AJMC® SUPPLEMENT
THE AMERICAN JOURNAL OF MANAGED CARE®

March 2021
Vol. 27 • No. 3, Sup.

Improving Economic and Quality of Life Burden in Pulmonary Arterial Hypertension: A Review of Clinical Data and Strategies to Slow Progression

HIGHLIGHTS

Supplement to *The American Journal of Managed Care®*

Improving Economic and Quality of Life Burden in Pulmonary Arterial Hypertension: A Review of Clinical Data and Strategies to Slow Progression

Release date: March 10, 2021

Expiration date: March 10, 2022

Estimated time to complete activity: 3 hours

Type of activity: Application

Medium: Print with internet-based posttest, evaluation, and request for credit

Fee: Free

This activity is supported by an educational grant from United Therapeutics Corporation.

Intended Audience

Managed care payers, pharmacy directors, pharmacy benefit managers, specialty pharmacy directors, and any other pharmacist and/or healthcare professional interested in scientific advances in pulmonary arterial hypertension

Activity Overview

Pulmonary arterial hypertension (PAH) is a rare, progressive disorder with currently unknown etiology. Initial symptoms are often nonspecific and include shortness of breath and fatigue, with some patients experiencing these symptoms for more than 2 years before receiving a diagnosis. As PAH progresses, these symptoms may become more severe and occur for patients at rest, making early recognition of symptoms and early diagnosis imperative among healthcare providers. Current treatment goals include symptom management and maintaining patient quality of life, so clinicians should be familiar with goal-directed therapy as well as tests and risk assessment tools to monitor prognosis, treatment, and disease progression in PAH. Multiple classes of agents are used in PAH treatment, and some have been investigated as combination therapy; however, healthcare providers should be aware that certain combinations should be avoided due to increased adverse effects. These therapies are associated with significant cost burden for patients and the healthcare system, giving managed care professionals a significant opportunity to reduce costs and facilitate access of these medications. Mismanagement of patients with PAH stemming from delayed diagnosis is a main concern, so ensuring consistent application of guideline recommendations is important to the PAH treatment paradigm.

Statement of Educational Need

Pulmonary arterial hypertension (PAH) is a progressive disorder associated with significant morbidity and mortality. Annually, approximately 200,000 new cases of PAH are diagnosed in the United States, with twice the number of cases occurring in women compared with men. Unfortunately, many patients with PAH experience an incomplete or delayed diagnosis, with almost 20% of patients reporting symptoms for longer than 2 years before they receive a diagnosis. Once a diagnosis is made, patients must be closely monitored for disease progression and complications from associated comorbidities that could lead to hospitalizations and increased healthcare resource utilization. The progressive nature of PAH has a significant effect on health-related quality of life and patient-reported outcomes. Managed care professionals must be familiar with classification of PAH in order to ensure patients receive appropriate guideline-directed pharmacologic therapy. Potential misclassification of PAH status or patient risk level can lead to mismanagement and inaccurate estimations of prognosis, initiation of therapy, and incorrect dosing for monotherapy or combination therapies. New agents entering the therapeutic landscape of PAH can be significant drivers of direct costs for patients and the healthcare system, so it is imperative for managed care professionals to remain up-to-date on each agent's place in therapy and guideline recommendations for use. Equipped with this knowledge, managed care professionals can assist in reducing the high burden of disease associated with PAH and improve medication access. Many medications used for PAH require distribution according to a REMS program, and strict adherence to these requirements is important. By implementing these protocols to manage PAH diagnosis and treatment appropriately, managed care professionals can help improve patient quality of life through early diagnosis, prompt initiation of therapy, and reduced financial burden.

Educational Objectives

Upon completion of this activity, participants will be able to:

- Classify the pathophysiology, etiology, prognosis, and quality of life burden associated with pulmonary arterial hypertension (PAH).
- Explore the current treatment landscape, updated safety and efficacy data, and new and emerging therapies for PAH.
- Identify the costs associated with PAH and opportunities to slow progression and improve outcomes in this patient population.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care®*, managed care professionals will increase their knowledge of the therapeutic landscape of pulmonary arterial hypertension and guideline-recommended medications to reduce healthcare resource utilization.

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Brittany Hoffmann-Eubanks, PharmD, MBA; Marielle Fares, PharmD, BCGP; and **Jenna Wood, PharmD,** have no relevant financial relationships with commercial interests to disclose.

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REPORT

Pulmonary Arterial Hypertension: Updates in Epidemiology and Evaluation of Patients

Deborah Jo Levine, MD, FCCP

Introduction

Pulmonary hypertension (PH) describes a group of severe pulmonary vascular disorders characterized by elevated mean pulmonary arterial pressure (mPAP) at rest.[1] The World Symposium on Pulmonary Hypertension (WSPH) categorizes pulmonary hypertension into 5 groups (**Table 1**).[2] Pulmonary arterial hypertension (PAH), which corresponds to group 1 PH, and a focus of this article, is a complex and devastating disease that causes progressive vasoconstriction and vascular remodeling of the distal pulmonary arteries.[3] Currently, there is no cure, and the majority of patients with PAH go on to develop right heart dysfunction leading to death. Due to the progressive nature of PAH, it is crucial that the disease is diagnosed early with an accurate classification. Patients with PAH also must undergo a thorough evaluation to ascertain the severity of disease and future risk, and ideally have access to treatment at specialized care centers.[1]

The past 2 decades have been marked by significant advancements leading to novel therapeutics and improved understanding of the pathogenesis of PAH. As a result, the management of PAH is rapidly evolving.

Classification and Etiology of PAH

PAH includes several subgroups, all having similar pulmonary vascular pathobiology, clinical characteristics, and management strategies (**Table 2**).[4-6] PAH can be idiopathic, heritable, caused by drugs or toxins, or associated with other conditions such as connective tissue disease, congenital heart disease, or pulmonary hypertension.[1] Idiopathic PAH is responsible for more than 50% of all PAH cases. It requires extensive investigation (diagnosis of exclusion), whereas heritable PAH results from gene mutations or familial cases regardless of mutations.[7] The 6th WSPH updated the group 1 pulmonary hypertension classification to include new drugs and toxins as known agents associated with PAH.[6] For example, amphetamines, methamphetamines, and dasatinib were added to the definite association category.[8] Leflunomide, bosutinib, and direct-acting antivirals for hepatitis C virus (eg, sofosbuvir) were added as agents having a possible association.[9-15]

ABSTRACT

Group 1 pulmonary hypertension (or pulmonary arterial hypertension) is a rare, highly complex, and progressive disorder that is incurable and ultimately can lead to premature death. PAH causes significant physical, social, work, and emotional burdens among affected patients and their caregivers. Early diagnosis and initiation of treatment is required for best outcomes; however, the clinical presentation of PAH is nonspecific and frequently overlaps with several other conditions, often leading to a delay in diagnosis or misdiagnosis. In the past decades, increased understanding of the pathobiology of PAH has led to changes in its definition. Additionally, contemporary PAH registries have shown greater survival rates among patients with PAH and have allowed for the development of risk calculator tools that are now used to drive therapeutic goals. To date, multiple PAH-specific therapies have been developed, and all currently target one of 3 pathways that contribute to the endothelial dysfunction pathogenesis of PAH (prostacyclin, endothelin, and nitric oxide pathways). Because PAH is classified into 7 subgroups, it is essential that individuals are grouped appropriately for the efficacy of treatment and avoidance of harm. As health-related quality of life for PAH is multifactorial, it is important that patients are involved in the clinical decision-making process and have access to multidisciplinary care. The purpose of this review is to update healthcare professionals on the management of PAH with the most current information on epidemiology, pathophysiology, clinical presentation, and diagnostic considerations.

***Am J Manag Care*. 2021;27:S35-S41**

For author information and disclosures, see end of text.

A small subset of patients with PAH presenting with overt features of venous/capillary involvement was also recognized as a distinct category. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis (PVOD/PCH) were moved to a subset within group 1 as opposed to the prior iteration of the WSPH, where they were designated as group 1.[1,2] Typically, individuals with PVOD/PCH have similar clinical presentations and hemodynamic profiles as those with PAH; however, they have poorer prognosis, limited response to PAH treatment, and are at high risk for developing pulmonary edema from PAH therapeutics.[16] A separate group of individuals with long-term response to calcium channel blockers was included in the updated clinical classification based on accumulating improved survival data in this small subset of patients.[1,17]

Epidemiology

PAH is a rare disorder found in 15 to 50 persons per million within the United States and Europe.[1] Idiopathic, heritable, and anorexigen-induced PAH make up 52.6% of all PAH cases. Generally, PAH affects women aged between 30 and 60 years. However, it can occur in males and is often associated with worse clinical outcomes.[7] The National Institutes of Health (NIH) was a landmark registry that collected PAH data between 1981 and 1985.[5,18] This registry included 187 individuals having PAH of various etiologies. The registry largely consisted of females, found a mean age of PAH presentation of 36 years, and was primarily Caucasian. PAH-specific therapies were not available at this time, and registry participants had a median survival of 2.8 years (1 year, 68%; 3 year, 48%; and 5 year, 34%).[5,18]

Significant progress in the field of PAH pathophysiology and treatment have occurred in the 2 decades since the NIH registry. Contemporary PAH registries vary in their study populations, study design, and cohorts. The 2002 French Network on Pulmonary Arterial Hypertension (French PAH) registry included 674 people with PAH.[19] The French PAH registry found an estimated survival rate among those with idiopathic/familial/anorexigen-associated PAH of 82.9% at 1 year and 58.2% at 3 years.[20] This is a markedly higher survival rate compared with the NIH registry but consistent with other more recent PAH registry findings.[5,18,21]

REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) is a contemporary, multicenter, observational, US-based registry that began in 2006.[22] In contrast to the NIH registry, REVEAL was specifically designed to ascertain demographics, longitudinal clinical course, and management of PAH from a current US perspective.[21,23] Baseline characteristics for the 2967 individuals who met traditional hemodynamic criteria included a mean age of 53 (±14 years) and female sex in 79.5% with a female-to-male ratio of 4.8:1.[24] In addition, 46% of individuals had idiopathic PAH, 25% were associated with connective tissue diseases, and 10% were associated with congenital heart diseases. There was also a mean duration between symptom onset and diagnosis of 2.8 years.[25] Results of the REVEAL Registry showed a 1-year survival rate of 91% among 2716 individuals who were enrolled consecutively.[26] An additional analysis assessing long-term survival (N = 2635, between March 2006 and December 2009) found survival rates of 85% at year 3, 68% at year 5, and 49% at year 7 from time of diagnosis.[19] These increases in survival were attributed to various factors, including changes in treatment, increased patient support, and potentially, a difference in the PAH population cohort.

Pathogenesis

The triggering etiology that initiates the pathogenesis of PAH is likely multifactorial, including inappropriate angiogenesis, metabolic derangements, DNA damage, genetic mutations, and impaired vasoreactivity.[3] Endothelial cell injury along with impaired vascular regeneration, abnormal vascular remodeling, and loss of the small pulmonary arteries are all known to occur as part of the PAH pathogenesis.[27,28] Once endothelial dysfunction occurs,

TABLE 1. World Symposium on Pulmonary Hypertension (WSPH) Classification[2]

WSPH group
1 – Pulmonary arterial hypertension
2 – Pulmonary hypertension secondary to left heart disease
3 – Pulmonary hypertension from chronic lung diseases and/or hypoxia
4 – Pulmonary hypertension due to pulmonary artery obstructions
5 – Pulmonary hypertension from unexplained or multifactorial mechanisms

