

# AJMC<sup>®</sup> PERSPECTIVES

THE AMERICAN JOURNAL OF MANAGED CARE<sup>®</sup>

MAY 2023

## Exploring Emerging Therapies in Pulmonary Arterial Hypertension

### HIGHLIGHTS

- » Unmet Clinical Needs in the Diagnosis and Management of Pulmonary Arterial Hypertension
- » 2022 ESC/ERS Guideline-Recommended Management of Pulmonary Arterial Hypertension and Agents Under Clinical Development
- » Discussing the Importance of Early Treatment and Exploring Emerging Therapies for Optimal Outcomes in Pulmonary Arterial Hypertension: A Q&A With Paul M. Hassoun, MD
- » Payer Considerations in the Management of Pulmonary Arterial Hypertension: A Q&A With Derek van Amerongen, MD, MS

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# Unmet Clinical Needs in the Diagnosis and Management of Pulmonary Arterial Hypertension

**PULMONARY HYPERTENSION (PH)** is a complex, progressive, rare disease.<sup>1,2</sup>

PH is associated with considerable clinical burden and a high mortality rate. Pulmonary arterial hypertension (PAH) is a subtype of PH associated with high social, physical, and economic burdens. An estimated 500 to 1000 cases of PAH are diagnosed in the United States each year (2.3 cases per million Americans).<sup>3-5</sup> Although PAH can develop at any age, it is most commonly diagnosed in patients who are aged 65 years or more and predominantly affects women.<sup>5-7</sup> An estimated 30,000 people in the United States are living with PAH.<sup>8</sup>

Although some cases of PAH have known causes, such as genetic factors, many cases have no identifiable underlying cause and are designated as idiopathic. Early diagnosis and treatment are critical for improving patient outcomes, and patients should receive appropriate specialized care as soon as possible after diagnosis. Treatments are available for improving the symptoms and delaying the progression of PAH, but the disease remains incurable. Various treatments that are currently undergoing phase 2 and 3 clinical trials show potential for overcoming the limitations of previous therapies.

## Pathophysiology

Clinically, PH is described as high blood pressure that develops in the vessels between the lungs and heart, which leads to increased muscle development in the vessel walls.<sup>9</sup> Vascular remodeling involving narrowing of the arteries traveling from the right ventricle of the heart to the lungs results in restricted flow, leading to increased blood pressure in these arteries. This excess workload on the heart can cause weakness and failure of the heart muscle.<sup>4</sup> With fewer vessels available to transport oxygen, blood oxygen levels are decreased. When there is insufficient oxygenation, the kidneys release the vasoconstrictor renin to activate the renin-angiotensin-aldosterone system, through which a series of hormones is stimulated to eventually cause further systemic vasoconstriction and ultimately increase blood pressure.<sup>10</sup>

PH is divided into 5 subtypes according to the underlying associated heart or lung disease.<sup>7,11,12</sup> Specifically, group 1 is represented by PAH. The etiology and pathophysiology of PAH are multifactorial and not well-understood but are known to involve the endothelin pathway, prostacyclin pathway, and nitric oxide pathway.<sup>13,14</sup>

## Guidelines, Diagnosis, and Classification

The classification of PH based on the proceedings from the Sixth World Symposium on Pulmonary Hypertension were retained in the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines. These proceedings resulted in the development of a treatment algorithm based on risk stratification of patients with PAH.<sup>15</sup> The updated guidelines were endorsed by the International Society for Heart and Lung Transplantation and European Reference Network for rare respiratory diseases.<sup>7</sup> The updated ESC/ERS guidelines outlining the criteria for classifying patients with PAH into 6 subgroups are shown in **Table 1**.<sup>7,12</sup>

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Approximately 50% to 60% of all PAH cases are idiopathic,<sup>7</sup> although several risk factors (eg, diet, environment, genetics) can contribute to the disease risk and severity.<sup>16-18</sup> The *BMP2* gene is the most common and well-studied gene associated with PAH.<sup>7</sup> Individuals with *BMP2* mutations have a 20% lifetime risk of developing PAH; women who carry the mutated gene have a 42% risk compared with a 14% risk in men.<sup>7</sup>

### Diagnostic Approaches

Physical examination, laboratory assessments, and other diagnostic tools are used to determine the cause of PAH and potential associated comorbidities.<sup>7</sup> Laboratory testing can reveal the levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), which are increased in the plasma of patients with PAH and right ventricular (RV) dysfunction. A BNP level more than 2-fold higher than normal levels indicates an increased risk of developing PAH.<sup>19</sup> Echocardiogram, chest x-ray, and spirometry are important tools that are used to make a preliminary diagnosis of PH. Ultimately, hemodynamic assessment by right heart catheterization (RHC) is required to confirm a PAH diagnosis.<sup>6</sup>

### Inappropriate and Delayed Diagnosis

The diagnosis of PAH is complex because symptoms can be heterogenous and nonspecific. These symptoms include dyspnea upon exertion, chest pain, and fatigue. Most symptoms are related to progressive RV dysfunction.<sup>7</sup>

Patients with PAH present with dyspnea, chest pain, arrhythmias, hemoptysis, syncope, and signs of right-sided heart failure (eg, fluid retention, reduced renal blood flow, activation of the renin–angiotensin–aldosterone system).<sup>5-7,11,20</sup> Symptoms of PAH are often observed for several years before an accurate diagnosis is reached; without appropriate treatment, this can result in disease progression.<sup>13</sup> Misdiagnosis or delayed diagnosis of PAH is common and occurs in up to 85% of at-risk patients.<sup>20</sup>

### Screening Tools

The 2022 ESC/ERS guidelines provide detailed risk stratification charts and subsequent treatment recommendations for PAH. These guidelines recommend annual echocardiography screening for PAH in asymptomatic first-degree relatives of patients with identified PAH-causing mutations (eg, *BMP2* mutations).<sup>7</sup> Blood biomarkers (BNP, NT-pro-BNP, and serum urate) are also included in PAH screening algorithms.

The time from symptom onset to diagnosis is often more than 2 years, highlighting the need for improved screening for PAH, particularly because therapies may be more effective when initiated early.<sup>7</sup> Despite the frequent use of health care services prior to diagnosis, there are many missed opportunities for screening. Also, further research is needed to identify surrogate blood biomarkers as a potential screening tool for PAH, which may reduce the time to diagnosis.<sup>21</sup>

A multidisciplinary team of cardiologists, pulmonologists, thoracic surgeons, and others must ensure that they are educated on PAH screening tools to improve outcomes.<sup>7</sup> A single-center, retrospective study of patients with PAH (n = 580) was conducted using data from 2008 to 2018 to determine if management at specialty care centers (SCCs) is associated with improved outcomes.<sup>22</sup> Study results showed that patients who received care at an SCC had significantly longer survival times and fewer hospital admissions compared with those not managed at an SCC ( $P < .001$ ). In addition, medication use (vasodilator use [ $P < .001$ ]) and disease monitoring (repeated pulmonary function testing and repeated transthoracic echocardiogram;  $P < .024$  and  $P < .004$ , respectively) were significantly more frequent in patients treated at SCCs compared with the frequency in those not undergoing care at an SCC.<sup>22</sup> The findings strongly support that health care providers should refer patients with PAH to SCCs as early as possible.

