ASK THE EXPERT

What Are Some Pitfalls and Promises of the Current PAH Treatment Guidelines?

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Medical therapies for the treatment of pulmonary arterial hypertension (PAH) have evolved rapidly over the last 2 decades. From December 1995 to December 2015, 11 different drugs have been approved for treatment of PAH in the United States, including 1 that can be delivered by 4 different routes, thus providing 14 medical therapies that can be used as outpatient treatment for PAH. Considering the rapid pace with which these medications have become available, it is not surprising that clinicians have sought advice from professional societies on how they should be used. Since the turn of the last century, more than 50 articles have been published that include the words *pulmonary hypertension treatment guidelines* in the title. To be fair, the bulk of these are brief reviews or commentaries on the handful of more comprehensive treatment guidelines published by major professional societies.

The first comprehensive, evidence-based guidelines for treatment of PAH were published in 2004, and included separate manuscripts from the World Symposium on Pulmonary Hypertension (WSPH) in June,[1] the American College of Chest Physicians (ACCP/CHEST) in July,[2] and a joint task force of the European Society of Cardiology and European Respiratory Society (ESC/ERS) in December.[3] Quality data generated by randomized controlled trials at that time were limited. As a result, nearly half of the 17 recommendations in the ACCP guidelines were based on expert opinion, and the level of evidence for most of the remainder was rated as low. These limitations notwithstanding, the 2004 guidelines provided a modern summary of PAH treatments available at the time and produced the first treatment algorithms. In 2009, The American College of Cardiology Foundation and American Heart Association (ACCF/AHA) Task Force on Expert Consensus Documents published treatment guidelines that were developed in collaboration with CHEST, the American Thoracic Society (ATS), and the Pulmonary Hypertension Association (PHA).[4] That publication explained that guidelines were developed as an "expert consensus document" because the treatment of PAH was not considered sufficiently well developed to be evaluated by the formal ACCF/AHA practice guidelines process.

Since 2004, most of the aforementioned organizations have updated their treatment guidelines multiple times. The CHEST guidelines were updated in 2007 and 2014,[5,6] and the European guidelines in 2009 and 2015.[7,8] The WSPH guidelines were updated after subsequent meetings in 2008 and 2013.[9,10] With each update, the guidelines have grown in size and in scope. The last iteration of the CHEST guidelines contained 79 recommendations, while the most recent guidelines document for diagnosis and treatment of PAH from the ESC/ERS was more than 50 pages long, not including references or supplemental materials. The length and complexity of these recommendations have led to numerous commentaries and review articles that summarize recommendations or frame how they should be used, thus providing "guidelines" for the guidelines.[11-13]

PAH treatment guidelines have become complex for several reasons. The first is the large number of medications currently available. With the approval of the first soluble guanylyl cyclase stimulator and non-prostanoid prostacyclin receptor agonist, 5 different classes of PAH-specific drugs are now available. Although they all target one of 3 vascular signaling pathways, the different mechanisms of action and various routes of administration present a plethora of choices for patients and practitioners. The second reason is the limited number of studies for each drug and the lack of similarity between studies that examined their efficacy. For example, studies of earlier approved medications were conducted in treatment-naïve patients with fairly advanced disease, whereas more recently approved drugs were generally studied in older patients with more comorbidities who were often on other PAH medications. Further, study endpoints have recently shifted from improvement in 6-minute walk distance to delay in time to clinical worsening. The final challenge to development of simplified guidelines is the lack of comparator studies among drug classes, routes of administration, and patient types. Very few prospective studies have examined one drug class vs another and none has compared the relative efficacy of oral vs parenteral or inhaled administration.

As a result of the problems described above, evidence-based treatment guidelines have given similar levels of recommendation for most available drugs without providing much guidance on which drugs should be used on which patients. This is particularly true for monotherapy with oral agents where no differences have been identified between short- or long-acting phosphodiesterase type 5 inhibitors, selective or nonselective endothelin receptor antagonists, or a soluble guanylate cyclase stimulator vs a prostacyclin receptor agonist.

Considering these limitations, how should health care providers use current treatment guidelines? Perhaps the best answer is to ensure that the few recommendations that do favor one drug type over another are followed. A general consensus among the guidelines has stated that patients with an acute vasodilator response be given a trial of calcium channel blocker therapy, and that patients with advanced disease who are at high risk for 1-year mortality be treated with intravenous epoprostenol. Despite this fairly clear advice, recent evidence suggests that these guidelines are not often followed. For example, data from the Registry to Evaluate Early and Long-Term PAH Disease Management suggest that only about half of patients who die due to PAH have been treated with intravenous prostacyclins.[14] Likewise, data from the Pulmonary Arterial Hypertension Quality Enhancement Research Initiative show that only 7% of patients being treated with calcium channel blockers for PAH met guidelines for vasoreactivity therapy.[15]

This year CHEST is in the process of producing its fourth edition of treatment guidelines for PAH, and the World Health Organization task force on pharmacologic therapy is updating its treatment algorithms for the sixth international WSPH meeting in Nice, France, in 2018. What new information will the next round of guidelines provide? First, a formal review of the safety and efficacy of soluble guanylate cyclase stimulators and prostacyclin receptor agonists is expected. Although recommendations for riociguat and selexipag were included in the most recent European guidelines in 2015, those recommendations were developed before either drug was approved and before the sentinel studies responsible for their approval were published. Similarly, recommendations for the use of up-front combination therapy were developed in the ESC/ERS guidelines before the results of the AMBITION trial (initial therapy with ambrisentan and tadalafil vs either drug alone) were published. Future guidelines will have the benefit of a formal analysis of the data from these trials and any additional data that have been published since. Finally, although clinical data are limited, there continues to be a desire among patients and practitioners to discuss additional treatments such as pulmonary rehabilitation, vaccinations, and palliative care.

As the armamentarium for treatment of PAH continues to expand, treatment guidelines are anticipated to remain a popular tool for management of PAH. Interest has been expressed in generating a consensus document among the major professional societies and in developing an electronic real-time or "living guideline," where new data are reviewed and incorporated into the current guidelines as they become available rather than waiting to update the guidelines every 3 to 4 years. These modifications to the process of guideline development should lead to a more streamlined and up-to-date tool that health care providers can use to improve the treatment of PAH.

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