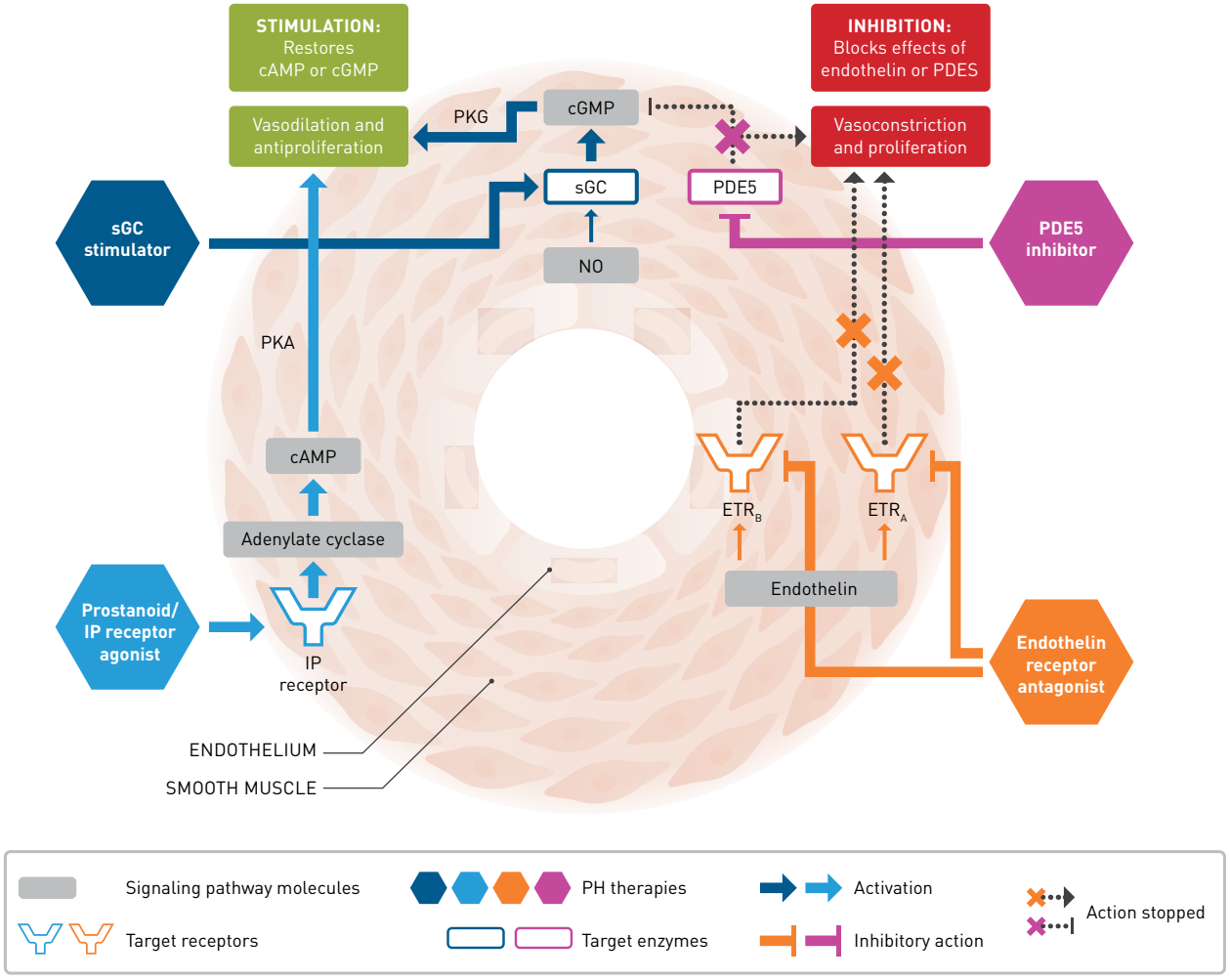
TABLE 2. Classification of PAH[4-6]

1. Pulmonary Arterial Hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug and toxin induced
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1.5 PAH long-term responders to CCBs
1.6 PAH with overt features of PVOD/PCH
1.7 Persistent PH of the newborn

CCB, calcium channel blocker; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.

progressive vascular remodeling of the distal pulmonary arteries ensues, causing significant proliferation and resistance to apoptosis of pulmonary artery resident cells.[3] As a result, pulmonary vascular lumen occlusion occurs, leading to increased pulmonary vascular resistance (PVR) and mPAP.[3,29] The abnormal PVR and mPAP lead to right ventricle dilation and dysfunction, which can ultimately lead to a decreased cardiac output (CO). Additionally, an imbalance exists between vasodilation and vasoconstriction favoring vasoconstriction with an increase in circulating vasoconstrictors (ie, thromboxane, endothelin, and serotonin) and a decrease in circulating vasodilators (ie, prostacyclin, nitric oxide [NO], and vasoactive intestinal polypeptide).[5] The improved understanding of the pathophysiology of PAH has led to development of therapies targeting the NO pathway, prostacyclin pathway, and endothelin pathway (**Figure**[30]). The pathology of PAH had previously been thought to be limited to the small pulmonary arteries; however, recent evidence suggests that systemic vascular manifestations also occur.[31] For example, patients with PAH exhibit impaired brachial artery flow-mediated dilation, abnormal cerebral blood flow, skeletal myopathy, and intrinsic kidney disease. Although some of these manifestations can be explained as a consequence of right ventricular dysfunction, Nickel et al argue that there is also

FIGURE. Therapeutic Targets in PAH[30]



The molecular targets, signaling pathways, and modes of action of approved pulmonary hypertension (PH) therapies. cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ETR$_A$, endothelin receptor A; ETR$_B$, endothelin receptor B; IP, prostacyclin; NO, nitric oxide; PDE5, phosphodiesterase type 5; PKA, phosphate kinase A; PKG, cGMP-dependent protein kinase; sGC, soluble guanylate cyclase.

evidence to support a mechanistic link with PAH pathophysiology. More research is needed to fully understand the systemic effects of PAH.[31] Tragically, as the disease progresses, the compensatory mechanisms of the right heart can fail, and lead to premature death.[3] Autoantibodies, proinflammatory cytokines, and inflammatory infiltrates have also been implicated in the pathogenesis of PAH. Individuals with PAH have increased von Willebrand factor levels, plasma fibrinopeptide A, plasminogen activator inhibitor-1, serotonin (5-HT), and thromboxane.[32] In addition, tissue plasminogen activator, thrombomodulin, NO, and PGI2 are decreased, creating an imbalance that favors thrombosis.[32]

Genetics

Over the past 20 years, there have been significant advancements in the understanding of the genetics of PAH.[33,34] Approximately 6% to 10% of persons with PAH have a family history.[35] Those who were previously identified as having idiopathic sporadic PAH are now known to have a genetic cause and would fall into the heritable PAH group instead. The most well-known genetic mutation associated with PAH is the bone morphongenetic protein receptor 2 (*BMPR2*) mutation. Seventy percent to 80% of patients with heritable PAH and 10% to 20% of individuals with idiopathic PAH have the *BMPR2* mutation.[35] Presence of this genetic mutation markedly increases the risk of developing heritable PAH and guidelines recommend genetic counseling for families and patients.[36-38] Additional mutations that are implicated in PAH development involve ligands of *BMPR2* and include *GDF2* (encoding BMP9), type I receptor (*ACVRL1*), and *SMAD9* (encoding Smad8). Potassium channel subfamily K member 3 (*KCNK3*) mutations and caveloin-1 (*CAV1*) mutations have also been identified along with many others.[5] Interestingly, PAH mutations are autosomal dominant with low penetrance. As a result, some patients may never exhibit disease, further supporting the assertion that the trigger of disease is multifactorial.[1]

Mitochondrial metabolism impairments have also been associated with development of PAH.[36] The female preponderance in PAH may be explained by the link between sex hormone metabolism differences and right ventricular function.[36] More research is needed to elucidate this theory entirely. *BMPR2* mutation penetrance also varies significantly, 14% of men and 42% of women, further suggesting that sex hormones and their metabolism may be associated with the pathogenesis of PAH.[1]

Clinical Presentation and Diagnosis

A thorough history, physical examination, and complete workup is imperative to determine if a patient truly has PAH. The first presenting symptoms include exertional dyspnea, fatigue, and weakness.[7,39,40] As the disease progresses, dyspnea may occur at rest, and other symptoms such as chest pain, presyncope, syncope, lower extremity edema, jugular venous distension, and abdominal bloating and distension may occur.[7] Less common symptoms include cough, hemoptysis, and hoarseness. The assessment of symptoms includes placing the patient in a World Health Organization functional class (WHO-FC) based on level of impairment in physical activity. Patients in WHO-FC I have no limitation of physical activity; WHO-FC II is characterized by slight limitation in physical activity with ordinary activity causing undue dyspnea, fatigue, chest pain, or near syncope; WHO-FC III is characterized by marked limitation of physical activity with no discomfort at rest but less than ordinary physical activity causing undue dyspnea, fatigue, chest pain, or near syncope; finally, WHO-FC IV is characterized by an inability to perform any physical activity without symptoms with signs of right ventriculat failure and symptoms at rest with discomfort increasing by any physical activity. In addition to a thorough history and physical examination, initial tests such as chest radiography and electrocardiography should be done. If findings from the workup or clinical findings suggest the presence of PH and right ventricular dysfunction, a 2-dimensional transthoracic echocardiography (TTE) with doppler should be employed as an initial screening measure. TTE is the best test to screen for possible PH and PAH, but only a right heart catheterization (RHC) can assess the pulmonary hemodynamics needed to diagnose PH and PAH. The RHC is required to assess the mPAP, PVR, and CO. It is the gold standard and used to confirm a diagnosis of PH.[7,40]

Historically, PAH has been defined by an mPAP of greater than or equal to 25 mm Hg at rest plus a pulmonary wedge pressure (WP) less than or equal to 15 mm Hg, and PVR greater than or equal to 3 Wood units (WU) using RHC.[41] However, at the 6th WSPH, the expert task force recommended to lower the hemodynamic definition for the first time since the inception of the WSPH in 1973 based on accumulated evidence suggesting a normal resting mPAP of 14 ± 3.3 mm Hg and that the upper limit of normal (or 2 standard deviations) for mPAP is greater than 20 mm Hg.[1,42] The change in hemodynamic criteria was primarily driven by increasing evidence suggesting that those who fall within the 20 to 24 mm Hg mPAP range exhibited poorer outcomes and tended to progress to overt PH (especially those with systemic sclerosis, chronic thromboembolic pulmonary hypertension, and family history of PAH-causing genes) more often than those with an mPAP less than or equal to 20 mm Hg.[43-47] The change in hemodynamic criteria has not occurred without opposition by some experts who argue that the 2 standard deviation argument is not consistent because pulmonary arterial WP and PVR cutoff values do not follow the same criteria. They suggest that the new hemodynamic criteria could create yet another cohort of individuals who could be "missed" by the previous and current cutoffs.[48] Still, the evidence is clear that an mPAP greater than 20 mm Hg is considered above normal, and more research is required in patient cohorts to further elucidate the relationship between clinical presentation and long-term outcomes.[1]

Risk Stratification

PAH treatment is based on the severity of disease at diagnosis and assessing how the individual will respond to treatment using multiple factors to stratify risk based on predicted mortality.[1] Other treatment considerations include patient/clinician preference, drug interactions, tolerability, and potential adverse effects.[49] Several risk stratification tools (RSTs) have been developed using retrospective analysis of large patient registries to aid in determining prognosis and guiding therapy for patients with PAH (**Table 3**[49]). The RSTs use multiple data points such as demographics, functional status, laboratory values, and hemodynamic information to stratify patients into low, intermediate, or high risk. The categories are then used as a baseline for initiating treatment, determining prognosis, and monitoring response and disease progression long term.[1,48]

The REVEAL RST consists of 12 to 14 variables used to determine the risk of 1-year mortality. The RST has been validated for predicting survival at baseline, 1-year follow-up, and at 5 years.[19,48,50,51] The most recent REVEAL 2.0 calculator can also predict clinical worsening and mortality among those who have survived PAH for a minimum of 1 year from their initial enrollment by including hospitalizations in the past 6 months and estimated glomerular filtration rate.[1,48]

Another RST, COMPERA, was developed by a European group and uses fewer data points than REVEAL but classifies individuals similarly. The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) PH guidelines RST uses a multidimensional approach that focuses on the most frequent determinants of prognosis.[39] All of the variables do not have to be assessed at each visit, but should include FC determination and at least one exercise capacity measurement (eg, 6-minute walking distance). It is also recommended to assess RV function by measuring brain natriuretic peptide (BNP)/N-terminal pro-brain BNP (NT-proBNP) or by echocardiography. Patients are then stratified into low, intermediate, and high risk based on determinants assessed. The RST can assist in guiding therapeutic decisions; however, application to individual patients should be done with care. A comprehensive assessment that also includes other risk factors such as signs of right heart failure, syncope, and comorbidities should be included to optimize clinical decision making.[39]

The Swedish PAH Register and the French Pulmonary Hypertension Network have also developed RSTs from large registries. Regardless of which RST is used, all have similar efficacy in identifying individuals at high risk. It is important to note that the tools utilize retrospective data and have some limitations, including measurement of nonmodifiable risk factors and inclusion of data points that are not routinely collected in PAH. Thus, despite which tool is selected, RSTs can help clinicians determine which individuals with PAH are at high risk for 1-year mortality, prioritization of therapies, and referral for transplant.[48]

Quality of Life

The impact of PAH disease symptoms on a person's functional mobility and psychosocial state adversely affects health-related quality of life (HRQOL).[52] Although there have been significant advancements in the understanding of PAH and targeted therapies that have decreased mortality, these improvements have not necessarily been paralleled from the perspective of individuals with PAH.[1] PAH affects all parts of a person's daily life that influence their HRQOL, including physical activity, well-being, and emotional and social functioning.[52] The debilitation level experienced by patients is considered at least as severe as chronic obstructive pulmonary disease and renal failure.[52]

A report from the European Pulmonary Hypertension Association (PHA Europe) found that 83% (n = 326) of people with PAH surveyed reported difficulty climbing stairs, and 97% stated PAH affected their ability to participate in sports and exercise to some degree.[52] Similarly, the FDA Patient Voice survey (≈85 participants) reported that breathlessness and fatigue were also restrictive on daily

TABLE 3. PAH Registries Assessing Risk Scores[49]

	REVEAL	Swedish PAH Register	COMPERA	French Pulmonary Hypertension Network[a]
Required variables (n)	12-14	8	8	4
Patients at baseline (n)	2716	530	1588	1017
Patients at follow-up (n)	2529	383	1094	1017
Associated PAH included	Yes	Yes	Yes	No
Definition of low risk	≤6 REVEAL score	<1.5 average score	<1.5 average score	3-4 of 4 low-risk criteria
1-year mortality by risk group (low/intermediate/high) (%)	≤2.6/7.0/≥10.7	1.0/7.0/26.0	2.8/9.9/21.2	1.0/NA/13.0-30.0

COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; NA, not available; PAH, pulmonary arterial hypertension; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management.
[a]Incident patients only.

physical activities. Both surveys also found that reduced physical activity had negative implications for long-term outcomes among persons with PAH.[52]

PAH also has considerable psychological effects, such as feelings of social isolation, lack of understanding or knowledge about the disease in the community (not a "visible" disease), and friends and family.[53] A study also found that 48% of individuals with PAH experienced mild to extremely severe symptoms of anxiety, 32.6% had symptoms of depression, and 27.6% had symptoms of stress.[54] As the psychological impact of PAH is often underrecognized, it is vital to assess patients during all encounters, especially if and when functional class worsens.