Differential diagnosis among PH groups is important to correctly diagnose PAH. Most patients with PH display abnormal findings on chest radiography; however, normal chest X-ray results do not exclude PH, including PAH.<sup>7</sup> Echocardiography can be performed to screen for PAH in patients presenting with characteristic symptoms (eg,

**TABLE 1.** Group 1 PAH Subcategories<sup>7,12</sup>

Subcategory
1.1 Idiopathic
1.1.1 Nonresponders at vasoreactivity testing
1.1.2 Acute responders at vasoreactivity testing
1.2 Heritable <sup>a</sup>
1.3 Associated with drugs and toxins <sup>a</sup>
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH with features of venous/capillary involvement
1.6 Persistent PH of the newborn

HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

<sup>a</sup>Patients may be acute responders.

unexplained breathlessness) or to confirm a PAH diagnosis.<sup>7,21</sup> Echocardiogram findings during RHC showing an elevated heart rate and RV dysfunction strongly indicate a diagnosis of PAH<sup>23</sup>; right axis deviation and RV hypertrophy also are common.<sup>11</sup>

Suspected cases of PAH can be distinguished from other forms of PH based on how patients respond to vasodilator challenge in vasoreactivity testing performed during RHC as part of the echocardiogram. A positive result is considered as a decrease in the pulmonary arterial pressure of at least 10 mmHg to a mean pulmonary arterial pressure of no more than 40 mmHg. The test results can provide insight that is useful for making treatment recommendations. This method can be used to identify patients who may respond to treatment with calcium channel blockers (CCBs). In a landmark study performed in 1992, Rich and colleagues selected patients who showed a positive acute vasodilator response (responders) to CCBs in vasoreactivity testing for further treatment with these blockers.<sup>24</sup> The authors demonstrated that patients identified in testing and subsequently treated with CCBs showed significantly improved survival rates after 1 year compared with the survival rate of nonresponders (94% vs 55%, respectively;  $P = .003$ ).<sup>24</sup>

Additionally, pulmonary function testing is important for distinguishing between PH groups, assessing comorbidities, and determining severity. These tests should include forced spirometry, body plethysmography, lung diffusion capacity for carbon dioxide, and analysis of arterial blood gas.<sup>7</sup>

### *Follow-up Assessments of Patients With PAH*

Referring patients to specialized centers is essential to ensure that patients are provided with education, informed on behavioral modifications, and given access to social and psychological support.<sup>7</sup> Regular risk assessment of patients diagnosed with PAH is recommended to achieve or maintain a low-risk status. For example, as part of pulmonary function testing,<sup>21</sup> the 6-minute walk test (6MWT) is widely performed to evaluate the exercise capacity and predict the prognosis of patients with PAH.<sup>7,25</sup> In a multinational, prospective registry (COMPORA) of newly diagnosed patients with PAH ( $n = 2391$ ) receiving targeted medical therapy, cut-off values for the 6MWT were identified as prognostic factors for the risk of death and as clinically relevant and important therapeutic targets.<sup>25</sup>

Despite the availability of assessment tools, a survey of US providers in 2017 showed that after a PAH diagnosis, patient follow-up and the frequency of assessments (clinic visits, 6MWT, echocardiogram, BNP level measurement, and RHC) varied among providers and were not aligned with guideline recommendations.<sup>26</sup> After a patient is diagnosed with PAH, echocardiography and cardiac MRI

should be performed at baseline and every 3 to 6 months after changes in therapy, both in stable patients and in cases of clinical worsening, to assess whether the disease is stable or progressing.<sup>7</sup>

### *Classification*

The clinical classification of PH has undergone several revisions over the last 50 years.<sup>12</sup> Guidelines from the American College of Chest Physicians (CHEST) were updated in 2019 and are used in the United States to provide guidance for diagnosing and managing patients with PAH, and are generally in alignment with the ERS/ESC guidelines.<sup>7,19</sup> The 2022 ESC/ERS guidelines state that PAH is characterized as a mean pulmonary artery pressure of at least 25 mmHg, pulmonary wedge pressure of no more than 15 mmHg, and pulmonary vascular resistance of at least 3 Wood units.<sup>6,11,27</sup> According to most PAH registries, idiopathic PAH is the most common subtype (approximately 50%–60% of all cases); PAH associated with connective tissue disease, coronary heart disease, and portal hypertension comprises the remaining cases.<sup>7</sup>

Although therapies are available for managing PAH symptoms, they do not treat the underlying cause of the disease.<sup>7</sup> Various PAH-specific treatments, particularly combination therapies, have been shown to delay disease progression.<sup>14</sup> However, currently available PAH therapies cannot reverse vascular remodeling; thus, although delayed, the disease still progresses.<sup>28</sup>

Advances are needed to support the early identification and diagnosis of patients with PAH. Additionally, tools for risk assessment to predict disease worsening should be developed. These approaches will allow for earlier treatment initiation with safe and effective options that prevent PAH progression and improve patient outcomes compared with those obtained using current approaches.<sup>28</sup>

### *Burden of Disease*

PAH remains a deadly disease and is associated with various burdens on patients and their families. The clinical burden, comorbidities, economic impact, and quality of life (QOL) impact of PAH are discussed below.

### *Clinical Burden*

PAH remains a deadly disease with high mortality rates. According to analysis of the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), the 1-, 2-, and 3-year mortality rates of patients with PAH are 10%, 19%, and 25%, respectively.<sup>29</sup> Chang et al stratified patients using various validated risk scores and found that the 3-year mortality rates of patients stratified into the low-, intermediate-, and high-risk groups were 7% to 11%, 18% to 20%, and 28% to 55%, respectively. Thus, results show

that patients with high-risk disease have low survival rates after 3 years. The 1-year mortality rate of patients treated with a combination of therapies was lower than that in patients treated with monotherapy (7% vs 13%, respectively), although there was no difference between groups at 2 and 3 years.<sup>29</sup>

### Comorbidities

PAH often occurs simultaneously with other conditions that have similar symptoms, which can complicate the identification of PAH and lead to diagnostic delays. Additionally, comorbid conditions that increase pulmonary artery pressure and cardiac output can promote PAH progression. PAH is associated with various conditions such as connective tissue disease (including systemic sclerosis and lupus), HIV infection, coronary heart disease, portal hypertension, and congenital abnormalities.<sup>7,30</sup> Prevalence of comorbidities is higher in older patients compared with younger patients. Hjalmarsson and colleagues found that among patients with PAH, 22% of older patients ( $\geq 65$  years) had at least 4 comorbid conditions vs 4% of younger patients ( $\leq 65$  years).<sup>31</sup> Older patients tend to show increased rates of ischemic heart disease, coronary artery disease, hypertension, atrial fibrillation, diabetes, and hypothyroidism.<sup>32</sup> Lower survival rates may be related to the number of comorbidities. However, the risk factors for PAH are not independent from those of other conditions, and therefore some treatments may reduce the severity of comorbid diseases.

There is no cure for PAH, and many patients experience an aggressive disease course and poor survival outcomes.<sup>33</sup> According to an analysis of data from the REVEAL registry ( $n = 2635$ ; up to February 2013), the 5- and 7-year survival rates of patients with PAH are 57% and 49%, respectively, despite treatment with PAH-specific therapies.<sup>34</sup>

### Economic Impact

The high economic impact of PAH has also been widely recognized. Because of its high morbidity and mortality, PAH-related hospitalizations are a driving factor in health care costs. Drivers of indirect costs related to PAH include productivity losses and short-term disability

expenses, which total in the thousands of dollars per patient per month (PPPM) (2018 US\$) (Table 2).<sup>35</sup> In a retrospective analysis of the economic burden of PAH using the MarketScan Health and Productivity Management Database, patients with PAH (age, 18-64 years) were defined as incident (diagnosed  $\leq 6$  months before enrolling in the study;  $n = 1293$ ) or prevalent (diagnosed  $> 6$  months before enrolling in the study;  $n = 455$ ).<sup>35</sup> Control participants matched by age, sex, and region were also evaluated for comparison. Both prevalent and incident cases were associated with more inpatient stays PPPM compared with those of controls (0.07 days for prevalent patients and 0.10 days for incident patients vs 0.00 days in the control group) ( $P < .001$  for both comparisons). The length of hospital stays PPPM showed the same trend (0.63 days for prevalent cases vs 0.02 days in the control group; 0.92 days for incident patients vs 0.01 days in the control group;  $P < .001$  for both comparisons). Mean all-cause health care costs were significantly higher in the prevalent (\$9915 vs \$359 PPPM;  $P < .001$ ) and incident (\$9353 vs \$336 PPPM,  $P < .0001$ ) populations compared with those in the control group. Key drivers of expenditures in the prevalent patient population were inpatient (46.6%) and pharmacy (28.0%) costs, whereas inpatient costs (66.0%) were the largest contributor to expenditures in the incident population.<sup>35</sup>

