Recent Developments in Systemic Sclerosis and Pulmonary Arterial Hypertension

Lung Disease in Systemic Sclerosis

Systemic Sclerosis and Pulmonary Hypertension: Emerging Therapeutic Options

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Introduction

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Post-Test and Evaluation

TARGET AUDIENCE

This educational activity is designed for physicians and other health care professionals involved in the care and clinical management of patients with systemic sclerosis, particularly those patients with pulmonary manifestations.

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EDUCATIONAL NEEDS

Systemic sclerosis is an uncommon but incurable connective tissue disorder. The condition has an especially poor prognosis in patients with major organ involvement. In recent years, pulmonary disease— including pulmonary arterial hypertension (PAH) and interstitial lung disease—has supplanted renal failure as the principal cause of death in patients with systemic sclerosis.

Advances in diagnostic techniques, particularly right-heart catheterization, have improved clinicians’ ability to distinguish PAH from the broader category of pulmonary hypertension, a key step toward earlier, more appropriate therapy. Clinical management remains symptom driven, although expansion of therapeutic options has created the potential to improve symptom control, quality of life, and survival.

LEARNING OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Describe the pathogenesis, manifestations, and symptoms of systemic sclerosis with pulmonary involvement
- Appreciate the consequences and implications of pulmonary disease in systemic sclerosis
- Understand the approach to the diagnostic workup
- Recognize current therapeutic strategies for systemic sclerosis complicated by pulmonary disease.

DISCLOSURE

Dr Furst has received honoraria for being a consultant and/or a member of an advisory board for Abbott Laboratories, Actelion, Amgen, Bristol-Myers Squibb Company, Biogen Idec, Centocor, Consortium of Rheumatology Researchers of North America, Inc. (CORRONA), Genentech, Gilead, GlaxoSmithKline/Merck, Nitec, Novartis, F. Hoffmann-La Roche Ltd., UCB Inc., Wyeth, and XOMA.

Dr Oudiz has received grant research support and/or honoraria for being a consultant and/or serving on the speakers bureau for Actelion, Bayer, Gilead, Eli Lilly and Company, Pfizer, and United Therapeutics.

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Introduction

Systemic sclerosis, or scleroderma, is an uncommon but not rare disease. The condition affects multiple organ systems, and the prognosis varies by the nature and extent of organ involvement. Systemic sclerosis confers a high mortality risk, but the principal cause of mortality has shifted in recent years from renal disease to lung disease. Pulmonary involvement in systemic sclerosis manifests as interstitial lung disease (ILD) or pulmonary arterial hypertension (PAH). ILD accounts for a majority of scleroderma-related lung disease, whereas 15% to 20% of patients with scleroderma have associated PAH, making scleroderma-associated PAH more common than idiopathic PAH. Moreover, PAH associated with systemic sclerosis has a higher mortality risk than do other categories of PAH. The following discussion offers a review of current epidemiologic and pathogenetic trends in systemic sclerosis.

Epidemiology of Systemic Sclerosis and PAH

Both the prevalence and the incidence of systemic sclerosis have increased substantially over the past 40 to 50 years.1,2 Early studies suggested a prevalence of less than 5 per million people and an incidence of less than 1 per million. Recent prevalence estimates range between 300 and 700 per million, and incidence exceeds 20 per million. Accepting a midrange prevalence estimate for systemic sclerosis would result in a prevalence of 60 to 75 per million people for scleroderma-associated PAH. In contrast, idiopathic PAH has a prevalence of about 6 per million.3

Scleroderma has a female predominance on the order of 4:1 or 5:1 and is more common in blacks than in whites.2 African American patients are younger at diagnosis and are more likely to have diffuse disease, which correlates with younger age at onset and a shorter interval from symptom onset to diagnosis.