In addition, patients with PAH are also frequently affected by a loss of household income due to loss of work or inability to remain working.[53] A European PHA survey found that 73% of patients who had to give up work or needed assistance to maintain employment had a loss in average household income. Moreover, 1 in 6 reported their income decreasing by half. Also, 35% of caregivers reported a reduction in income to care for the individual with PAH.[53]

Age has contributed to the burden of patients with PAH.[55] The prevalence of PAH is increasing among people aged 50 to 65 years who are more likely to be diagnosed with advanced stages of disease, and have lower exercise capacity and a higher number of comorbidities. Multiple comorbidities are associated with a delay in diagnosis among older patients and could explain the challenge of disease recognition in earlier years among this patient population.[55] Women of childbearing age are also at increased risk of complications during pregnancy due to poor tolerance of hemodynamic and physiologic changes that can cause right ventricular failure and arrhythmias.[56] Due to a significantly higher associated mortality rate, it is recommended that women with PAH avoid pregnancy.[39]

Multiple factors contribute to an individual's perception of their overall well-being. Therefore, the WSPH expert task force recommends that management of individuals with PH should occur at specialized care centers with a patient-centered multidisciplinary team that focuses on quality of life, shared clinical decision making, and access to palliative care. Although numerous studies have demonstrated that PH treatments improve HRQOL, it is important to recognize that HRQOL is one component and may not capture the depth and complexity of psychosocial issues experienced by patients and caregivers. In other words, both individual and patient population-level perspectives should be considered.[1] Several patient-reported outcome (PRO) instruments have been developed to evaluate the effect of PAH therapies on patient symptoms and the impact of the symptoms on patients' lives and use of these are recommended to be incorporated as secondary end points in clinical trials. Two of these instruments are the psychometric validation of the pulmonary arterial hypertension-symptoms and impact (PAH-SYMPACT) questionnaire and the emphasis-10 questionnaire.[57,58]

The WSPH task force encourages clinicians to participate in narrative medicine where individuals with PAH can express their concerns and challenges related to their individual health.[1] Patients with PAH also need improved access to palliative care, as they may experience low HRQOL and high disease burden.[59] Concerning the population level, continued support for patient groups and associations, patient education, and public awareness are needed.[1] The interdisciplinary healthcare team can help patients navigate intolerable adverse effects and make recommendations for treatment adjustments and avoidance of drug interactions as required to optimize therapy and treatment acceptance and/or adherence.

Conclusions

PAH is a devastating life-limiting progressive disorder. Over the past 20 years, significant advancements have occurred due to an improved understanding of PAH pathogenesis and specific therapies that help decrease mortality. As more evidence has accumulated, changes to the evaluation and management of PAH have occurred. Contemporary registries continue to provide crucial information to help risk-stratify patients, determine prognosis, and monitor and manage therapeutic goals. Patients with PAH experience significant effects on their HRQOL, which is correlated to their functional, emotional, work, and social abilities. Healthcare providers should assess a patient's HRQOL during each encounter to improve patient satisfaction. Furthermore, as the factors that affect individual HRQOL are multifactorial, it is important that patients are involved in the clinical decision-making process. A multidisciplinary approach with multiple layers of support should be available to all patients, and importantly, they must be aware of the existence of such services. ■

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Funding source: This activity is supported by an educational grant from United Therapeutics Corporation.

Author disclosure: Dr Levine has no relevant financial relationships with commercial interests to disclose.

Authorship information: Substantial contributions to concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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REPORT

The Evolving Treatment Landscape of Pulmonary Arterial Hypertension

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a severe disease with poor prognosis and shortened life expectancy. Treatment has traditionally involved the sequential use of endothelin receptor agonists, prostacyclin therapies, and nitric oxide pathway modulators, which each have distinct mechanisms of action leading to pulmonary vasodilation, and improvement in exercise capacity, hemodynamic measures, and clinical outcomes for patients with PAH. This article provides a review of goals of therapy in PAH, determinants of prognosis and levels of patient risk, and additional factors that guide treatment decision making. Recent research in combination therapies has created a paradigm shift in the treatment of PAH and will be reviewed. Additionally, recent updates to the American College of Chest Physicians guidelines will be reviewed along with the updated evidence-based treatment algorithm. Finally, trial data will be evaluated for the recently developed agent selexipag and improved treprostinil delivery formulations that may provide enhanced convenience.

Am J Manag Care. 2021;27:S42-S52

For author information and disclosures, see end of text.

Goals of Therapy in Pulmonary Arterial Hypertension

The goals of therapy in pulmonary arterial hypertension (PAH) include alleviation of symptoms, improved exercise capacity, improvement in quality of life (QOL), preservation of right ventricular (RV) function, and reduction of mortality risk.[1,2] The European Society of Cardiology and the European Respiratory Society (ESC/ERS) 2015 guidelines propose several factors that aid in determining whether a person with PAH has a low, intermediate, or high risk of 1-year mortality. These factors include presence of right heart failure, progression of symptoms, syncope, World Health Organization functional class (WHO-FC), N-terminal pro b-type brain natriuretic peptide (NT-proBNP) levels, 6-minute walk distance (6MWD), cardiopulmonary exercise testing (CPET), imaging, and hemodynamic parameters (**Table 1**[1]). According to the ESC/ERS guidelines, an important goal is achieving or maintaining a low-risk status. Low-risk status is characterized by good exercise capacity, QOL, RV function, and reduced risk of mortality (1-year mortality from PAH is less than 5% when patients are low risk).[1] Therefore, the initial and ongoing assessment of patients with PAH includes determination of functional capacity, measurement of exercise capacity via 6MWD or CPET, and assessing RV function through measurement of NT-proBNP or by echocardiography. In addition, patients with PAH should undergo a comprehensive assessment for the presence of comorbidities and disease complications, presence of right heart failure, and the rate of disease progression. Evaluation of all prognostic information and therapy decisions should be made individually.[1]

The 6-minute walking test is included in the PAH risk assessment and is the most widely adopted test. Several factors may affect 6MWD results including age, sex, height, weight, comorbidities, learning curve, and motivation. The threshold of greater than 440 meters is an acceptable goal for patients who are elderly and those with comorbidities, but a higher goal may be needed for younger, otherwise healthy patients. An improvement of 33 meters in 6MWD is considered clinically relevant by the American College of Chest Physicians (CHEST) guidelines. CPET provides important information about exercise capacity and cardiac function during exercise,

TABLE 1. Risk Assessment in PAH[1]

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5%-10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165-440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11-15 mL/min/kg (35%-65% pred.) VE/VCO_2 slope 36-44.9	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50-300 ng/L NT-proBNP 300-1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal pericardial effusion	RA area >26 cm^2 Pericardial effusion
Hemodynamics	RAP <8 mm Hg CI ≥2.5 L/min/m^2 SvO_2 >65%	RAP 8-14 mm Hg CI 2.0-2.4 L/min/m^2 SvO_2 60%-65%	RAP >14 mm Hg CI <2.0 L/min/m^2 SvO_2 <60%

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; CMR, cardiac magnetic resonance; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; VE/VCO_2, ventilatory equivalents for carbon dioxide; VO_2, oxygen consumption; WHO, World Health Organization.

[a]Most of the proposed variables and cutoff values are based on expert opinion. They may provide prognostic information and may be used to guide therapeutic decisions, but application to individual patients must be done carefully. One must also note that most of these variables have been validated mostly for idiopathic PAH and the cutoff levels used above may not necessarily apply to other forms of PAH. Furthermore, the use of approved therapies and their influence on the variables should be considered in the evaluation of the risk.

[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient.

[c]Repeated episodes of syncope, even with little or regular physical activity.

such as peak oxygen consumption or uptake (peak VO_2) that is mostly used in practice. CPET measurements add to the information provided by 6MWD. Variables measured in the CPET provide important prognostic information. Natriuretic peptides and brain natriuretic peptide (BNP)/NT-proBNP are markers of myocardial stress and have prognostic value in PAH. They are commonly used in clinical practice in diagnosis and follow-up assessments and as end points in clinical trials.[1]

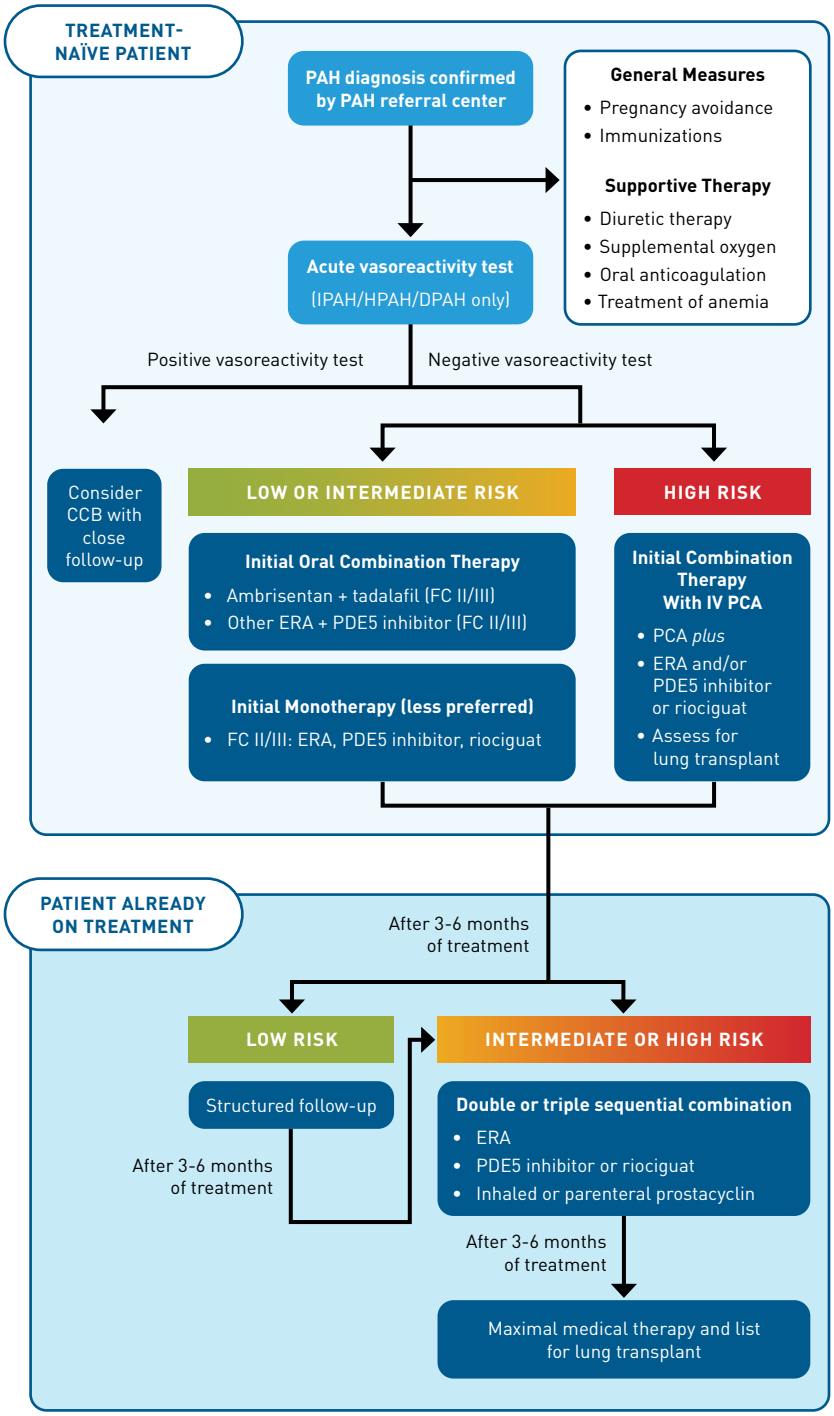
Guidelines for the Pharmacologic Treatment of PAH