### Quality of Life

Worsening PAH symptoms, such as dyspnea, fatigue, and a lack of energy, can lead to functional impairments. Patients with PAH have difficulty completing everyday tasks, including climbing stairs, doing housework, and shopping for household needs.<sup>32</sup> The health of patients can be evaluated using the 36-item Short Form Health Survey (SF-36), which is used to query patients on 8 categories including vitality, physical functioning, physical role functioning, emotional role functioning, social role functioning, and mental health. A higher score on the SF-36 indicates a higher QOL. Patients reported a low QOL according to the results of the SF-36 survey, specifically because of the high prevalence of physical pain, stress, sleep disorders, anxiety, and depression.<sup>30</sup> The caregivers of patients with PAH experience similar QOL impairments.<sup>32</sup> Losses of productivity because of the inability to work full-time (or work at all) affect patients, families, employers, and payers.<sup>35</sup>

### Conclusions

PAH is a rare but serious progressive condition with a high mortality rate. There are currently no curative treatments; although PAH-specific

**TABLE 2.** Costs of Short-term Disability Related to Patients With PAH<sup>35</sup>

	Patients with PAH	Patients without PAH	P value
Short-term disability length	6.0 days	1.5 days	$P < .0001$
Short-term disability costs	\$1226 PPPM	\$277 PPPM	$P < .0001$

PAH, pulmonary arterial hypertension; PPPM, per patient per month.

Adapted from Ogbomo A, Tsang Y, Mallampati R, Panjabi S. The direct and indirect health care costs associated with pulmonary arterial hypertension among commercially insured patients in the United States. *J Manag Care Spec Pharm.* 2022;28(6):608-616. doi:10.18553/jmcp.2022.28.6.608

treatments help delay progression, these medications mostly address the disease symptoms and not the underlying pathophysiology. There are several unmet needs in the management of PAH, including the need for earlier diagnosis, more frequent evaluations once diagnosed, improved adherence to treatment along with referrals to specialized treatment centers, and drugs that target the underlying disease mechanisms. Furthermore, pharmacologic therapy for PAH requires a lifelong commitment, along with costly and frequent monitoring.<sup>36</sup> Improvements in drugs that target the specific disease mechanisms with further enhanced disease-stabilizing effects are urgently needed. ♦

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# 2022 ESC/ERS Guideline-Recommended Management of Pulmonary Arterial Hypertension and Agents Under Clinical Development

**IN PATIENTS WITH** pulmonary hypertension (PH), high blood pressure occurs in the vessels between the lungs and heart, resulting in increased muscle development in the vessel walls and greater resistance in the pulmonary arteries.<sup>1</sup> Heart failure (HF) is among the most severe downstream effects of PH.<sup>2</sup> Pulmonary arterial hypertension (PAH) is a subtype of PH defined as a mean pulmonary artery pressure of at least 25 mm Hg, mean pulmonary artery pressure (PAP) of at least 25 mm Hg, and pulmonary artery occlusion pressure of no more than 15 mm Hg.<sup>3,4</sup> Idiopathic PAH is believed to be the most common form of PAH (50%-60% of all cases).<sup>5</sup>

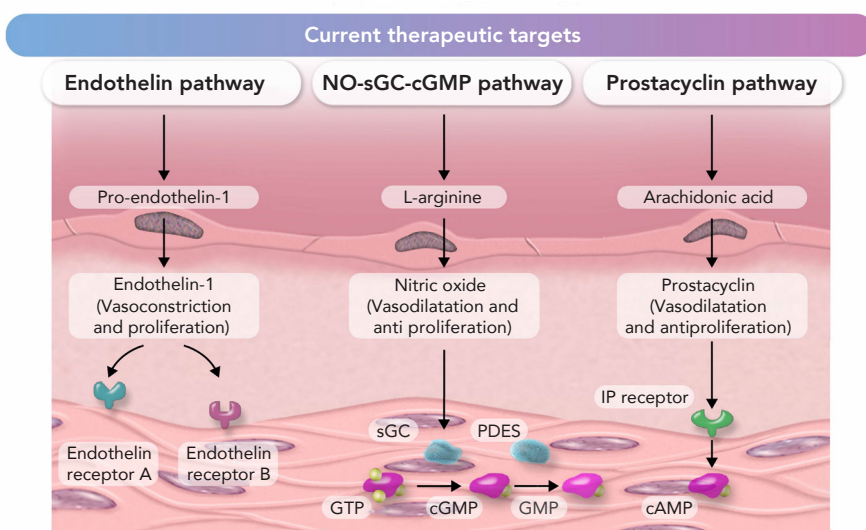
Although PAH remains difficult to diagnose and treat, the clinical application of results from recent clinical studies has changed the way that the disease is diagnosed and managed, as reflected in the revised guidelines for managing PAH jointly developed in 2022 by the European Society of Cardiology (ESC)/European Respiratory Society (ERS). These guidelines were endorsed by the International Society for Heart and Lung Transplantation and the European Reference Network on rare respiratory diseases.<sup>5</sup> Proceedings from the Sixth World Symposium on Pulmonary

Hypertension that were retained in the 2022 ESC/ERS guidelines were used to develop a treatment algorithm based on risk stratification in patients with PAH.<sup>6</sup> The following treatment recommendations were outlined in the proceedings<sup>6</sup>:

- In treatment-naïve patients with PAH, initial monotherapy improves exercise capacity, hemodynamics, and outcomes when compared with those noted among untreated patients.
- In patients who are newly diagnosed with PAH and treatment-naïve, initial combination therapy can improve symptoms, exercise capacity, and outcomes compared with those in individuals who receive initial monotherapy.
- In patients with PAH already receiving treatment, sequential combination therapy can improve exercise capacity, hemodynamics, and outcomes compared with the effects of background therapy alone.

Numerous available and emerging approaches can be used to align with the guideline recommendations.

**FIGURE.** Current Therapeutic Targets in PAH<sup>5</sup>



IP receptor, prostacyclin I2 receptor; NO, nitric oxide; PAH, pulmonary arterial hypertension.

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## Overview of Available PAH Treatments

### Pharmacologic Therapies

Currently available agents for treating PAH target the NO-sGC-cGMP, endothelin, or prostacyclin (PGI<sub>2</sub>) pathways (**Figure**).<sup>5</sup> Although the use of these therapies has been associated with improved survival in patients with PAH in recent years, their specific impact and those of related treatment strategies require further study.<sup>5</sup>

### CALCIUM CHANNEL BLOCKERS

Vasoreactivity testing can be performed to determine how patients with idiopathic, heritable, or drug- or toxin-induced PAH respond to vasodilator challenge. This method is not indicated for patients with other forms of PAH, as they typically do



not exhibit vasoreactivity.<sup>7</sup> The results of this test can help guide treatment selection, as patients with PAH who show a positive response in acute vasoreactivity testing may benefit from calcium channel blocker (CCB) therapy with nifedipine, diltiazem, felodipine, or amlodipine.<sup>5,8</sup> CCBs inhibit vasoconstriction by preventing the influx of calcium ions into vascular cells.<sup>9</sup> However, Sitbon and colleagues showed that less than 10% of patients with idiopathic PAH respond to CCBs, highlighting the need for advanced therapies.<sup>10</sup>