Mortality remains high in patients with scleroderma compared with that in the general population, although survival has improved in recent years as a result of more effective therapies. Even with modern therapy, however, the estimated 5-year mortality rate is 25% to 30%.1

Systemic sclerosis also confers a worse prognosis when associated with other conditions. For example, a comparison of patients with PAH-associated systemic lupus erythematosus (SLE) versus systemic sclerosis showed a 2-year survival rate of approximately 90% in the patients with SLE compared with about 70% in the patients with scleroderma.4 Data from a registry of patients with systemic sclerosis and PAH revealed respective survival rates of 81%, 63%, and 56% at 1, 2, and 3 years.5

The causes of death in patients with systemic sclerosis have changed considerably in recent years. Prospective follow-up of patients from 1972 to 1997 showed that mortality rates related to renal disease declined from 42% of scleroderma-related deaths to 6%. During the same time frame, the proportion of deaths attributable to pulmonary disease increased from 6% to 33%.6

Multisystem Involvement

Systemic sclerosis affects multiple organ systems. Major disease foci include the skin, lungs, heart, kidneys, and gastrointestinal tract. To a lesser extent, the condition may affect structures of the head and neck, joints, muscles, nerves, and reproductive organs. To the extent that psychosocial function can be viewed as an organ system, the substantial adverse impact of systemic sclerosis should not be overlooked or underestimated.

The nature and extent of organ involvement have a major influence on survival in systemic sclerosis. Patients who have no involvement of the heart, lungs, or kidneys have the most favorable prognosis.7 Scleroderma-associated lung disease other than PAH confers a slightly worse survival. Patients with scleroderma and PAH have a particularly unfavorable outlook for survival. One frequently cited study showed a 1-year mortality rate of 50% in patients with scleroderma-associated PAH, and no patient lived as long as 6 years.8

Pulmonary Pathology

Scleroderma is associated with two principal types of pulmonary disease: ILD and PAH. About half of patients with systemic sclerosis have pulmonary fibrosis by x-ray at diagnosis, possibly more when computed tomography (CT) is used to evaluate the lungs. Lung function declines rapidly during the first 5 years after diagnosis, and then the rate of functional decline slows but does not stop. About 10% of patients eventually develop pulmonary failure.9

Interstitial Lung Disease

A majority of patients with scleroderma have some degree of ILD at autopsy.10 About a third of patients have clinically significant ILD. The disease spectrum varies greatly from mild and self-limited to aggressive and rapidly progressive.11

The pathogenesis of scleroderma-associated ILD involves several abnormalities, including inflammation and vascular injury. In particular, chronic inflammation is widely perceived as a significant driver of the fibrotic process.

Patients with scleroderma produce a variety of autoantibodies, but the ones most closely associated with lung disease are antitopoisomerase antibodies (ATAs), which are strongly associated with pulmonary fibrosis. A handful of other autoantibodies also increase the risk of lung disease but are not as closely associated with ILD as are ATAs.11

The most common histology seen in scleroderma ILD is nonspecific interstitial pneumonia,12-14 exhibiting a homogeneous pattern of inflammatory and fibrotic infiltrates. High-resolution CT imaging also revealed substantial homogeneity, predominately ground-glass opacification.15

Impaired lung function may have several manifestations, reflecting the different contributing factors to impairment. The diffusion lung capacity for carbon monoxide (DLCO) is the most sensitive marker of lung impairment in scleroderma-related ILD15 but should be assessed in association with lung volumes. Pure ILD has a restrictive ventilatory pattern associated with reduced forced vital capacity (FVC), reduced total lung capacity, increased forced expiratory volume in 1 second/FVC ratio, and reduced DLCO.11

Respiratory symptoms have proven unreliable as an indication of the severity of ILD. Lung function tests offer a readily available and accurate means of determining whether a patient has clinically significant ILD.11 Two parameters frequently used to define clinically significant ILD are DLCO ≤50% and FVC <70%.16 In most cases, significant abnormalities on high-resolution CT, if available, plus DLCO ≤50% and...
Systemic Sclerosis and Pulmonary Hypertension: Emerging Therapeutic Options

Ronald J. Oudiz, MD

Until fairly recently, a single term—pulmonary hypertension (PH)—comprised what specialists in the field now recognize as a multitude of conditions that differ with respect to etiology, pathogenesis, and treatment. In 2003, authorities in the field settled on a five-category classification system reflecting different etiologies; this classification was further refined in 2008 (Table 1).

All but one category have multiple subgroups that further delineate the origin and nature of the disease process. All told, the PH classification system encompasses more than two dozen types of disorders that fall under the broad categorical umbrella of “pulmonary hypertension.”