The approach to PAH treatment begins with nonpharmacologic management, which includes physical activity and rehabilitation, infection prevention, vaccinations against influenza and pneumococcal disease, counseling women with childbearing potential to avoid pregnancy as it may affect cardiopulmonary function, and counseling before travel. Supportive therapy is employed with oxygen when oxygen saturation is less than 90% or a PaO_2 less than 60 mm Hg, loop diuretics, oral anticoagulation, and lifestyle modifications such as smoking cessation counseling and adherence to a low-sodium diet.[1,2]

The next step in initial management is vasoreactivity testing, which is recommended in patients with idiopathic PAH, heritable PAH, and drug- or toxin-induced PAH. This testing is done to determine whether high-dose calcium channel blockers (CCBs) are a treatment option for these individuals.[1] Approximately 10% to 20% of patients will have a positive or vasoreactive response and are considered eligible for CCBs. Commonly used CCBs include nifedipine 30 mg daily or diltiazem 120 mg daily increased to the maximum tolerated dose over days to weeks, with monitoring of blood pressure, heart rate, and oxygen saturation during titration. Doses required for efficacy in PAH are often higher than those used for systemic hypertension (eg, amlodipine 20 mg daily, diltiazem 720 mg daily, nifedipine 240 mg daily). It is important to note that the efficacy of CCBs is short lived and 50% of patients will lose response within a year. Patients maintained on CCBs should therefore be reassessed after 3 to 6 months to determine if the CCB needs to be replaced with double or triple therapy.[1]

Individuals who are considered nonvasoreactive are not expected to benefit from CCBs and will be initiated on pharmacotherapy with single or dual combination therapy according to functional class and patient characteristics.[1] Patients typically present in WHO-FC II and should be assessed for the risk of disease progression before therapy is initiated. Treatment is generally selected based on risk status, functional class, and patient preference. In treatment-naïve

FIGURE 1. PAH Treatment Algorithm[3,17]



CCB, calcium channel blocker; DPAH, drug-induced pulmonary arterial hypertension; ERA, endothelin receptor antagonist; FC, functional class; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; PCA, prostacyclin analog; PDE, phosphodiesterase.

patients with low or intermediate risk, the preferred treatment is dual combination with an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 (PDE5) inhibitor. The 2019 CHEST guidelines provide new recommendations for pharmacologic treatment in patients with WHO-FC II-III. A treatment algorithm that guides clinical decision making is provided based on patient functional class, disease progression, and response to treatment (**Figure 1**[3]). The expert panel reviewed the literature and added recommendations to the treatment algorithm. The most important addition by the panel based on literature review was the recommendation to initiate combination treatment with ambrisentan and tadalafil in treatment-naïve patients with WHO-FC II-III to improve 6MWD (strong recommendation).

Pharmacologic Therapy for PAH

Pharmacologic therapy for PAH in those who are nonvasoreactive includes endothelin receptor agonists (ERAs) (ambrisentan, bosentan, and macitentan), PDE5 inhibitors (sildenafil and tadalafil), soluble guanylate cyclase stimulator (sGC) (riociguat), and prostacyclin therapies (epoprostenol, iloprost treprostinil, and selexipag) (**Table 2**[1]). Phase 3 studies of PAH-specific therapies have evaluated and demonstrated varying outcomes (**Table 3**[4-12]).

Combination therapy targets the multiple signaling pathways involved in PAH, resulting in improved hemodynamic parameters, symptomatic relief, and improved exercise capacity. Evidence from several clinical trials pointing to benefits of upfront combination therapy has shifted treatment of PAH, leading to changes in guidelines recommending this strategy in WHO-FC II-III patients who can tolerate it, with the strongest level of evidence for ambrisentan plus tadalafil.[1] While ambrisentan and tadalafil is currently the only FDA-approved combination specifically endorsed by CHEST guidelines as initial therapy for patients with less severe symptoms, alternative combination treatments that have shown benefit in clinical trials include macitentan plus sildenafil (SERAPHIN), tadalafil plus bosentan (PHIRST), riociguat plus bosentan (PATENT-1 and -2),

selexipag plus ERA or PDE5 inhibitor (GRIPHON), and oral treprostinil plus ERA, riociguat, or PDE5 inhibitor (FREEDOM-EV).[5,6,8,13-16] Considerations for use of individual agents and evidence for double and triple therapy as well as emerging agents will be discussed below. Parenteral prostanoids (intravenous [IV] epoprostenol, IV or subcutaneous [SC] treprostinil) are recommended in patients with rapidly progressing disease or WHO-FC IV to improve 6MWD. In these patients, combination therapy should be started, which must include prostacyclin therapy.

Patients who cannot tolerate combination treatment can receive monotherapy with ambrisentan, sildenafil (strong recommendation); bosentan, macitentan, tadalafil, or riociguat (consensus-based recommendation).[17] In addition, single-agent monotherapy may be appropriate in patients with a low-risk profile and who have been stable for several years (>5-10 years), in patients with comorbidities with risk factors for heart failure or with contraindications to combination therapy such as severe liver disease; a complete list is included in **Table 4**.[3] In patients with inadequate response to bosentan, ambrisentan, or inhaled prostanoids, addition of riociguat to therapy has been shown to improve 6MWD, delay time to clinical worsening, and improve FC.[17] Additionally, sequential combination therapy can be considered if there is inadequate response with monotherapy.[17]

Endothelin Receptor Antagonists

Endothelin receptor antagonists block the action of endothelin, a powerful vasoconstrictor and mitogen for smooth muscle associated with greater PAH severity and poor prognosis. The ERAs bosentan, ambrisentan, and macitentan are all administered orally and indicated in patients with PAH with WHO-FC II to IV. Bosentan and macitentan are nonselective, dual-action ERAs, and ambrisentan is a selective antagonist of endothelin receptor A (how differences in selectivity affect clinical outcomes remains unclear). Bosentan is initiated at 62.5 mg twice daily for 4 weeks and then increased to 125 mg twice daily; ambrisentan is initiated at 5 mg daily and increased to 10 mg daily; and macitentan is administered at 10 mg daily. ERAs are effective in improving exercise capacity, WHO-FC, hemodynamic parameters, and time to clinical worsening. AEs for the ERAs include peripheral edema, anemia, nasal congestion, and hepatotoxicity requiring monitoring of liver function tests. Bosentan is the most hepatotoxic and requires monthly monitoring of liver function tests as part of its REMS program, while occasional monitoring is recommended with macitentan and ambrisentan. Peripheral edema is mostly seen with bosentan and ambrisentan and can be managed with diuretics. All 3 ERAs require REMS enrollment for use due to teratogenicity and are contraindicated in pregnancy. Female patients with childbearing potential should have monthly pregnancy tests and receive counseling regarding dual contraception.[18]

TABLE 2. Pharmacologic Therapies for PAH[1]

Class	Drug (brand)	Generic available?
Endothelin receptor antagonists	Ambrisentan (Letairis)	Yes
	Bosentan (Tracleer)	Yes
	Macitentan (Opsumit)	No
Phosphodiesterase-5 inhibitors	Sildenafil (Revatio)	Yes
	Tadalafil (Adcirca)	Yes
Soluble guanylate cyclase stimulator	Riociguat (Adempas)	No
Prostacyclin receptor (IP) agonist	Selexipag (Uptravi)	No
Inhaled prostacyclins	Iloprost (Ventavis)	No
	Treprostinil (Tyvaso)	No
Oral prostacyclin	Treprostinil (Orenitram)	No
Parenteral prostacyclins	Epoprostenol (Flolan, Veletri)	Yes
	Treprostinil (Remodulin)	Yes

TABLE 3. Select Outcomes of PAH Therapies[4-12]

Class	6MWD	WHO-FC	QOL	TTCW	Survival
ERA	✓	✓	✓	✓	
PDE5i	✓	✓	✓	✓	
sGC	✓	✓	✓	✓	
Oral treprostinil	✓	✓[a]		✓[a]	
IP agonist	✓[b]			✓	
Inhaled prostacyclins	✓	✓	✓	✓[a,c]	
Parenteral prostacyclins	✓	✓	+/-	✓	✓[d]

ERA, endothelin receptor antagonist; PDE5i, phosphodiesterase-5 inhibitor; sGC, soluble guanylate cyclase stimulator; IP, prostacyclin; 6MWD, 6-minute walk distance; QOL, quality of life; TTCW, time to clinical worsening; WHO-FC, World Health Organization functional class.
[a]Only demonstrated when evaluated as add-on therapy.
[b]Statistically but not clinically significant.
[c]Iloprost only.
[d]Mortality benefit only observed with epoprostenol.
+/- QOL benefits are unclear due to implications of managing parenteral therapy.

TABLE 4. Potential Role for Initial Monotherapy in Specific PAH Subsets[3]

IPAH, HPAH, and drug-induced PAH patient responders to acute vasoreactivity tests with WHO-FC I/II and sustained hemodynamic improvement (same or better than achieved in the acute test) after at least 1 year on CCBs only
Long-term–treated historical PAH patients with monotherapy (>5-10 years) stable with low-risk profile
IPAH patients aged >75 years with multiple risk factors for heart failure with preserved LVEF (high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, obesity)
PAH patients with suspicion or high probability of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis
Patients with PAH associated with HIV infection or portal hypertension or uncorrected congenital heart disease, as they were not included in RCTs of initial combination therapy
PAH patients with very mild disease (eg, WHO-FC I, PVR 3-4 WU, mPAP <30 mm Hg, normal right ventricle at echocardiography)
Combination therapy unavailable or contraindicated (eg, severe liver disease)

CCB, calcium channel blocker; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; RCT, randomized controlled trial; WHO-FC, World Health Organization functional class; WU, Wood units.

Nitric Oxide Pathway Modulators

PDE5 Inhibitors

The PDE5 inhibitors sildenafil and tadalafil and the guanylate cyclase stimulator riociguat all target the nitric oxide (NO)-cyclic guanosine monophosphate pathway (cGMP). PDE5 inhibitors prevent the breakdown of cGMP and increase the effects of NO leading to vasodilation and antiproliferative effects on vascular smooth muscle cells. Sildenafil improves exercise capacity, FC, and hemodynamic parameters (mean pulmonary arterial pressure [mPAP]) and is approved for the treatment of PAH at 20 mg three times daily, although doses up to 80 mg three times daily are often used in practice. Tadalafil 40 mg per day is FDA approved for PAH and was shown to increase 6MWD, time to clinical worsening, and health-related quality of life (HRQOL). Common adverse effects (AEs) include headaches and flushing. Patients may experience changes in vision, such as blue-tinted vision or sudden loss of vision, which warrant drug discontinuation. Additionally, there is a risk of systemic hypotension and both agents are contraindicated with nitrates and riociguat due to an increased risk of hypotension.[18]

Riociguat

Riociguat is a soluble guanylate cyclase (sGC) stimulator that enhances the production of NO through a direct stimulation of sGC and increase in intracellular cGMP. It is initiated at 1 mg three times daily and titrated by 0.5 mg every 2 weeks to a maximum dose of 2.5 mg three times daily. Riociguat improved exercise capacity, pulmonary vascular resistance (PVR), NT-proBNP, time to clinical worsening, and WHO-FC in patients with PAH.[17,18] Switching from a PDE5 inhibitor to riociguat in patients who do not respond to PDE5 inhibitors was shown to improve exercise capacity and hemodynamics.[19] Riociguat is generally well tolerated with common AEs including headache, dizziness, dyspepsia, peripheral edema, and hypotension. Riociguat is contraindicated in pregnancy due to risk of teratogenicity and requires Risk Evaluation and Mitigation Strategy (REMS) enrollment for use. Women of childbearing potential require pregnancy tests and counseling for use of dual contraceptive methods. Concomitant administration with PDE5 inhibitors is contraindicated due to the increased risk of hypotension and lack of evidence of positive benefit/risk ratio. Smoking status should be assessed while on therapy, as smoking reduces riociguat concentrations by 50% to 60% and may require higher doses. While not the focus of this review, riociguat is the only agent currently approved for WHO group 4 pulmonary hypertension, otherwise known as chronic thromboembolic pulmonary hypertension.[17]

Prostacyclin Analogs and Prostacyclin Receptor Agonists

Prostacyclin analogs (epoprostenol, treprostinil, iloprost) and the prostacyclin receptor agonist selexipag increase cyclic adenosine monophosphate and cause nonselective pulmonary vasodilation. These agents have antiplatelet, antithrombotic, anti-inflammatory, and antiproliferative effects on pulmonary endothelial tissue.[18]