#### ENDOTHELIN RECEPTOR ANTAGONISTS

The exercise capacity of patients with PAH may be increased by treatment with endothelin receptor antagonists (ERAs) (ambrisentan, bosentan, and macitentan).<sup>5</sup> Drugs in the PDE5 inhibitor (PDE5i) and soluble guanylate cyclase (sGC) stimulator classes may improve exercise capacity, symptoms, and hemodynamics in patients with PAH.<sup>5</sup> Therapies supported by the ESC/ERS guidelines include the PDE5is sildenafil and tadalafil and sGC stimulator riociguat. Treatment with certain PDE5is also lowers the PAP and pulmonary vascular resistance (PVR) and improves the cardiac index of patients with PAH.<sup>11</sup>

#### PROSTACYCLIN ANALOGS AND RECEPTOR AGONISTS

PGI<sub>2</sub> analogs and PGI<sub>2</sub> receptor agonists are associated with improvement in vasodilation, inhibition of platelet aggregation, and exertion of cytoprotective and antiproliferative effects.<sup>5</sup> Examples of drugs in these classes that are recommended for treating PAH include epoprostenol, iloprost, treprostinil, beraprost, and selexipag. **Table 1** summarizes findings on available pharmaceutical agents.<sup>12-24</sup>

#### *Supportive Pharmacologic Therapies*

Various supportive therapies are available for treating patients with PAH. These treatments can improve disease symptoms and the quality of life (QOL) of patients.

#### ANTICOAGULATION THERAPY

Use of anticoagulation therapy in patients with PAH is not supported by the results of randomized controlled trials. However, the ERS/ESC guidelines highlight several reasons to consider this approach on an individual basis.<sup>5</sup> Abnormalities in the coagulation and fibrinolytic system have been observed in patients with PAH, and in situ thrombosis of pulmonary vessels has been observed in histopathological samples from the lungs of affected patients. Patients with PAH who are prescribed anticoagulants must be followed closely because of the increased bleeding risk associated with these agents.

#### DIURETIC THERAPY

It is important for clinicians to implement measures that avoid fluid retention in patients with PAH.<sup>5</sup> If signs of

right-sided HF and edema develop, it is recommended that clinicians prescribe diuretics and restrict the patient's fluid intake. Patients with PAH who are given diuretic therapy should be monitored closely; it is important that they regularly weigh themselves and contact their health care provider if they gain weight.

#### OXYGEN THERAPY

Although evidence for its use is sparse, oxygen therapy may benefit some patients with PAH, including those with concomitant chronic obstructive pulmonary disease or those who experience oxygen desaturation during exercise or sleep.<sup>5</sup>

#### ANTIHYPERTENSIVE DRUGS

The usefulness and safety of drugs for hypertension or left-sided HF in patients with PAH are unclear, and no recommendations are provided in the ESC/ERS guidelines. Importantly, these drugs can cause dangerous drops in blood pressure and/or heart rate.<sup>5</sup>

#### THERAPY FOR MINERAL DEFICIENCY

Iron deficiency is common in patients with PAH; it is associated with impaired myocardial function, aggravated symptoms, and an increased risk of death. Therefore, the iron status of patients with PAH should be closely monitored.<sup>5</sup>

#### *Supportive Nonpharmacologic Therapies*

Physical activity or exercise training and supervised rehabilitation can improve the exercise capacity (as measured using the 6-minute walk distance [6MWD] test) and QOL of patients with PAH, as long as the specific functional limitations of each patient are observed.<sup>5</sup> The ESC/ERS guidelines report that most studies on QOL included patients who were stable on medical treatment. Therefore, patients with PAH should reach a stable clinical condition before exercise training and supervised rehabilitation are prescribed. Patient-reported outcome measures are considerably underused in clinical trials of treatments for PAH.<sup>5</sup> Validated outcome measurement tools (eg, Cambridge Pulmonary Hypertension Outcome Review, emPHasis-10 score, Living with Pulmonary Hypertension Questionnaire, and Pulmonary Arterial Hypertension-Symptoms and Impact [PAH-SYMPACT] score) should be used to assess changes in the health-related QOL of individuals with PAH as well as patients' functional status, clinical deterioration, and prognosis.<sup>5</sup>

Patients diagnosed with PAH often develop psychological, emotional, and social issues; health care providers must address these concerns with empathy and hope. Frequent delays in diagnosis along with the development of physical limitations can lead to depression, anxiety, and adjustment disorders, particularly because PAH severely

**TABLE 1.** Pharmacologic Therapies for Pulmonary Arterial Hypertension<sup>12-24</sup>

Drug	Administration route	Mechanism of action	Adverse events	Special considerations
Epoprostenol	• IV	Prostacyclin analog	<ul style="list-style-type: none"> <li>• Jaw pain</li> <li>• Headache</li> <li>• Diarrhea</li> <li>• Vasodilation</li> <li>• Elevated liver enzyme levels</li> </ul>	<ul style="list-style-type: none"> <li>• Escalation to clinically effective doses can take 6 mo.</li> <li>• Short half-life necessitates a permanent catheter.</li> <li>• Risk of bloodstream infection exists.</li> </ul>
Iloprost	• Inhaled	Prostacyclin analog	<ul style="list-style-type: none"> <li>• Jaw pain</li> <li>• Vasodilation</li> <li>• Syncope</li> <li>• Headache</li> <li>• Insomnia</li> <li>• Nausea</li> <li>• Hypotension</li> <li>• Vomiting</li> </ul>	<ul style="list-style-type: none"> <li>• Hypotension can lead to syncope.</li> <li>• Cannot be administered to patients with systolic blood pressure &lt; 85 mmHg.</li> </ul>
Treprostinil	<ul style="list-style-type: none"> <li>• Inhaled</li> <li>• Oral</li> <li>• IV</li> <li>• SC</li> </ul>	Prostacyclin analog	<ul style="list-style-type: none"> <li>• Dizziness</li> <li>• Nausea</li> <li>• Fatigue</li> <li>• Diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>• IV delivery requires an implantable pump.</li> <li>• Drug has a short half-life.</li> </ul>
Ambrisentan	• Oral	ERA	<ul style="list-style-type: none"> <li>• Teratogenicity</li> <li>• Peripheral edema</li> <li>• Headache</li> <li>• Nausea</li> <li>• Nasal congestion</li> </ul>	• REMS is required.
Bosentan	• Oral	ERA	<ul style="list-style-type: none"> <li>• Teratogenicity</li> <li>• Hepatotoxicity</li> </ul>	• REMS is required.
Macitentan	• Oral	ERA	<ul style="list-style-type: none"> <li>• Teratogenicity</li> <li>• Hepatotoxicity</li> <li>• Decreased spermatogenesis</li> <li>• Headache</li> <li>• Nasopharyngitis</li> <li>• Anemia</li> </ul>	• REMS is required.
Sildenafil	<ul style="list-style-type: none"> <li>• Oral</li> <li>• IV</li> </ul>	PDE5i	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Headache</li> <li>• Dizziness</li> <li>• Abnormal vision</li> </ul>	• Low bioavailability has been reported.
Tadalafil	• Oral	PDE5i	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Myalgias</li> <li>• Vasodilation</li> </ul>	• Potentially severe drug interaction effects have been reported.
Riociguat	• Oral	GC stimulator	<ul style="list-style-type: none"> <li>• Teratogenicity</li> <li>• Headache</li> <li>• Gastritis</li> <li>• Dizziness</li> <li>• Nausea</li> <li>• Diarrhea</li> <li>• Hypotension</li> <li>• Anemia</li> </ul>	• REMS is required.
Selexipag	<ul style="list-style-type: none"> <li>• Oral</li> <li>• IV</li> </ul>	Prostacyclin receptor agonist	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Jaw pain</li> <li>• Diarrhea</li> <li>• Nausea</li> <li>• Musculoskeletal pain</li> <li>• Vomiting</li> </ul>	<ul style="list-style-type: none"> <li>• Tolerability issues have been reported.</li> <li>• Bioavailability may be decreased in combination therapy.</li> <li>• Dosage is limited in patients with hepatic impairment.</li> <li>• Weak clinical evidence exists on effectiveness.</li> </ul>

