorder, discussing the risks of foregoing treatment, and reviewing each therapy available and their side effects, as well as the associated studies supporting their use."

A team approach to diagnosing and treating PAH also is essential. Discourse regarding therapeutic options across specialties (e.g., pulmonologists, rheumatologists, cardiologists, and other physicians with psychologists, nurses, and dietitians) optimizes care by expediting comprehensive data collection, enhancing clinical decision-making, augmenting experience and knowledge, and fostering continuity of care.

"Optimal therapy has to be individualized for each patient," explains Lee Golden, MD, Cardiologist and Senior Director of Medical Affairs, Actelion Pharmaceuticals. Dr. Golden reports that "Actelion is at the forefront of this approach with several ongoing clinical trials." Research is exploring different combinations of treatments for patients, such as concomitant use of the dual endothelin receptor antagonist Tracleer® (bosentan) and sildenafil, to improve symptom relief and clinical outcomes.

Tracleer® and Concomitant Sildenafil

Identifying effective combination therapies is crucial because these protocols address the multiple pathophysiological mechanisms of the disease.

The COMPASS studies focus on the efficacy (hemodynamic and morbidity and mortality benefits) as well as safety of Tracleer® in concert with sildenafil. COMPASS-1 is designed to explore for any potential pharmacodynamic interactions of single-dose sildenafil on top of Tracleer® therapy. The study will report results at the European Society of Cardiology Congress this summer.

In the clinic, Dr. Trow is "seeing what the early studies of Tracleer® suggested, we should see

improvements in functional status, 6-minute walk distances, and the ability for patients to hold their own regarding exercise performance for longer periods of time before additional therapies are needed." He adds that with Tracleer® there are "observable improvements in the majority of patients," and "if they have the luxury of time based on their functional class and hemodynamic parameters, most patients prefer a pill."

Special Research: BENEFiT Study in CTEPH Patients

Actelion's BENEFiT study investigated the use of Tracleer® in Chronic Thromboembolic Pulmonary Hypertension (CTEPH)—inoperable CTEPH and post-operative, residual PH. The complete data set from this trial will be presented at the 2007 International Conference of the American Thoracic Society (ATS) in San Francisco. Preliminary results, released March 2007, reported:

- Significant reduction in pulmonary vascular resistance (PVR)
- Notable improvement in breathlessness with exercise
- Trends towards prevention of worsening WHO functional class

Dr. Golden says the BENEFiT study will help both CTEPH patients and physicians understand which medications may work to optimize therapy.

Clinical Practice Therapy: The Future

Clinical practice for PAH is fueled by both "advances in our understanding of the genetics of the disease and as well as identification of a number of new mediators that may play a role has excited a natural curiosity in researchers in the field to explore new therapeutic products," says Dr. Trow.

Dr. Golden adds that research conducted by Actelion demonstrates that "unmet patient needs exist" and it propels treatment options more to the forefront. He continued, "we are constantly striving for a greater understanding of PAH pathophysiology and improvement in patient care."

Actelion currently is recruiting for the COMPASS-2 study, evaluating the safety and efficacy of sildenafil monotherapy versus the combination of sildenafil and Tracleer,® and the COMPASS-3 Phase IV study. This open label, non-comparative study is investigating whether Tracleer® (as monotherapy or concomitantly with sildenafil) enables PAH patients to achieve 6-minute walk distances (380 meters after 16 weeks), where attainment of this threshold has been correlated to improved patient outcomes in retrospective analyses, after 28 weeks of therapy. The study will also evaluate use of noninvasive tests (e.g., cardiac MRI) to assess improved functional capacity in PAH and explore correlation with other parameters.

For more information concerning PAH treatments, Tracleer,® and other Actelion products, please call 1-866-228-3546; or visit the company's Web sites at www.actelion.com and www.tracleer.com.

Tracleer®

Dual Endothelin Receptor Antagonist

- Only ERA showing significant improvement in 4 key hemodynamic parameters (RAP, CI, PVR & PAP)[4]
- Only ERA that significantly improves functional class status[5]
- Consistently demonstrated significant delay in time to clinical worsening[5]
- Low incidence of associated edema[6]
- Proven clinical experience: Over five years clinical PAH experience and prescribed to more than 40,000 patients[7]
- No clinically relevant interactions with key PAH medications such as sildenafil, iloprost or warfarin[6]

Please see full prescribing information

Tracleer® can cause liver problems and major birth defects. Most common side effects include anemia, headache, inflamed throat and nasal passages, hot flashes, ankle and leg swelling, low blood pressure, irregular heart beats, upset stomach, tiredness, rash, and itching.

Actelion Pharmaceuticals US, Inc. (San Francisco, CA) produces Tracleer.® Known worldwide for innovation, Actelion is currently working on drug discovery targeting cardiovascular, cardiopulmonary, immunological, and infectious diseases, as well as metabolic and central nervous system disorders.

References:

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