Selexipag

Selexipag is the most recent prostacyclin agent to receive FDA approval. It is a nonprostanoid oral agent with high selectivity to the prostacyclin-receptor (IP) over prostanoid receptors and promotes vasodilation in pulmonary vasculature, inhibition of platelet aggregation, and causes antiproliferative effects on smooth muscle cells. Selexipag is approved for the treatment of PAH to delay disease progression and reduce the risk of hospitalization and has shown benefits in patients with WHO-FC II-III. Compared with other prostanoids, selexipag provides the convenience of oral, twice-daily administration, and may have fewer gastrointestinal AEs. The dose is initiated at 200 µg twice daily with incremental dose increases every week to the highest tolerable dose, up to a maximum of 1600 µg twice daily.[20]

In the randomized double-blind, placebo-controlled phase 3, event-driven, Prostacyclin (PGI2) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) trial, selexipag added to background therapy significantly reduced the risk of primary composite end point of death or complications related to PAH compared with

placebo (HR, 0.6; 99% CI, 0.46-0.78; *P* <.001). The treatment effect was driven by differences in disease progression and hospitalization. Study patients had either no therapy or had a stable dose of ERA, PDE5 inhibitor, or both.[16,17] The most common AEs included headache, diarrhea, and nausea that were mild to moderate in nature and consistent with AEs observed with other prostacyclin therapies. Other AEs included anemia and hyperthyroidism.[16] GRIPHON was the largest randomized controlled study in patients with PAH with 1156 patients enrolled; the study showed no significant difference in mortality between study groups. Because the improvement in 6MWD did not meet a clinically significant threshold of 33 meters and a composite was used as a primary end point, these results were considered insufficient evidence by the CHEST guidelines to provide a recommendation for or against the use of selexipag, given the committee's consideration of 6MWD as the clinically relevant outcome; of note, this is inconsistent with prior guidelines, which recommended selexipag as a monotherapy option in WHO-FC II-III and as add-on therapy for WHO-FC IV.[16,17] Recent post hoc analysis of the GRIPHON trial presented at the American Thoracic Society (ATS) International Conference showed greater benefit associated with early initiation of selexipag. Patients who started treatment within 6 months of their PAH diagnosis had a 55% risk reduction in morbidity and mortality versus placebo, whereas those initiated after 6 months experienced a 30% risk reduction versus placebo. Additionally, a more pronounced treatment response was observed in patients treated earlier.[13] Observational real-world studies from database registries of 250 patients taking selexipag 1 year or longer (SPHERE) showed that patients maintained on selexipag remained in the same risk group or improved to a less severe risk group. Patients treated earlier were more likely to be WHO-FC II and treatment naïve from Asia/Eastern Europe than those treated later.[21]

Iloprost

Iloprost is an inhaled formulation of prostacyclin for PAH indicated for WHO-FC III-IV. In studies, iloprost has been shown to improve exercise capacity and FC. Iloprost is administered via the Adaptive Aerosol Delivery inhalation system at a starting dose of 2.5 µg given 6 to 9 times per day (every 2 hours during waking hours) to achieve clinical effect due to its short half-life of 25 minutes. Its use is limited in practice due to the frequency of administration, which takes about 10 minutes per dose, and preference to initiate parenteral therapy in patients with more severe illness. It is well tolerated, and the main AEs include flushing and jaw pain. Additional AEs include cough and throat irritation due to its route of administration.[1]

Treprostinil

Treprostinil is FDA approved for patients with WHO-FC II-IV. It is available in parenteral (for IV or SC use), inhaled, and oral formulations.[18]

ORAL TREPROSTINIL IN COMBINATION WITH BACKGROUND THERAPIES

Treprostinil diolamine oral formulation has been shown to improve exercise capacity as monotherapy in treatment-naïve patients with WHO-FC III.[18,22] The treprostinil extended-release tablet is initiated at 0.125 mg three times daily with food or 0.25 mg twice daily with food, titrated in increments of 0.125 three times daily or 0.25-0.5 mg twice daily every 3 to 4 days as tolerated. The treprostinil dose should be adjusted in patients with hepatic impairment (Child-Pugh class A) and avoided in those with Child-Pugh class B liver impairment.[22] Recent data from the pivotal trial FREEDOM-EV (A Phase III, International, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Clinical Worsening Study of UT-15C in Subjects With Pulmonary Arterial Hypertension Receiving Background Oral Monotherapy) showed that initiation of oral treprostinil reduced the risk of clinical progression by 25% in patients who were maintained on PAH monotherapy. Delayed time to clinical worsening in the oral treprostinil group was largely due to a 61% reduction in risk of disease progression (HR, 0.39; 95% CI, 0.23-0.66; *P* <.001). Administration of oral treprostinil decreased plasma levels of NT-proBNP and led to improvements in 6MWD and WHO-FC starting at week 12 through week 48. There were reduced requirements for initiation of inhaled or parenteral prostacyclin in the oral treprostinil group.[8] The most common AEs were headache, diarrhea, flushing, nausea, vomiting, jaw pain, dizziness, pain in extremities, and myalgia.[8] Additionally, a follow-up hemodynamics study was conducted in 61 patients who received right-heart catheterization at baseline and week 24. A 19% significant reduction in PVR (−134.09 vs −9.20; *P* = .0241) and 8% increase in cardiac output (0.42 vs −0.30; *P* = .0051) compared with placebo was demonstrated. There were no significant changes in mPAP, mean pulmonary arterial wedge pressure, or right atrial pressure.[23] Importantly, the results of these studies have not yet been incorporated into current guideline recommendations.

INHALED TREPROSTINIL IN COMBINATION WITH BACKGROUND THERAPIES

Inhaled treprostinil was shown to improve exercise capacity and QOL predominantly as add-on therapy in patients with WHO-FC III-IV. Inhaled treprostinil is recommended by the 2019 CHEST guidelines in combination with a PDE5 inhibitor and an ERA in patients with WHO-FC IV who cannot tolerate IV prostanoids.[17] In the TRIUMPH-I (Double Blind Placebo Controlled Clinical Investigation Into the Efficacy and Tolerability of Inhaled Treprostinil Sodium in Patients With Severe Pulmonary Arterial Hypertension) trial, inhaled treprostinil was administered with a target dose of 54 µg four times daily as an add-on to background therapy bosentan or sildenafil. This benefit was sustained for 2 years after initiation.[9,24,25] Treprostinil inhaled solution must be taken through the Tyvaso inhalation system in 4 daily sessions every 4 hours, at 3 breaths per

treatment session (18 µg each). The dose is increased by 3 breaths per session at 1- to 2-week intervals to 9 breaths (54 µg each) per session as tolerated.[24] Common AEs include throat irritation, cough, headache, nausea, dizziness, and flushing. Additionally, patients require monitoring for systemic hypotension, especially those on concomitant antihypertensives or vasodilators. Inhaled treprostinil recently demonstrated benefits related to 6MWD, NT-proBNP, and clinical worsening in WHO group 3 pulmonary hypertension secondary to interstitial lung disease and led to submission of a new drug application (NDA) for this indication.[26]

PARENTERAL TREPROSTINIL

Treprostinil injection for SC or IV use is recommended in patients with WHO-FC III with rapid disease progression and patients in WHO-FC IV. Treprostinil has a half-life of about 4 hours, allowing more flexibility and lower risk of rebound pulmonary hypertension with discontinuation as compared with epoprostenol. It is prescribed for patients to diminish symptoms associated with exercise intolerance and in those who require transition from epoprostenol to reduce the rate of clinical deterioration. While parenteral treprostinil has not demonstrated survival benefits, this agent is often used interchangeably with epoprostenol based on patient-specific factors and institution preferences. The risks and benefits of each drug should be considered before selection and/or transition. Treprostinil is initiated at 1.25 ng/kg/min and titrated based on efficacy and tolerability. Patients being considered for parenteral therapy currently require both an ability to mix the prescribed drug and manage an external pump. The SC route is preferred to decrease risk of complications related to IV therapy, but the drug can be administered by central IV if the patient cannot tolerate the SC route. The CADD-Legacy 1 pump is an external device used for continuous IV delivery and provides up to 2 days' supply of medication, while the more compact CADD-MS 3 pump used for SC administration provides a 72-hour supply of treprostinil. SC infusion may cause infusion-site pain and injection reactions that may warrant consideration of the IV route. Other AEs include headache, diarrhea, vasodilation, edema, jaw pain, and hypotension.[27] As of March 2019, a generic treprostinil infusion had been approved for IV and SC use, although currently available SC delivery systems are not patented to deliver this formulation.[28,29]

Epoprostenol

Epoprostenol is a synthetic prostacyclin analog with a short half-life of 3 to 5 minutes requiring a continuous infusion. Epoprostenol is the first and only PAH-specific agent to have demonstrated survival benefits to-date.[30] Additionally, IV epoprostenol was shown to improve exercise capacity and hemodynamics and is approved in patients with WHO-FC III-IV. Of note, there are currently 2 available formulations of epoprostenol available, Flolan and Veletri. Important differences in these formulations include the diluents used for reconstitution and resulting stability. Flolan originally required a glycine buffer diluent for a stability of 8 hours at room temperature, creating a need for ice packs while administering. Since then, a pH 12 sterile diluent has been developed, allowing for 72 hours of thermostability. Veletri may be mixed with sterile water or normal saline and is thermostable for up to 72 hours at room temperature, depending on concentration. Hospitalization is required for initiation of both epoprostenol and treprostinil. Epoprostenol must be administered via a pump through central venous catheter at a starting dose of 2 ng/kg/min and is increased to a target dose of 25 to 40 ng/kg/min based on efficacy and tolerability. The titration rate depends on disease severity, symptoms, and AEs; the maximal dose has not been established. AEs that may occur during titration and are common to all prostanoids include headache, nausea, vomiting and diarrhea, flushing, hypotension, and jaw pain.[18,31] Severe AEs may occur with this complex delivery system and include infection, thrombosis, pump malfunction, and interruption of the infusion, which is considered a medical emergency. A backup supply of the drug and pump are required to ensure patient safety should the pump malfunction. The rate of central venous catheter infection was estimated at 2% per year and contributes to morbidity and mortality with continuous epoprostenol.[18]

Combination Therapies

Ambrisentan and Tadalafil

The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial evaluated therapies with different intracellular target pathways (PDE5 inhibitor tadalafil 40 mg and ERA ambrisentan 10 mg) that did not have pharmacokinetic interaction. Results of AMBITION demonstrated that the upfront use of combination therapy with ambrisentan and tadalafil in patients with PAH who were treatment naïve significantly reduced the risk of clinical failure events compared with either ambrisentan or tadalafil monotherapy. The primary end point of the study was time to event of clinical failure defined as composite of death, hospitalization for worsening of PAH, disease progression, or unsatisfactory long-term clinical response until patients' final assessment. Patients in the combination therapy group had a 50% lower risk of clinical failure than in the pooled monotherapy group (HR, 0.5; 95% CI, 0.35-0.72; P <.001), and had greater improvements in 6MWD and greater reductions from baseline in NT-proBNP than in the pooled monotherapy group (P <.001). Additionally, there was a 63% reduction in risk of PAH-related hospitalization when compared with pooled monotherapy (HR, 0.372; 95% CI, 0.217-0.639; P = .0002). The most common AEs in the combination group were peripheral edema, headache, nasal congestion, and anemia, but there was no difference in drug discontinuation due to AEs.[32] Results of the AMBITION trial led to the combination being approved by the FDA

as a first-line treatment in patients with WHO-FC II and prompted the updated CHEST guideline recommendations for the initial use of ambrisentan and tadalafil in PAH.[17,32]

Other Dual Combination Therapies

Combination treatment with alternative PDE5 inhibitors and ERAs has also been shown to be safe and effective, such as macitentan plus sildenafil and tadalafil plus bosentan; these were shown to improve clinical outcomes such as time to clinical failure in the SERAPHIN and PHIRST studies, respectively. Benefits have also been demonstrated with riociguat plus bosentan in the PATENT-2 study. In the GRIPHON trial, selexipag added to background therapy demonstrated a 49% decrease in clinical worsening regardless of type of background therapy (ERA, PDE5 inhibitor, or combination). While the ambrisentan and tadalafil combination is specifically endorsed by the guidelines, clinical experts consider these other combinations as appropriate treatment options. Currently, the CHEST guidelines make no specific recommendations for or against the use of selexipag.[3,5,6,14,15]