ERA, endothelin receptor agonist; GC, guanylate cyclase; IV, intravenous; mo, month(s); PDE5i, PDE5 inhibitor; REMS, risk evaluation and mitigation strategy; SC, subcutaneous; wk, weeks.

affects the ability of patients to work. Patients should be assessed using psychosocial screening tools and referred to appropriate care, including psychosocial specialists and patient support groups.<sup>5</sup> Validated tools such as the updated REVEAL Registry Risk Score 2.0 can help health care providers and patients to make more informed decisions, and they should be applied more frequently in clinical practice.<sup>25</sup> Simplified tools, such as the REVEAL Lite 2 Risk Calculator, can differentiate between a low, intermediate, and high risk of death in 1 year based on 6 modifiable factors (functional class, systolic blood pressure, heart rate, 6MWD, BNP/N-terminal pro-BNP level, and renal insufficiency).<sup>25</sup> This tool is simple to implement, and may be useful in routine clinical practice.

### Interventional Therapies

Several interventional therapies are available to patients with PAH when drug treatment is not successful. Balloon atrial septostomy or a Potts shunt procedure can be employed to decompress the right heart and increase systemic blood flow, thereby improving systemic oxygen transport despite arterial oxygen desaturation.<sup>5</sup> These complex and high-risk procedures should only be performed at specialized centers. Patients with PAH and advanced right ventricular (RV) failure may require intensive treatment to manage triggers of right-sided HF (eg, infection, arrhythmias, anemia, other

comorbidities).<sup>5</sup> Fluid management is critical in these patients, as a negative fluid balance is necessary to reduce the RV preload and improve RV function. Patients may require mechanical circulatory support, which is available at specialized centers.<sup>5</sup> Venoarterial extracorporeal membrane oxygenation, the most common therapy, is often used as a bridge to lung transplantation, but it can also be used to treat potentially reversible RV failure.

Lung transplantation is a critical option for patients with PAH who do not respond to optimal therapy.<sup>5</sup> Early referral to a lung transplant center is necessary for patients with PAH who show a poor response to pharmacologic treatment, particularly to combination therapy, or for those who present with an intermediate to high risk of death. Most transplant patients with PAH undergo double-lung transplantation; those with untreatable cardiac conditions may undergo heart-lung transplantation.<sup>26</sup>

### PAH Treatment Options in Development

Several treatments for PAH are in late-stage development (Table 2).<sup>5,27-36</sup> Two agents, sotatercept and ralinepag, are being investigated in phase 3 trials.<sup>5,27</sup>

#### Sotatercept

Sotatercept is an activin receptor type IIA-Fc fusion protein being tested in clinical trials as a first-in-class treatment

**TABLE 2.** PAH Agents Under Investigation<sup>5,27-36</sup>

Drug name	Drug class	Route of administration	Manufacturer	Phase 3 trials	Primary end point
Ralinepag	Prostacyclin receptor agonist <sup>5</sup>	Oral	United Therapeutics	<ul style="list-style-type: none"> <li>NCT04084678</li> <li>NCT03626688</li> <li>NCT03683186</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline in peak oxygen consumption assessed by CPET</li> <li>Time from randomization to the first adjudicated protocol-defined clinical worsening event</li> <li>Number of subjects with treatment-emergent adverse events (safety and tolerability)</li> </ul>
Aurora-GT	Autologous EPCs transfected with the human NOS3 gene	IV	Northern Therapeutics	<ul style="list-style-type: none"> <li>NCT03001414 (Phase 2/3)</li> </ul>	<ul style="list-style-type: none"> <li>Change in 6MWD from baseline</li> </ul>
Sotatercept	Activin receptor type IIA-Fc fusion protein <sup>27</sup>	SC injection	Merck	<ul style="list-style-type: none"> <li>1 completed</li> <li>NCT04576988</li> <li>3 recruiting</li> <li>NCT04811092</li> <li>NCT04896008</li> <li>NCT04796337</li> </ul>	<ul style="list-style-type: none"> <li>Change from baseline in 6MWD</li> <li>Time to clinical worsening</li> <li>Time to first confirmed morbidity or mortality event</li> <li>Long-term safety (eg, adverse events, changes in clinical laboratory results, and vital signs)</li> </ul>
Udenafil	PDE5 inhibitor	Oral	Mezzion	<ul style="list-style-type: none"> <li>NCT02304198 (Phase 2/3; completed in 2016)</li> </ul>	<ul style="list-style-type: none"> <li>Long-term safety</li> </ul>

6MWD, 6-minute walking distance; CPET, cardiopulmonary exercise testing; EPCs, endothelial progenitor cells; IV, intravenous; PAH, pulmonary arterial hypertension; SC, subcutaneous.

for PAH.<sup>27</sup> It has been granted a Breakthrough Therapy Designation by the FDA. Sotatercept restores signaling mediated by ActRIIA/Smad2/3 and BMPRII/Smad1/5/8; this signaling is involved in remodeling of the pulmonary arterial wall and right ventricle.<sup>27,37</sup>

In the phase 2, multicenter PULSAR trial, 106 adults with PAH who were receiving background therapy were randomly assigned to receive sotatercept 0.3 mg/kg or 0.7 mg/kg every 3 weeks or a placebo for 24 weeks. Both doses of sotatercept were associated with significant changes in PVR (ie, the primary end point) from baseline to week 24 (decreases of 162.2 and 255.9 dyn/s/cm<sup>-5</sup> in the 0.3-mg/kg and 0.7-mg/kg groups, respectively) ( $P < .01$ ).<sup>38</sup> Thrombocytopenia, the most common adverse event (AE) of interest, occurred in 2 patients in the 0.3-mg/kg group (6.0%), 5 patients in the 0.7-mg/kg group (12.0%), and none of the patients in the placebo group (0%).<sup>38</sup> An increased hemoglobin level was observed as a hematologic AE in patients given sotatercept at week 24 (0.3 mg/kg: 1 patient [3%; mean (SD), 1.2 (1.2) g/dL]; 0.7 mg, 7 patients [17%; 1.5 (1.1) g/dL]; placebo: 0 patients [0%]). An increased hemoglobin level was also reported in previous trials.<sup>38,39</sup>

A total of 97 patients continued with an open-label extension of PULSAR for assessment of the long-term safety and tolerability of sotatercept.<sup>40</sup> The safety profile of sotatercept was consistent with that recorded in prior clinical trials. Leukopenia, neutropenia, and thrombocytopenia were observed in 18 (17.3%) of 104 patients evaluated for treatment-emergent AEs (TEAEs).<sup>40</sup> No serious TEAEs considered to be related to sotatercept use led to treatment or study discontinuation, and no deaths were attributed to use of the drug.<sup>40</sup> Telangiectasia was observed as a new event in 11 patients (10.6%); all cases were mild, and additional monitoring is necessary to determine the clinical significance of this AE.<sup>40</sup> Data from the placebo-controlled study and open-label extension support using a dose of 0.7 mg/kg in further phase 3 studies.<sup>40</sup>