To date, the only PH category for which there are approved treatments is pulmonary arterial hypertension (PAH), which includes idiopathic PAH (IPAH) and PAH associated with other underlying diseases (APAH). Unfortunately, PAH also carries the poorest prognosis. The remaining four PH categories comprise a variety of more common conditions that have different etiologies and pathophysiologies: PH owing to left heart disease is probably the most common cause of PH in developed nations; PH related to lung diseases and/or hypoxemia is also much more common than is PAH; chronic thromboembolic PH is not uncommon and can sometimes be treated surgically. The last PH group is that of PH with unclear multifactorial mechanisms, some of which can share some commonality with PAH.

More common types of PAH include PAH associated with connective tissue diseases (CTD), such as systemic sclerosis (SSc), or scleroderma. Epidemiologic studies have suggested that 10% to 15% of patients with CTD have PAH.2,3 The prevalence of pulmonary vascular disease in patients with CTD may even be higher. A postmarketing surveillance study of almost 5,000 patients treated with the endothelin antagonist bosentan showed that 28% of the patients had PAH related to CTD; most patients in this study had SSc (75% of cases).4

The number and variety of therapeutic options for PAH have increased in recent years, and several other candidate therapies have entered clinical evaluation or will in the near future. Nonetheless, morbidity and mortality remain high.5,6 The discussion that follows addresses recent clinical developments and ongoing efforts to improve clinical management and outcomes for patients with PAH, with particular emphasis on PAH related to SSc.

Table 1. Clinical Classification of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroups</th>
</tr>
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<tbody>
<tr>
<td>Pulmonary arterial hypertension (PAH)</td>
<td>- Idiopathic PAH (IPAH)</td>
</tr>
<tr>
<td></td>
<td>- Heritable</td>
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<tr>
<td></td>
<td>- Bone morphogenetic protein receptor type II (BMPR2)</td>
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<td></td>
<td>- Activin receptor-like kinase-1, endoglin (with or without hereditary hemorrhagic telangiectasia)</td>
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<tr>
<td></td>
<td>- Unknown</td>
</tr>
<tr>
<td></td>
<td>- Drug- and toxin-induced</td>
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<tr>
<td></td>
<td>- Associated with</td>
</tr>
<tr>
<td></td>
<td>- Connective tissue diseases</td>
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<tr>
<td></td>
<td>- HIV infection</td>
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<td></td>
<td>- Portal hypertension</td>
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<tr>
<td></td>
<td>- Congenital heart diseases</td>
</tr>
<tr>
<td></td>
<td>- Schistosomiasis</td>
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<tr>
<td></td>
<td>- Chronic hemolytic anemia</td>
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<tr>
<td></td>
<td>- Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td>Pulmonary hypertension owing to left heart disease</td>
<td>- Systolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>- Diastolic dysfunction</td>
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<tr>
<td></td>
<td>- Valvular disease</td>
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<tr>
<td>Pulmonary hypertension due to lung diseases and/or hypoxemia</td>
<td>- Chronic obstructive pulmonary disease</td>
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<tr>
<td></td>
<td>- Intestinal lung disease</td>
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<tr>
<td></td>
<td>- Other pulmonary diseases with mixed restrictive and obstructive pattern</td>
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<tr>
<td></td>
<td>- Sleep-disordered breathing</td>
</tr>
<tr>
<td></td>
<td>- Alveolar hypoventilation disorders</td>
</tr>
<tr>
<td></td>
<td>- Chronic exposure to high altitude</td>
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<tr>
<td></td>
<td>- Developmental abnormalities</td>
</tr>
<tr>
<td>Chronic thromboembolic pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension with unclear multifactorial mechanisms</td>
<td>- Hematologic disorders: myeloproliferative disorders, splenectomy</td>
</tr>
<tr>
<td></td>
<td>- Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangio-leiomomatosis, neurofibromatosis, vasculitis</td>
</tr>
<tr>
<td></td>
<td>- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders</td>
</tr>
<tr>
<td></td>
<td>- Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis</td>
</tr>
</tbody>
</table>