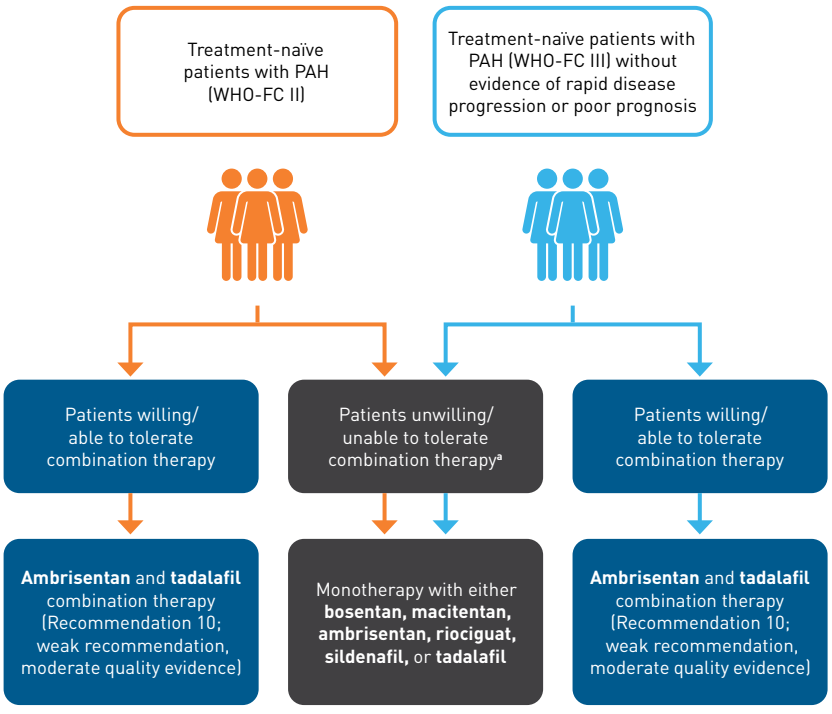
Not all evaluations of upfront combination therapy have demonstrated positive results. In the BREATH-2 study, the combination of IV epoprostenol plus bosentan was no better than epoprostenol alone.[33] More recent evidence suggested this combination may improve hemodynamics but not clinical outcomes such as mortality.[34] CHEST guidelines do not recommend routine addition of bosentan in patients when initiating parenteral prostacyclin therapy. While these guidelines make no specific recommendation for upfront combination therapy in patients with WHO-FC IV symptoms, they acknowledge the need for studies to evaluate preferred combination therapies in patients with advanced illness.[17] The decision for which combination to use should include consideration of patient-specific factors (eg, risk assessment, preferences, tolerability). In general, upfront combinations of oral therapies discussed above are most appropriate in patients with low or intermediate risk (WHO-FC II-III without rapid progression), while consideration should be given for therapy that includes a parenteral prostacyclin in patients with high-risk features (**Figure 2**[17]).

Triple Combination Therapy

Despite the known benefits of upfront dual therapy, the merits of triple combination therapy remain unclear. A study of 21 patients with newly diagnosed PAH treated with a combination of ambrisentan, tadalafil, and SC treprostinil was associated with improvements in hemodynamics, WHO-FC, and 6MWD at a median of 2 years follow-up.[35] Similar results were also demonstrated in a pilot study evaluating upfront triple combination therapy with IV epoprostenol, bosentan, and sildenafil.[36] While the results of this study were largely positive, it is difficult to draw conclusions based on its retrospective nature and lack of a comparator group.

More recently, the phase 3b TRITON study evaluated initial triple therapy with selexipag, macitentan, and tadalafil in comparison to initial dual therapy with macitentan and tadalafil in 247 patients with newly diagnosed PAH. Results of the study were recently presented at the ATS 2020 International Conference. Initial triple therapy reduced the risk of disease progression by 41% (HR, 0.59; 95% CI, 0.32-1.09, $P = .087$), and while there was an improvement in the primary end point of change in PVR and in secondary end points of 6MWD, NT-proBNP, and worsening of FC at week 26, these were nonsignificant. Reported AEs were consistent with known profile of drug classes (headaches, diarrhea, nausea, pain in extremities, jaw pain, and vomiting) and occurred in higher frequency in the triple therapy group. These results did not provide sufficient evidence to

FIGURE 2. Considerations for Combination Therapy[17]



PAH, pulmonary arterial hypertension; WHO-FC, World Health Organization functional class.

[a]Combination therapy carries with it costs as well as multiple medications, including the potential for increased adverse effects that may be undesirable for some patients. In these situations, patients are unwilling or unable to tolerate combination therapy and the panel suggests monotherapy.

support upfront triple therapy and the benefit of adding selexipag remains unclear; however, the trend toward improved measures warrants further investigation. The full publication is awaited to assess whether initial triple therapy versus dual therapy improves long-term outcomes.[37]

Current guidelines make no specific mention of upfront triple combination therapy. Limitations of current evidence include lack of robust study designs and heterogenous nature of therapies evaluated (ie, oral vs parenteral). Special consideration should be given to patient preference in this setting, given the overwhelming nature of a new PAH diagnosis and the implications for adjusting to multiple new therapies, particularly as this relates to parenteral therapy. Given the limited data available, the role of this strategy remains unclear but may be considered for specific patients (ie, those with high-risk features willing and able to tolerate triple combination therapy).

Emerging Pharmacotherapeutic Modalities

Treprostinil Infusion Systems

The Remunity pump delivery system, initially cleared by the FDA in May 2019 for patients aged 22 years and older, provides continuous SC delivery for 3 days (72 hours). This system provides a compact design that is water resistant, simplicity of prefilled cassettes, and is programmable with a wireless remote and is approved for commercial distribution as of February 2021. The cassettes used in the pump are prefilled in a specialty pharmacy and delivered to the patient.[27,38-40] An implantable system for Remodulin (ISR) is also under development that allows patients to receive IV prostacyclin therapy without an external pump or tubing, decreasing the risk of bloodstream infections, line malfunctions, and infusion-site pain. The pump is surgically implanted in the patient's abdomen. The trial is ongoing with initial implants expected to occur this year in 2021.[41] The Trevyent PatchPump system is a prefilled and preprogrammed disposable skin patch pump system that received the FDA Orphan Drug designation in 2016. It is designed to deliver treprostinil SC for 2 days (48 hours) with decreased site pain. The device manufacturer is awaiting review of the NDA submitted in 2019; a decision is expected later this year.[42]

Treprostinil dry powder inhalation

LIQ861 is a formulation of treprostinil administered through a disposable dry powder inhaler (DPI) using a novel technology that optimizes drug delivery into the lung. The delivery system provides 25 µg four times daily increased by 25 µg weekly until symptomatic relief as tolerated. The novel Particle Replication in Nonwetting Templates (PRINT) technology aims to improve current inhaled therapies and the DPI device has the potential to improve treatment satisfaction, offers convenience and improved QOL for patients with PAH, requiring 4 to 8 breaths per day compared with currently available treatment options that require 36 breaths per day and use of a nebulizer.[43] LIQ861 was evaluated in the phase 3 open-label Investigation of the Safety and Pharmacology of Dry Powder Inhalation of Treprostinil (INSPIRE) trial in 121 patients transitioned from Tyvaso or stable on less than or equal to 2 nonprostacyclin therapies.[43] At baseline, the majority of patients were female (81.8%) with the majority (66.1%) being in New York Heart Association (NYHA)-FC II and the rest in NYHA-FC III (33.9%). At 2 months follow up, 75.9% of patients maintained their NYHA-FC and 20.5% improved with similar results between patients transitioning from Tyvaso and in stable patient groups. Improvements were also noted in 6MWD and QOL scores. LIQ861 was evaluated at doses ranging from 26.5 µg to 159 µg with no serious AEs observed.[44,45] Following an NDA submission, a complete response letter was issued from the FDA in November 2020.

Other dry powder formulations for treprostinil are currently under development, including treprostinil inhalation powder. Like LIQ861, the purpose of this formulation is to create convenience in administration and enhance the delivery of inhaled treprostinil. The DPI uses a Technosphere particle technology (TreT) allowing for a high concentration of the drug to be delivered into the lungs. Doses administered to healthy volunteers in a dosing study varied from 30 µg to 180 µg per dose and produced clinically relevant concentrations of treprostinil. TreT was well tolerated and the most frequently reported AEs were cough and headache.[46] The safety and tolerability of TreT is currently being evaluated in the BREEZE study. This open-label, phase 1b study is evaluating the transition of patients on a stable dose of inhaled Tyvaso to an equivalent dose of DPI formulation for a minimum of 3 weeks. Outcomes of interest include pharmacokinetic data, 6MWD, safety, and patient satisfaction. BREEZE is anticipated to be completed in March 2022 with an NDA filing anticipated in April 2021.[47]

Ralinepag

Ralinepag is a selective nonprostanoid prostacyclin receptor agonist formulated as an oral, extended-release tablet taken once daily. In a phase 2 randomized placebo-controlled trial, ralinepag significantly reduced PVR compared with placebo (–29.8%; $P = .03$) in 61 patients receiving mono- (41%) or dual- (59%) background therapy. Ralinepag was initiated at a dose of 10 µg twice daily and titrated as tolerated over 9 weeks to a maximum total daily dosage of 600 µg (300 µg twice daily). Reported AEs included headache, nausea, diarrhea, jaw pain, and flushing.[48,49] Ongoing phase 3 studies, part of the ADVANCE clinical program, are evaluating the effect of ralinepag on clinical outcomes and exercise capacity. ADVANCE OUTCOMES will assess the impact of once-daily ralinepag on morbidity and mortality, including disease progression, clinical worsening, and survival in 700 patients randomized 1:1 to receive ralinepag or placebo plus PAH-specific therapy.[50] This trial is estimated to be completed in

December 2021. The effect of ralinepag on exercise capacity after 28 weeks of treatment is being assessed in ADVANCE CAPACITY (using change in VO_2 derived from CPET).[49,51] The trial is currently recruiting and estimated to be completed in September 2023.

Sotatercept

Disruptions in the transforming growth factor (TGF)-β and bone morphogenetic protein receptor type II (*BMPR2*) pathways lead to cellular proliferation and vascular remodeling seen in PAH. Sotatercept is a first-in-class, selective ligand trap for members of the TGF-β superfamily (activins, growth differentiation factors, others) that can rebalance *BMPR2* signaling and restore vascular homeostasis. It is administered as an SC injection every 3 weeks.[52] Phase 2 results presented at the ATS 2020 conference showed sotatercept in combination with background therapies reduced mPAP, increased 6MWD, reduced NT-proBNP, and improved WHO-FC compared with placebo (N = 106). Notable AEs in the sotatercept group included a hemoglobin increase (n = 7) and thrombocytopenia (n = 7); other AEs included headache, diarrhea, peripheral edema, dizziness, fatigue, hypokalemia, and nausea.[52-54] Sotatercept has received breakthrough therapy designation from the FDA and the ongoing STELLAR phase 3, randomized, double-blind, controlled trial is evaluating sotatercept 0.7 mg/kg SC every 3 weeks plus background therapy compared with placebo in 284 patients; it is planned for completion in December 2022. The primary end point of the trial is change from baseline in 6MWD with secondary outcomes including hemodynamic improvements, WHO-FC changes, time to death or clinical worsening, and changes in QOL scores.[55]

Conclusions

Recent developments in pharmacotherapy for the treatment of PAH led to new FDA approvals of agents such as ERAs, nitric oxide modulators, and prostacyclin therapies that target the underlying pathophysiology of the disease. Combination therapy with these agents has increased effectiveness and reduced the risk of death and disease progression. Survival is expected to increase with earlier initiation of combination therapies and application of an individualized treatment approach. Advances in pharmacotherapy and latest results from pivotal trials evaluating different agents in combination have shifted the treatment paradigm of PAH. Emerging therapies and novel delivery formulations provide new options to the therapeutic armamentarium of PAH management. These therapies promise added convenience, with the potential for reduced AEs and optimized clinical outcomes. ■

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Funding source: This activity is supported by an educational grant from United Therapeutics Corporation.

Author disclosure: Dr Gale has no financial relationships with commercial interests to disclose.

Authorship information: Substantial contributions to analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

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REPORT

Reducing Economic Burden and Improving Quality of Life in Pulmonary Arterial Hypertension

Douglas S. Burgoyne, PharmD, FAMCP

Impact of Pulmonary Arterial Hypertension on Survival

Pulmonary arterial hypertension (PAH) is a rare medical condition with a worldwide prevalence estimated at 15 million to 50 million, with 200,000 new cases diagnosed annually in the United States.[1] Based on the incidence of PAH, a hypothetical health plan with 5 million patients can expect to have between 60 and 250 patients with PAH, with 12 to 38 new cases annually.[2] Symptoms of PAH are similar to other diseases, which may lead to delay of diagnosis.[3] Although there have been recent advances in treatment as well as earlier detection and diagnosis of PAH, it is still associated with a poor prognosis. Delayed treatment significantly impacts survival. Prior to the advent of targeted therapies for PAH, median survival from diagnosis to death was estimated at 2.8 years.[1]

Most epidemiologic data for PAH is from the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) and resulting observational studies. This registry consisted of more than 3500 patients in the United States with World Health Organization (WHO) group I PAH. REVEAL data estimated 1-, 3-, 5-, and 7-year survival from diagnosis for patients with PAH to be 85%, 68%, 57%, and 49%, respectively, with median survival of approximately 7 years.[4] An analysis aimed to evaluate main predictors of survival found independent variables associated with increased mortality were pulmonary vascular resistance greater than 32 Wood units (hazard ratio [HR], 4.1; 95% CI, 2.0-8.3), PAH associated with portal hypertension (HR, 3.6; 95% CI, 2.4-5.4), modified New York Heart Association/WHO functional class IV (HR, 3.1; 95% CI, 2.2-4.4), men aged older than 60 years (HR, 2.2; 95% CI, 1.6-3.0), and family history of PAH (HR, 2.2; 95% CI, 1.2-4.0).[5] New large-scale registries such as the REVEAL, which was completed in 2012, are needed to provide insight of epidemiologic data and survival impact of current treatment therapies for PAH.