The efficacy and safety of sotatercept for treating PAH as an add-on to background therapy (monotherapy, double therapy, or triple therapy) was evaluated in the STELLAR trial, a phase 3, randomized, double-blind, placebo-controlled, multicenter study.<sup>30</sup> A total of 323 adult patients (mean [SD] age, 47.9 [14.8] years) with PAH were randomly assigned 1:1 to receive sotatercept or placebo via subcutaneous administration once every 3 weeks. Patients in the sotatercept group experienced a significant and clinically meaningful improvement in the primary end point of exercise capacity (as measured in by the 6MWD at 24 weeks). Changes from baseline in the 6MWD were a median of 34.4 m (95% CI, 33.0-35.5 m;  $P < .001$ ) in the sotatercept group and 1.0 m (95% CI, -0.3 to 3.5 m) in the placebo group.<sup>30</sup> Improvements were observed in 8 of 9 secondary efficacy end points, including the proportion of participants

achieving multicomponent improvement (ie, improvements in 6MWD, N-terminal pro-BNP level, and either improvement in World Health Organization [WHO] functional class or maintenance of WHO functional class II) and time to death or the first clinical worsening event. Only the cognitive/emotional impacts domain score of PAH-SYMPACT did not differ significantly between the sotatercept and placebo groups. At least 10% of patients in both groups reported AEs over the 24-week treatment period, with nosebleed, telangiectasia, and dizziness being the most commonly reported. Twenty-three patients (14.1%) in the sotatercept group and 36 patients (22.5%) in the placebo group experienced serious AEs; these events led to treatment discontinuation in 3 (1.8%) and 10 (6.2%) patients, respectively.<sup>30</sup>

### Ralinepag

The efficacy and safety of ralinepag, an oral PGI<sub>2</sub> receptor agonist, are currently being tested in phase 3 trials.<sup>28</sup> In a phase 2, double-blind, multicenter trial, 61 adult patients with PAH who were receiving monotherapy or dual background therapy were randomly assigned 2:1 to receive ralinepag or placebo for 22 weeks.<sup>41</sup> The primary efficacy end point was the absolute change in PVR from baseline to week 22. Secondary end points included the percentage change from baseline in PVR, 6MWD, time to clinical worsening, safety, and tolerability. Ralinepag was associated with a significant reduction in the median PVR at 22 weeks compared with the effects of the placebo ( $P = .02$ ). There was a 29.8% reduction in the least-squares mean PVR versus the effects of the placebo ( $P = .03$ ). At week 22, the least-squares mean change from baseline in the 6MWD with ralinepag did not significantly differ from that of the placebo group (increase of 36.2 m with ralinepag vs 29.4 m with placebo). Although the percentage of patients who showed clinical worsening was lower with ralinepag (2.5%) than with placebo (9.5%), the difference was not significant ( $P = .26$ ).

Almost all patients in both study groups experienced at least 1 AE. Among AEs attributed to ralinepag, 20% were mild, 47.5% were moderate, and 37.5% were severe. The most common AEs reported in the ralinepag group were headache (78%), nausea (50%), and diarrhea (48%). Ralinepag was well-tolerated in most patients during the 22-week study, and the noted AEs were consistent with those observed for other PGI<sub>2</sub> receptor agonists.<sup>41</sup> The rate of serious AEs was lower in the ralinepag group (10%) than that in the placebo group (28.6%). One patient in the ralinepag group experienced electrocardiographic QT prolongation as a serious AE. However, this patient had a prior condition (intraventricular conduction disturbance) that may have contributed to QT prolongation. Five patients (12.5%) withdrew from the study because of AEs that may have been related to use of the study drug;

2 patients (10%) in the placebo group withdrew from the study. The frequency of AEs decreased during the dose titration period as the dose of ralinepag was increased.

### Other Therapies

A recent network meta-analysis of data from 53 randomized controlled trials of FDA-approved drugs and investigational agents from database inception through 2021 was conducted to compare the efficacies of PAH medications.<sup>42</sup> Combination therapy with an ERA and PDE5i was associated with a reduced risk of clinical worsening (120.7 fewer events/1000 patients; 95% CI, 93.4-136.8 fewer events/1000 patients) compared with the effects of each therapy alone (51.5-85.3 fewer events/1000 patients). Riociguat therapy led to similar outcomes, but the results showed greater uncertainty (133.6 fewer events/1000 patients; 95% CI 85.3-151.3 fewer events/1000 patients).<sup>42</sup>

The long-term safety of the oral PDE5i udenafil was assessed in 18 patients with PAH in phase 2 studies.<sup>31</sup> Both high and low doses (50 mg and 100 mg) of udenafil improved hemodynamic parameters and reduced the systolic PAP in patients with PAH while causing no serious AEs.<sup>43</sup> Hemodynamic monitoring revealed maximum mPAP reductions of 11.0 mm Hg and 8.0 mm Hg in patients treated with 50 mg and 100 mg of udenafil, respectively, whereas the placebo group showed no significant change. In a related double-blind, placebo-controlled study of 63 patients, udenafil improved the exercise capacity of patients with PAH, as demonstrated by results from the 6MWD test (changes of 46 m vs 21 m in the udenafil vs placebo group, respectively;  $P = .0873$ ).<sup>44</sup>

Gene-based therapies also are being investigated for PAH. Aurora-GT is an angiogenic cell therapy that will be investigated for PAH in a phase 2/3 trial (SAPPHIRE) at several Canadian locations.<sup>29,45</sup> The therapy involves monthly infusions of autologous endothelial progenitor cells transfected with the human *NOS3* gene to restore eNOS enzyme, which dilates the pulmonary blood vessels.

### Conclusions

PAH is a rare but serious progressive condition associated with a high mortality rate. There are currently no curative treatments available, and medications only address disease symptoms. There are several unmet needs in managing PAH, including the need for earlier diagnosis, more frequent evaluation once patients receive a diagnosis, improved adherence to treatment, and treatments that control disease progression. The results of studies demonstrated improved clinical outcomes with delays in disease progression; however, currently available PAH-specific therapies do not target the specific mechanisms of the disease. New agents are currently being developed in existing drug classes; these include the PGI<sub>2</sub> receptor

agonist ralinepag being investigated in phase 3 clinical trials and the PDE5i udenafil being studied in phase 2/3 trials. The fusion protein sotatercept is being tested in phase 3 trials, and the gene therapy Aurora-GT is being evaluated in phase 2/3 trials. Recent advancements in the understanding of the molecular mechanisms of PAH have led to the development of promising therapies that may improve symptoms, delay clinical worsening, and promote a better QOL for affected patients. ♦

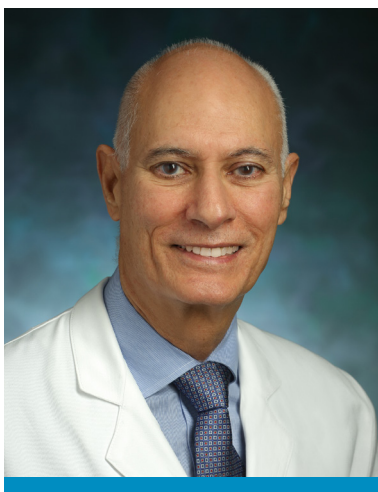
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# Discussing the Importance of Early Treatment and Exploring Emerging Therapies for Optimal Outcomes in Pulmonary Arterial Hypertension

A Q&A With Paul M. Hassoun, MD



## PAUL M. HASSOUN, MD

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**AJMC:** Can you explain the etiology and progression of PAH and the importance of early diagnosis?

**HASSOUN:** Pulmonary arterial hypertension (PAH) refers to World Health Organization (WHO) group 1 pulmonary hypertension.<sup>1</sup> It includes many different diseases, such as idiopathic PAH or heritable PAH, wherein the patient has genetic mutations that lead to the disease; this type of PAH can affect families or individuals. PAH is a severe disease characterized by significant remodeling of the small vessels in the lungs. This remodeling can increase resistance in pulmonary circulation and lead to remodeling of the right ventricle and eventually failure. Right ventricular failure is the main cause of morbidity and death in pulmonary hypertension.

Patients who receive a diagnosis with PAH are assessed through the WHO functional classification (WHO-FC) to determine the severity of PAH symptoms.<sup>2</sup> Class I would be considered “normal,” wherein patients are not experiencing any symptoms of breathlessness during rest or activity. Patients in class IV experience severe and debilitating symptoms, even at rest, and usually have very limited survival unless they receive treatment.

Oftentimes, when patients present to specialists in pulmonary hypertension, they are already in functional class II or class III and are already late in their disease course. Clinicians need to do a better job at diagnosing patients with PAH earlier so that they can start on treatment earlier. There are actions that can help to address this. For example, although there is nothing that can help with earlier identification of idiopathic PAH, for those patients who are known to be predisposed to the disease—such as those with connective tissue disease (eg, scleroderma, lupus, dermatomyositis, or mixed connective tissue disease)—screening through echocardiography and other laboratory tests can help ensure that the disease is identified earlier.

**AJMC:** How should clinicians confirm or rule out a PAH diagnosis in patients who show signs and symptoms of the disease?

**HASSOUN:** The first rule, if a clinician suspects their patient has pulmonary hypertension, is to refer him or her directly to a center with expertise in the field. This is imperative. Clinicians can find US-based Centers of Excellence that have received accreditation through the Pulmonary Hypertension Association’s website.<sup>3</sup> These centers “have demonstrated an ability to properly diagnose [pulmonary hypertension] and have the capability to manage these complex patients” based on a site review conducted by physicians and coordinators with expertise in the disease.

Because survival can be very limited if patients are not started on appropriate therapy early, it is important to refer patients with pulmonary hypertension and/or PAH to these centers so they can receive the multidisciplinary care they need. In our group at Johns Hopkins, for example, we pulmonologists work very closely with cardiologists, rheumatologists, radiologists, echocardiographers,

and others—all with expertise in pulmonary hypertension in order to coordinate care of these patients.

**AJMC: What are the current unmet clinical needs in PAH?**

**HASSOUN:** There are many unmet needs in PAH, the greatest of which is that there is no cure and that survival is dependent upon the health of the patient's right ventricle. However, treatment of PAH has greatly improved in the last 40 years. Currently, there are about 15 different treatments available, and these essentially target 3 mechanistic pathways in PAH: the endothelin, nitric oxide, and prostacyclin pathways.<sup>4</sup> Before there were PAH-targeting therapies, the median survival for patients with PAH was less than 3 years. The use of these PAH-targeting therapies has increased the median survival to about 10 years for patients with idiopathic PAH. That is a considerable improvement in patient health and survival; however, there is still no cure, and there are no treatments that target the right ventricle when it fails. There are no treatments that can deremodel the abnormal pulmonary vasculature.

“ **The use of these PAH-targeting therapies has increased the median survival to about 10 years for patients with idiopathic PAH. That is a considerable improvement in patient's health and survival.** ”

**AJMC: What would be the value of a therapy that could address the root cause of the disease?**

**PAUL M HASSOUN, MD:** Some patients with PAH have genetic mutations that mainly affect the bone morphogenetic protein receptor 2 (BMP2) signaling pathway. These mutations can occur in families, as well as in patients without any family history. This type of PAH is called heritable PAH, but regardless of the presence of this mutation, patients with pulmonary hypertension have decreased signaling of the BMP2 pathway. Recently, research has been completed on the use of sotatercept, a treatment that seems to target this pathway. Sotatercept is a fusion protein that is a trap for activin. Activins typically bind to a TGF- $\beta$  receptor, which is part of the TGF- $\beta$  superfamily. There is a ying-yang between TGF- $\beta$  and BMP2 to keep the pulmonary vasculature in check.

Sotatercept seems to target the disequilibrium that exists between BMP2 signaling and TGF- $\beta$ . As a result, there is a lot of hope for this new therapy. This is the first drug that really gets us closer to treating the underlying mechanism in the pathogenesis of PAH. Based on what I've seen, the results of phase 2 and phase 3 trials have been extremely positive.<sup>5-8</sup> Currently, there are no treatments that can improve BMP2 signaling when it is deficient in patients with or without mutations.

Furthermore, over the last 10 to 15 years, the use of dual therapy for PAH has been shown to have better outcomes than monotherapy. It is possible that triple therapy targeting different pathways would be better than mono- or dual therapy. From what I've seen, treatment with sotatercept [in trials] was associated with positive outcomes, regardless of whether patients were also on mono-, dual, or triple therapy. Whether sotatercept alone can improve the remodeling and improve PAH is unclear but adding it to existing therapies seems to be beneficial. There is no evidence to support improved survival yet; it is still too early.

**AJMC: What other interventions are in the pipeline for PAH?**

**HASSOUN:** This is a very active field, and there are several ongoing trials for different therapies. One therapy being studied is imatinib, a tyrosine kinase inhibitor (TKI) used for the treatment of some forms of blood cancers. Preclinical (animal model) data showed that imatinib seemed to improve pulmonary hypertension and counteract remodeling of the pulmonary vasculature.<sup>9</sup> Clinical data from both phase 2 and phase 3 trials seemed to show improvement in functional status and hemodynamics in patients who received imatinib.<sup>10,11</sup> However, some patients experienced severe adverse events (eg, subdural hemorrhage in some patients who were on background anticoagulants) during the trial. An inhaled form of imatinib is being studied in early clinical trials.<sup>12</sup> The hope is that by delivering the drug to the lung, where the remodeling occurs, the systemic effects can be avoided. Until we have the results, however, it remains to be seen whether imatinib will be a good addition to our armamentarium of treatments for PAH. There are alternative pathways that are being targeted through other research, but, in my mind, the most promising treatments are sotatercept, which targets the TGF- $\beta$  signaling pathway, and imatinib or other TKIs that might be helpful in preventing or inhibiting further remodeling of the vessels.

**AJMC: How are patients with PAH involved in shared decision-making for treatment?**

**HASSOUN:** Generally, patients with PAH are started on dual therapy—a combination of an endothelin receptor



antagonist and a phosphodiesterase 5 inhibitor—administered within 2 to 3 weeks of each other. This combination has been associated with improved survival and improved hemodynamics (eg, in the AMBITION trial).<sup>13</sup> Patients with severe PAH are more likely to be offered enrollment in ongoing phase 2 or phase 3 trials. Johns Hopkins has a large center specialized in pulmonary hypertension and, as in other academic centers, the team is involved in multi-center trials, such as those involving sotatercept or inhaled imatinib, for example. Patients with PAH are usually very motivated to participate in clinical trials—they want to get better, and so they are open to participating in new trials that may help them.

Furthermore, although treatments are covered by insurance, they can be costly. The least costly drug we have is still about \$8000 to \$9000 a year, whereas others can be upwards of \$90,000 to \$100,000 a year per patient. Once the diagnosis of PAH is firmly established, we work with the patient's insurer to secure treatment approval. The process can be burdensome and challenging. Despite letters of support, occasionally insurers do not accept providers' recommendations for treatment with dual therapy or for a specific drug. In these instances, oftentimes pharmaceutical companies offer assistance programs that help patients to afford treatment. The hope is that with time, these treatments may become more affordable.

### **AJMC:** How may the management of PAH change in the years ahead?

**HASSOUN:** This is a very exciting time in the field of PAH. Treatments that have been approved in the last 30 years have been associated with improved survival and improved quality of life in patients with PAH. Although we are still far from finding a cure for the disease, there are many research opportunities available. These include the ability to work closely with the National Institute of Health—which has a specific interest in pulmonary vascular disease—and pharmaceutical companies to design better treatments and targeted therapies. PAH is a disease that necessitates collaboration between not only cardiologists and pulmonologists but also immunologists and geneticists, because many patients with PAH have an autoimmune disease or genetic mutations. There may be an opportunity to target inflammation as a potential protagonist in the remodeling of the vessels in the lung, or explore the use

of gene therapies. By targeting several aspects of the remodeling process, the hope is that pulmonary circulation can be restored to a quiescent, clear lumen that will return pulmonary vascular resistance to its normal low state. ♦

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# Payer Considerations in the Management of Pulmonary Arterial Hypertension

A Q&A With Derek van Amerongen, MD, MS



**DEREK VAN AMERONGEN, MD, MS**

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**AJMC:** What are some of the current unmet needs in the treatment and management of PAH?