Early diagnosis is an important first step to ensure optimal treatment outcomes. It has been reported that patients may come for referral already on one or 2 PAH therapies but have never had a right heart catheterization (RHC). In some cases, the RHC revealed that the patient was misdiagnosed and never had PAH in the first

ABSTRACT

Pulmonary arterial hypertension (PAH) is a rare, progressive disorder associated with a poor prognosis if not treated appropriately. Fortunately, new treatment options have significantly improved survival rates and prognosis. Despite these advances, many patients do not receive the diagnosis until years into their disease or are inappropriately diagnosed. Early referral to specialized treatment centers that allows for early diagnosis and initiation of treatment significantly improves patient outcomes including survival as well as reduction in hospital admissions, which are a main driver of economic burden of disease. It is important that evidence-based guidelines are followed and treatment is individualized based on patient-specific factors. Pharmacologic therapies carry a very high cost for PAH; however, extensive utilization of management strategies may hinder access to medication and may lead to disease progression. Cost containment strategies may help to facilitate care coordination for earlier diagnosis and initiation of treatment, adherence to PAH medications, and patient education to ensure they are using medications appropriately to optimize therapy. Managed care pharmacists can play a crucial role in the multidisciplinary team in terms of medication safety, adherence, patient education, and follow-up to improve patient engagement that leads to improved outcomes.

***Am J Manag Care*. 2021;27:S53-S58**

For author information and disclosures, see end of text.

place. Misdiagnosis leads to inappropriate treatment with expensive therapies that may negatively impact patients and incur avoidable economic expenses.[2] Unfortunately, misdiagnosis and delayed diagnosis are common because there is no simple test that can be performed to diagnose PAH early in the course of the illness, such as with diabetes and hypertension. On average, it may take 2.3 to 2.8 years for an accurate diagnosis, at which point the disease has likely progressed (**Figure 1**[6]). Delays in diagnosis result in patients being denied the opportunities for gained survival benefit associated with early and aggressive treatment.[7] Additionally, treatment at a later stage of disease is associated with increased hospitalization and length of stay with added costs associated with treating PAH. Therefore, early referral to expert care centers is important for improved outcomes as well as cost-containment strategies associated with PAH.[7]

Economic Burden of PAH

The economic impact of PAH can be substantial. Estimated direct per-patient per-month (PPPM) costs for PAH are 4 to 5 times higher than matched control patients with similar age, sex, geographic regions, and employment status.[7] A Kaiser Permanente Colorado review found the median total per-patient per-day and 3-year total expenditures for patients with PAH to be $56 and $50,599, respectively.[8]

A retrospective study was conducted that aimed to determine the correlation of functional decline in patients with PAH with increased healthcare utilization and costs. Data were obtained from Humana Research Database, which contained claims for US commercial and Medicare health plans for approximately 19 million members. Disease severity as indicated by higher functional class was found to be associated with greater likelihood of inpatient episodes and significantly higher PAH-related cost. This suggests patients who progress to advanced functional classes will utilize more services. Therefore, appropriate treatment of the disease to slow progression is a key component in cost mitigation (**Figure 2**[6]).[2] Annual pharmacy costs are estimated to be 17 to 21 times higher than those of the average Medicare part D patient.[6]

In a claims-based analysis of 504 patients with PAH in a large US managed care plan, researchers evaluated healthcare resource utilization associated with PAH treatment from 2004 to 2010. Patients were followed for 12 months following the index date, defined as the earliest date of a claim of a PAH-indicated medication. Healthcare resource utilization was compared between an annualized baseline period and the 12 months following the index date. Total healthcare costs were significantly lower during the follow-up period compared with the baseline period ($98,243 vs $116,681; P <.001). Pharmacy costs were significantly higher during the follow-up period ($38,514 vs $6440; P <.001). However, medical costs were significantly lower during the follow-up period ($59,729 vs $110,241; P >.001).[3]

These patients are also at high risk of rehospitalization and 79.3% of hospitalized patients with PAH were found to have a readmission within 1 year of discharge, with 1 in 5 patients having a readmission within 30 days of discharge.[9] The average cost of patients with at least 1 hospitalization totaled $46,118 (SD, $135,137), while readmission totaled $35,188 (SD, $152,006).[9]

There is a growing body of evidence in support of early initiation of combination therapy.[8] A systematic review examined drug cost, hospitalization burden, healthcare economics, and the effect of early intervention on clinical outcomes. Evaluating studies from 2005 to 2017, findings indicated that early therapy is effective. Results also showed benefit of combination therapy with a decrease in hospitalization, particularly in patients with FC II, but noted drug costs increased with combination therapy. A review of pharmacoeconomic studies indicated that an increase in pharmacy costs were at least partially offset by decreased healthcare resource utilization, particularly inpatient visits.[8] There is evidence that PAH treatment decreases hospitalization frequency, which in turn may lead to reduced healthcare utilization costs associated with PAH. As shown in the AMBITION trial, combination therapy with ambrisentan plus tadalafil compared with pooled monotherapy decreased hospitalizations due to PAH (4% with combined therapy vs 12% with monotherapy). Additionally, results of the SERAPHIN trial indicate that macitentan decreased hospitalizations due to PAH by 50% (HR, 0.50; 97.5% CI, 0.34-0.75). Furthermore, the risk of all-cause hospitalizations decreased by 19% and 32% in the 3-mg and 10-mg daily dosing arms compared with placebo. Risk of PAH-related hospitalizations was reduced by 43% (P <.001) and 52% (P <.001) in the 2 treatment arms.[8]

FIGURE 1. Median Survival by Functional Class Before Available Treatment[6]

Encouraging Appropriate Medication Use and Application of Evidence-Based Guidelines

Patients with PAH are typically fragile and have multiple comorbidities, necessitating an individualized management approach based on their risk and disease progression.[9] Current evidence suggests there are a variety of treatment options for patients with PAH including general guidance (eg, physical activity, oral anticoagulants, psychosocial support), nonspecific pharmacologic interventions (eg, calcium channel blockers), as well as targeted pharmacologic interventions depending on patient-specific factors.[9]

There is growing evidence to support early aggressive treatment with multiple therapies for treatment-naive patients. One study analyzed the effect of initial triple combination therapy (including intravenous or subcutaneous prostacyclin and 2 oral drugs) on long-term survival in patients newly diagnosed with PAH. Patients initiated with triple combination had more severe PAH compared with those on dual combination or monotherapy (P <.001). In patients initiated with triple combination therapy, the actual versus predicted overall survival rates at 1, 2, and 3 years were 94%, 92%, and 90%, versus 76%, 62%, and 51%, respectively. The use of triple combination therapy was shown to reduce the risk of death compared with mono- or dual-combination therapy (HR, 0.35; 95% CI, 0.17-0.71; P = .003).[10]

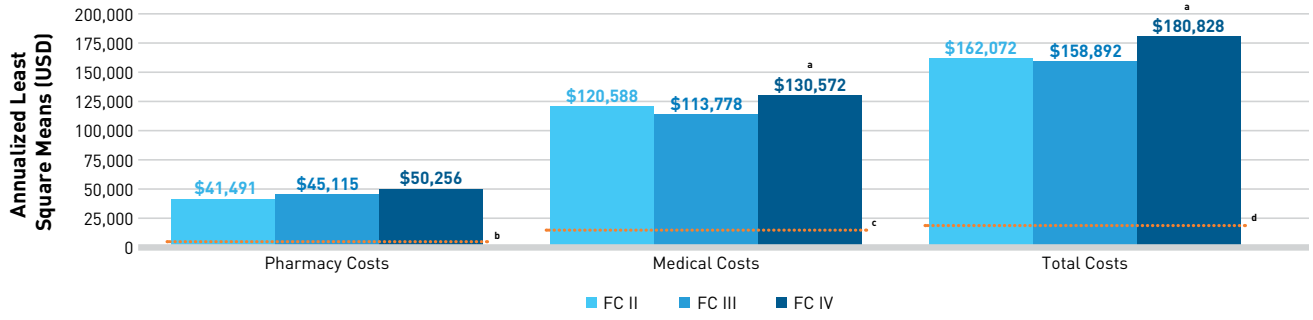
A 2016 meta-analysis included prospective, randomized, controlled trials of at least 12 weeks duration between 1990 and 2015 that compared combinations of approved PAH treatments with monotherapy having primary end points of clinical worsening or one or more secondary outcomes (all-cause mortality, PAH-related mortality, PAH-related admission to hospital, lung transplantation, treatment escalation, symptomatic progression, changes in WHO functional class, treatment discontinuation, and treatment duration). The meta-analysis included 17 studies (4095 patients) and found that combination therapy significantly reduced the risk of clinical worsening when compared with monotherapy (risk ratio, 0.65 [95% CI, 0.58-0.72]; P <.00001). Results were consistent among subgroups. Additionally, functional status was also improved with combination therapy. Data from this study strongly favor the use of combination therapy and have shaped treatment guidelines over time.

The REVEAL Registry has indicated that 46% of patients with PAH are on dual therapy, and 9% of patients are on triple therapy.[9] While combination therapy does elicit favorable results in many patients, the guidelines do recognize that not all patients with PAH may benefit from combination therapy and monotherapy is an appropriate option in some patients. This demonstrates a need for new and innovative treatment options for PAH, and access to current therapies in the interim.[9] Pharmacy wholesale acquisition costs range from $25,000 to $250,000 for "average dosing" of PAH medications.[9] These high prices have made payers interested in utilization management strategies including prior authorization, tiered use, and formulary restrictions. However, cost offsets could be achieved by earlier diagnosis of the disease and appropriate targeted treatment.

An economic model examined the potential impact of selexipag. The model assumed 1 million health plan members and a 2-year horizon calculated annual costs with 2 separate scenarios: 1 with selexipag and 1 without. The model predicted 22 patients with PAH in year 1 and 22 patients with PAH in year 2 would be treated with a prostacyclin pathway. They predicted the 2-year cost would be offset by a 15% reduction in costs with the addition of selexipag, which would result in a cost-savings of $0.04 per member per month (PMPM).[8]

It is critical that healthcare providers continue to tailor treatment regimens to the individual patient. Guidelines recommend the optimal approach is individualized based on severity of illness, route of administration of therapy, adverse effect profile, comorbid

FIGURE 2. Adjusted Healthcare Costs by Type and Functional Class (FC)[6]



[a] P<.01 vs FC II or FC III using Genmod regression models.
[b] Denotes the average annual pharmacy costs for Medicare Part D ($2363; CY 2012).
[c] Denotes the average annual medical costs for Medicare ($11,392; CY 2012).
[d] Denotes the average annual total costs for Medicare ($13,755; CY 2012).

illnesses, treatment goals, and clinician experience and preference. Due to this individualized approach, patients should be able to access clinically appropriate and approved treatments for PAH to allow for optimized outcomes. It is important to remember that PAH is a progressive disease and delays in initiation of optimal treatment regimens may be associated with deterioration in functional class, which has been a predictor of mortality.[9] If patients must move through a tier-by-tier restrictive utilization process, many patients may not recover the time lost or may experience complications due to comorbidities. Formulary exclusions may also impact optimal treatment when there are drug shortages. The appeal process for noncoverage or nonformulary items comes at a high cost due to wasted time and administrative burden. The 2020 Council for Affordable Quality Healthcare index estimates that overall spending on prior authorizations is $767 million in the United States, with 86% of the spending incurred by providers.[11] As many as 79% of prescribers report that they must resubmit appeals for repeated prescriptions for chronic conditions such as PAH. Rather than intensive utilization management strategies on PAH medications, it may be more appropriate to ensure these patients are being closely followed by care management and care coordination services.[6] Due to the progressive nature of the disease and the supporting literature that early, combination therapy has proven to demonstrate a benefit in terms of mortality, hospitalizations, and disease progression, payers should maintain flexibility to help facilitate an individualized treatment approach. Utilization management strategies that are too restrictive and add more time to receive therapies may negatively impact disease outcomes for progressive orphan diseases such as PAH.[9]

Educating Healthcare Providers and Patients With PAH

A patient-centered approach that takes into account the impact of illness on day-to-day activities and quality of life and aims to improve these is an important strategy for improved outcomes in PAH. Guidelines recommend early referral to expert centers to accurately diagnose and initiate treatment. According to the 2015 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines, the role of providers within an expert center is to assess and investigate all causes of PAH, manage PAH-specific therapies, and work collaboratively with other healthcare providers, including primary care, in order to optimize patient outcomes.[7] Despite educational initiatives, referrals to care centers are often delayed and continue to be problematic. Patients are often referred with incomplete diagnostic testing, misdiagnosis, inappropriate treatments, or are not referred until their disease has progressed significantly.[7] PAH is often diagnosed after symptoms have begun and patients may present with only vague symptoms including shortness of breath, fatigue, and activity limitation. They may also be inappropriately diagnosed with asthma or chronic obstructive pulmonary disease.[6]