**VAN AMERONGEN:** I think any patient would say that the number 1 unmet need in the treatment and management of PAH is a cure. As payers and providers, we always need to keep that in mind. The probability of finding a cure in the near future may be unrealistic right now, so the focus should be to help maximize patients' ability to accomplish activities of daily living, to be productive, and to maximize their quality of life (QOL). That is tremendously important. A prime focus for health plans is determining how to help individuals age in place and maintain a positive level of QOL in their homes or other preferred settings. Many patients do not want to be forced into any kind of long-term care facility, and there is great concern over losing independence. Ensuring that patients have access to the right treatment to help them function in their daily lives meets that need. The treatments that are available today are far better than [are those that were available], say, 20 or 30 years ago, but there's still a large opportunity for improvement.

**AJMC:** How can health plans help promote patient adherence to treatment plans that may include specialty drugs and medications with complicated dosage and administration requirements?

**VAN AMERONGEN:** One of the most important things that health plans bring to the table is the ability to understand their populations—to identify members who have these types of conditions and who are at risk for potential adverse events. Health plans can get these members into disease management programs and case management programs and act as coordinators for their care. Health plans don't treat patients, and that's an important point I always want to make. But, at the same time, health plans can frequently be the "air traffic controllers," as I've heard people say, to ensure that the member is connected with the right team of health care professionals to meet their complex care needs and to help ensure that all members of the health care team are talking to each other. Health plans can help ensure that the member understands their benefits and has opportunities for accessing the care that they need. Health plans can coordinate with the pharmacy benefit manager or the dispensing pharmacy, which is tremendously important; most health plans have pharmacists who are trained in specific disease areas and, therefore, they can track patients' use of medications and counsel patients on their medication regimens, which can be very complex. Health plans have an important supportive role, and care management is something that I think has made a big impact in medical care over the last 20 years.

**AJMC:** How can payers work to minimize barriers such as those associated with social determinants of health?

**VAN AMERONGEN:** I'm glad you mentioned social determinants of health. That's something that plans have been focused on quite a bit in the last 5 to 6 years, perhaps even before providers were focused on it. Health plans realized,

while reviewing the data, that although there are facilities, hospitals, and providers that are all connected in the plan, people still were not receiving preventive services. So that led to the obvious question—why? Why aren't members following up and filling their prescriptions for diabetes or heart disease, for example? And when you start peeling back the layers of the onion, you will find that it's very often related to an issue of the social determinants of health. The availability of transportation is a great example—you can have the greatest medical center in the world, but if a patient cannot get there, it doesn't matter. And for the patient, medical care may be fifth or sixth [entry] on their list of priorities, because they are worried about paying their rent. They may not have access to healthy food, because they live in a food desert. There are many other factors that can keep people from being able to access care, and we should address those. We cannot just say that it's the patient's responsibility to show up and do whatever the doctor tells him or her, and that's the end of the story. It's so much more complex.

“ **Health plans have an important supportive role, and care management is something that I think has made a big impact in medical care over the last 20 years.** ”

When viewed from a more holistic point of view, there have been many positive signs of improved outcomes in the last several years. Health plans have been instrumental in ensuring that considerations of social determinants of health are an important part of the routine conversation about optimizing health outcomes overall as opposed to just optimizing medical outcomes. Some examples of how health plans have approached care in a more holistic way include connecting members who do not have access to a car or those with disabilities with access to free transportation services provided by the local government; providing support services in the home for older adult members, such as housekeepers, to prevent them from being moved to long-term care; and using services like app-based transportation companies to deliver medications to members who may be homebound to ensure they continue to receive their treatments. This can be especially important after hospital discharge.

**AJMC:** How are members connected with the many resources available through their health plans?

**VAN AMERONGEN:** Great question. It must be a multifactorial process. On the back of the health care plan card, there is a number that members can call, and members can also go to the health plan's website for information. The real opportunity, however, is in proactive outreach. Larger national plans, in particular, have very sophisticated predictive models and algorithms to identify members [at risk], ideally before they get into trouble—before they end up in the hospital or in an emergency department. Someone from the plan will then reach out to the member, engage with them, and tell them about the resources that are available.... These services are free to the member. Health plans should leverage these data and their internal expertise in terms of case managers, pharmacists, and physicians to help coordinate care and ensure that the member understands a) [what] issues may be impacting their access to care; b) where they need to go to get their clinical care; and c) how to use their benefits effectively. Frequently, people do not understand all that is available in terms of what [their] coverage provides for them. We see this as a way to make investments early to avoid longer term clinical adverse outcomes. And, of course, if you decrease the complications, the adverse events, that will have an impact on cost as well.

**AJMC:** From the payer perspective, what do you see as the biggest challenge in PAH?

**VAN AMERONGEN:** One of the biggest challenges is identifying people who are at risk and then diagnosing PAH. There's no question in my mind that there are many people who have PAH who don't know it. PAH is associated with a complex set of symptoms, and it can be a challenging condition to diagnose. Therefore, the first step is to ensure that the patients who have PAH have been properly identified and that they have received a diagnosis. Once they have a diagnosis, then the challenge is connecting them with the proper care systems.

PAH is a complex disease that may require a higher level of care provided by specialists at tertiary care centers. These care centers are not available everywhere. Furthermore, the process of scheduling an appointment, and even following through with the appointment, at a tertiary care center can be very daunting. The medical establishment can be very intimidating for people who are not in medicine. That is an area where health plans can help. Plans can help members identify care centers, make the appointments, and make sure members get to the appointments.

There are also opportunities related to treatments. Again, I think everyone would agree that the treatments for PAH today are far superior to those that were available 20 [or] 30 years ago, but there is a lot of room for improvement.

Cost considerations for patients with rare diseases such as PAH cover 2 broad areas: direct clinical treatment costs (eg, provider visits, hospitalizations, testing, and other interventions) and drug costs. In the last 10 years, the focus has shifted mainly onto drug costs. Part of this is because we now have medications that are more effectively addressing signs of symptoms of these diseases and, thus, leading to a reduction in direct clinical treatment costs, partly because the costs for orphan drugs have substantially increased. Ideally, health plans also can address the issue of affordability, because it is concerning that there are patients who could, and should, be in treatment [but] who are not, because they cannot afford it. In some cases, patients do not have health insurance. However, even among those who are insured, the robustness of insurance coverage varies tremendously. There is no question in my mind that there are people who are insured, but, for various reasons, cannot afford the level of care that they need and deserve. I think all of those are challenges. The good news is, I think that they are all fixable. I am relatively optimistic about where we will be, say, in the next 5 to 10 years.

The pipeline is robust in so many therapeutic areas, including PAH. It's full. There are a lot of novel treatments coming. The challenge is always going to be

affordability—not just on the individual level, but on a societal level, as well. That being said, I think that affordability and cost not only to the individual, but to society as well, are being addressed. The Inflation Reduction Act<sup>1</sup> is an important first step in that direction, I think. And I also see it as an important step forward.

I am hopeful that maybe in the next few years, we will have an inflection of care moment for PAH, meaning that we have either a treatment to cure the disease or one that is associated with a considerable increase in survival, [ability to perform] activities of daily living, and QOL. The alignment of incentives between providers, health plans, and other stakeholders in the last few years has meant that there has been increasing use of care and interventions that support the long-term well-being of members, regardless of their conditions or health status. A growing emphasis on prevention, expanding access to all the elements that promote better clinical outcomes, and a desire to help people continue to live independently will help individuals experience the optimal health status they deserve. ♦

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