The lack of referrals for patients with PAH to care centers has led to the development of the Pulmonary Hypertension Care Center committee, which aspires to improve the overall quality of care and outcomes of patients with PAH. This committee oversees an accreditation program that promotes standards and adherence to guidelines as well as fosters collaboration among experts. These initiatives may potentially improve patient referrals to expert care and contribute to improved outcomes as well as cost containment. While early referral to expert care centers should remain a primary strategy, there is still a growing need for education. Healthcare providers including local primary care and specialty physicians should work together with care centers. Nonadherence to treatment guidelines leads to patients being undertreated, especially those patients with more progressed disease, who are often treated with inappropriate medication options.[7]

Managed care professionals can successfully engage patients through education and communication of high-quality information. There is growing evidence that patient engagement generally improves outcomes. Patients with PAH who are better informed find it easier to manage their disease in key areas such as health-related quality of life, health status, anxiety, depression, and self-management. A wealth of information is available on the internet, but there is potential for significant misinformation as well. It is important that disease information is communicated accurately about the patient's specific circumstances and disseminated at the appropriate time.[12] Additionally, the growing use of early aggressive combination therapy creates the need for greater monitoring and management of adverse effects (AEs).[7] Pharmacists are vital educators for patients on managing their disease, monitoring for AEs, and ensuring patients understand their medications. Additionally, with combination therapy now being routinely used, it may complicate a patient's treatment regimen and impact medication adherence.[13] Another challenge is that PAH may impair cognitive function, affecting verbal learning that may limit a patient's engagement in the management of their disease. A further challenge is that patients may not want to be engaged in the management of their disease as a coping mechanism to avoid dealing with the harsh realities of their diagnosis. It is important for healthcare professionals to communicate to patients the benefits that engagement can have on outcomes and to encourage participation.[12]

The ESC/ERS guidelines recommend increasing patient engagement through collaboration with other healthcare professionals, including psychologists, psychiatrists, social workers, and patient associations. For patients in rural areas unable to receive the type of care usually provided by large-scale healthcare institutions, it is important for local family physicians to collaborate with other healthcare professionals in the local community. This collaborative

approach can optimize patient engagement from a multitude of different standpoints. Additionally, receiving information from a diverse team of healthcare professionals may be beneficial because each individual may convey information differently.[12]

Another vital role for managed care professionals in a healthcare team is education on medication administration and safety. Specifically, parenteral prostanoids have a risk of medication errors and AEs. Epoprostenol is included on the Institute for Safe Medication Practice's list of high-alert medications. One survey has shown that of reported errors associated with this therapy, two-thirds were serious or potentially serious. Fatalities were also reported. Errors can include accidental bolus dosing (flushing the dedicated line), incorrect dosing (miscalculation, compounding, ordering errors), and pump-related errors. Pharmacists are needed to develop policies that reduce the risk of error and educate providers to ensure safe and appropriate medication use. This may include double checking calculations, confirming dosing with the patient's specialty pharmacy, minimizing storage of backup cassettes or bad preparation, and the use of different colored cassettes for different agents if available. Pharmacists can also help optimize therapy by ensuring appropriate dosing and titration of prostanoids, as dose tolerability is limited by patient-reported AEs. Pharmacists can also assist with drug–drug interactions, transitions between PAH therapies, and management of medications for other AEs.[1]

Assisting With Barriers Related to Medication Acquisition and Specialty Pharmacy

Specialty pharmacies can play a crucial role in the coordination of care for patients with PAH and mitigate medication-related barriers. Specialty pharmacists can improve drug adherence and outcomes for patients that optimizes their overall quality of life. In this setting, pharmacists can assist with insurance approval, patient counseling, overcoming financial constraints, and managing AEs.[14] The specialty pharmacy model has resulted in decreased provider and clinic burden, decreased time for medication approval and initiation, patient and provider satisfaction, and patient cost savings by facilitating and improving access to manufacturer discount programs. For these reasons, there is a rapid growth of specialty pharmacies for conditions that need to be more closely followed.[15]

Managed care professionals in the specialty care setting can also play an important role in impacting medication adherence. These therapies are very costly, so it is even more crucial to ensure that patients are taking the medications appropriately. Additionally, closely following these patients may play an important role in preventing rehospitalizations, for which patients with PAH are at high risk. One retrospective study included adult patients with PAH who were prescribed phosphodiesterase-5 inhibitor therapy by the center's outpatient clinic and who received medication management through the center's specialty pharmacy. Adherence was defined as proportion of days covered (PDC) greater than or equal to 80%. Of the 131 patients included in the study, 94% achieved optimal medication adherence greater than or equal to 80% of PDC. Of the total patients, 47% experienced an AE and 27% had at least 1 hospitalization. Patients with a PDC less than 80% were more likely to experience an AE when compared with patients with PDC greater than or equal to 80% ($P = .002$).[14]

Another aspect of PAH medication is regulatory compliance. Risk Evaluation and Mitigation Strategy programs exist for endothelin receptor antagonists as well as riociguat. These medications are only available through certified outpatient specialty pharmacies to manage their monitoring and compliance requirements.[16] Specialty pharmacy's care coordination allows access to medications with AE concerns (eg, embryo-fetal toxicity, hepatotoxicity) while still maximizing patient safety.

Conclusions

New therapies for PAH have significantly changed the landscape of available treatment options. Studies and guidelines now support use of combination therapies in appropriate patient populations. Although combination therapy is associated with significant pharmacy costs, there is evidence that such treatment can reduce hospitalizations, which is a main contributor of healthcare costs associated with PAH. Managed care pharmacists can play a key role in patient and provider education of therapies including dosing, medication counseling, and medication safety. Specialty pharmacies can also have a significant role in improving the care of patients with PAH by facilitating access to medication, improving medication adherence, and ensuring that appropriate safety and regulatory requirements are being followed. Generic medications may also impact treatments and managed care pharmacists can be a key resource in answering the many questions patients may have on generic availability and their impact. ■

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Funding source: This activity is supported by an educational grant from United Therapeutics Corporation.

Author disclosure: Dr Burgoyne has no financial relationships with commercial interests to disclose.

Authorship information: Acquisition, analysis, and interpretation of data; concept and design; critical revision of the manuscript for important intellectual content.

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Medical writing and editorial support provided by: Jenna Wood, PharmD

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POSTTEST

Improving Economic and Quality of Life Burden in Pulmonary Arterial Hypertension: A Review of Clinical Data and Strategies to Slow Progression

Release date: March 10, 2021
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Sample of Online Posttest

Choose the best answer for each of the following:

1. Pulmonary arterial hypertension (PAH) corresponds to which World Health Organization (WHO) Pulmonary Hypertension Group?

A. Group 1
B. Group 2
C. Group 3
D. Group 4

2. The triggering etiology that initiates PAH may include all of the following, EXCEPT:

A. Abnormal vascular remodeling
B. Endothelial cell injury
C. Increased vascular regeneration
D. Loss of small pulmonary arteries

3. Markers used in the diagnostic evaluation and assessment of PAH risk factors, and variables that influence goal-directed treatment decision making include all of the following, EXCEPT:

A. Goals of therapy in PAH include improved exercise capacity, alleviation of symptoms, maintenance or reversal of functional class (FC), and improvement of right ventricular (RV) function.
B. A BNP level >150 ng/L (high) and NT-proBNP level of 400 ng/L corresponds to PAH of high risk (>10%).
C. Six-minute walk distance (6MWD) is the main test used in practice to assess disease status; cardiopulmonary exercise testing is a maximal exercise test that provides information on peak VO_2.
D. Individual risk factors that impact classification include age, sex, comorbidities, PAH subtype, and absence or presence of heart failure.

4. Trial data of landmark clinical trials, including AMBITION and SERAPHIN studies, have shifted the approach to treatment in PAH, including:

A. Dual combination treatment with ambrisentan 10 mg and tadalafil 40 mg reduced by 50% the risk of clinical failure (AMBITION) and was associated with increases in 6MWD and reductions in proBNP.
B. All prostacyclin analogs have demonstrated improvement in survival, 6MWD, and quality of life in patients with WHO-FC III-IV. All prostacyclin analogs cause flushing, jaw pain, and bothersome injection-site reactions when administered intravenously (IV) or subcutaneously (SC).
C. Treprostinil given as IV, SC, or inhaled is recommended in patients added to a phosphodiesterase-5 inhibitor and an endothelin receptor antagonist in patients with WHO-FC III and rapidly progressing disease; oral treprostinil extended-release tid reduced clinical disease progression by 25% in the FREEDOM EV trial in patients on PAH monotherapy.
D. The combination of macitentan and sildenafil received a weak recommendation in the updated American College of Chest Physicians (CHEST) guidelines as initial treatment in patients with WHO-FC II-IV.

5. Which of the following is the gold standard measure used to confirm pulmonary hypertension?

A. Chest radiography
B. Electrocardiography
C. Two-dimensional transthoracic echocardiography
D. Right heart catherization

CASE VIGNETTE

6. **A 76-year-old patient, diagnosed with hereditary PAH WHO-FC II for 10 years, presents to the clinic with recently worsening symptoms of extreme fatigue, edema, a decrease in physical function, reduced quality of life, and complaints of dyspnea on exertion. He shares his concern of having further related complications, being admitted to the hospital during the COVID-19 epidemic, and dying alone. He explicitly requests a modification to his pharmacotherapy regimen. Clinical assessment shows a decrease in RV function, decreased exercise capacity (>20% decrease in 6MWD), NT-proBNP >1300 ng/mL, worsening of FC to class III and rapidly progressing disease. His medical history is pertinent for obesity and type 2 diabetes, depression, and declining renal function. Patient has been maintained on initial riociguat 2.5 mg tid therapy and sequential addition of ambrisentan 10 mg.**
   A. Add selexipag to current dual therapy based on results from GRIPHON and TRITON trials showing reduction in mortality risk and related PAH complications, improvement in exercise capacity, and reduced NT-proBNP levels.
   B. This patient is rapidly progressing and is eligible for addition of IV or SC prostanoids. Add SC treprostinil through the CADD-MS3 pump delivery system or the IV per the 2019 CHEST guidelines treatment algorithm.
   C. Initiate oral extended-release treprostinil tablet based on results of FREEDOM-EV showing a 25% reduction in the risk of clinical failure, and improvements in exercise capacity and NT-proBNP levels.
   D. Discontinue riociguat and add tadalafil and IV epoprostenol to ambrisentan.

7. **What statement regarding survival time of PAH is TRUE?**
   A. The treatment of PAH has advanced in recent years and patients now have a median survival time of 10 years.
   B. Despite advances in pharmacologic therapy, PAH has a median survival time of approximately 1 year.
   C. The REVEAL Registry estimated the 3-year survival rate of patients with PAH to be 68%.
   D. The REVEAL Registry showed women aged older than 60 years to be associated with a poorer prognosis.

8. **Which statement regarding the economic cost of PAH is TRUE?**
   A. Patients with PAH were found to have 4 to 5 times higher costs for payers when compared with control patients with similar age, sex, geographic regions, and employment status.
   B. Disease severity as indicated by higher FC is associated with significantly lower PAH-related costs including hospitalizations; therefore, prevention is key to cost mitigation.
   C. Pharmacy costs have been estimated to be less when compared with those of an average Medicare part D patient.
   D. Readmissions have not been shown to significantly impact the costs associated with patients with PAH.

9. **Which statement is most accurate regarding the use of evidence-based guidelines?**
   A. Patients should be treated with monotherapy until they progress to at least FC IV to receive either dual or combination therapy based on currently available studies.
   B. There is currently no available evidence that combination therapy significantly improves outcomes such as survival or clinical worsening.
   C. PAH can be easily diagnosed based on clinical presentation; therefore, pharmacologic treatment should be started promptly based on clinical presentation to prevent disease worsening.
   D. Although some patients may be appropriate for combination therapies, others may not be candidates. Treatment should be individualized based on severity of illness, route of administration of therapy, adverse effect profile, comorbid illnesses, treatment goals, and clinician experience and preference.

10. **What is the most accurate description of how specialty pharmacies help optimize treatment and care of patients with PAH?**
    A. Increase patient adherence of PAH medication regimens, assist with barriers such as insurance approval of medications and provide information about financial assistance programs offered by manufacturers, and ensure safe and appropriate medication use and regulatory compliance through Risk Evaluation and Mitigation Strategy (REMS) programs.
    B. Help implement referral programs to allow for earlier diagnosis and treatment leading to improved survival time.
    C. Help retail pharmacies in their compliance of the REMS programs.
    D. Implement additional utilization management strategies such as prior authorization that can decrease patient costs.

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