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Pathogenesis of PAH

PAH likely evolves from an insult to a vulnerable pulmonary vascular bed, triggering an insidious vasculopathy that leads to progressive narrowing of the pulmonary artery.7 The inciting disease process may be multifactorial, whereby a risk factor (such as CTD, congenital heart disease, portal hypertension, or human immunodeficiency virus [HIV] infection) and inherited or acquired susceptibility conspire to create a progressive and irreversible vascular injury. The vascular abnormalities include smooth-muscle hypertrophy and intimal/adventitial proliferation, with associated endothelial dysfunction and vessel narrowing all resulting in increased pulmonary vascular resistance (PVR). Eventually, plexogenic pulmonary arteriopathy develops, a neovascular (seemingly compensatory) mechanism that exacerbates the increase in PVR. In the absence of effective treatment, increasing PVR causes the right ventricle to hypertrophy and then to dilate, leading to right ventricular dysfunction/ right ventricle failure and death. The increase in PVR abnormalities leads to PH symptoms that most commonly manifest as exertional dyspnea, fatigue, edema, and, in more advanced stages, exertional syncope.

SSc and PAH

Because of their underlying comorbidity, patients with PAH related to SSc tend to be more compromised than do patients with idiopathic PAH; they have a less robust response to therapy and have overall higher mortality rates.8,9 Patients with CTD-associated PAH have poorer exercise capacity and pulmonary function and on average exhibit less clinical improvement during treatment than do patients who have idiopathic PAH. Patients with SSc and APAH, in fact, have a less favorable prognosis than do SSc patients who have associated interstitial lung disease.8

For reasons that are poorly understood, SSc associated with PAH also confers a worse prognosis than that for patients with idiopathic PAH.9 In addition, patients with SSc-associated PAH appear to have a
worse prognosis than do PAH patients with other types of CTD. Investigators involved in a large registry of patients with PAH in the United States compared patients who had PAH associated with systemic lupus erythematosus (SLE) to patients with PAH associated with SSC. Based on right heart catheterization and biopsy findings, both types of patients exhibited similar pathology. However, the patients with SSC-associated PAH had more severe right ventricular failure. Two-year survival rates were about 90% in patients with SLE-associated PAH and about 70% in patients with SSC and PAH. Considerable speculation surrounds the origin of the survival disparity.

More evidence of the unfavorable prognosis conferred by SSC can be gleaned from another registry of patients with SSC screened for PAH by echocardiography, lung function tests, and clinical assessment. In this registry, 12% of the patients who had PAH documented by right heart catheterization. These patients had survival rates of 81% at 1 year, 63% at 2 years, and 56% at 3 years. Predictors of worse survival included elevated mean right atrial pressure (markers of right ventricular failure) and elevated pulmonary arterial pressure.

Intuitively, the evidence points to a need for earlier diagnosis and treatment of CTD-associated PAH, preferably to detect the pulmonary vascular disease before increasing PVR leads to right ventricular decompensation and failure. Although medical intervention can sometimes be initiated early in the course of the disease process, all too often treatment begins much later, greatly limiting the potential to substantially alter the clinical course.

**Early Detection**

Early detection of PAH begins with clinical suspicion. A high suspicion for PAH is necessary when evaluating patients with known risks for PAH, such as those with SSC and other forms of CTD (as well as those with HIV infection, portal hypertension, or a family history of PAH). Unexplained dyspnea may represent an early clue to PAH, especially in these high-risk patients. Unfortunately, PAH does not affect a large enough population to warrant routine screening of the general population.

Screening for PAH should begin with a thorough history and physical examination. Physical examination may identify signs of right ventricular failure. Findings associated with an increased likelihood of PAH include an accentuated pulmonary component of the second heart sound audible at the apex (noted in >90% of patients with PAH), early systolic ejection click resulting from sudden interruption of the pulmonary valve opening, mid-systolic ejection murmur caused by turbulent transvalvular pulmonary flow, palpable left parasternal lift caused by the impulse of a hypertrophied right ventricle, right ventricular S4 gallop, and a prominent jugular “a” wave, indicative of high right ventricular filling pressure.

Echocardiography can help confirm or refute suspicion of PAH by providing information about tricuspid regurgitant velocity, and right atrial and right ventricular size and function. Unexplained dilation of the right atrium or right ventricle and/or right ventricular dysfunction strongly suggests pulmonary hypertension.

The ratio of forced expiratory volume in 1 second (FEV1) to diffusion lung capacity for carbon monoxide (DLCO) can provide additional evidence to confirm or rule out a diagnosis of PAH in patients with SSC. DLCO reflects the vascularity and integrity of the pulmonary capillary bed, and a declining DLCO indicates loss of capillary bed.

The strategy of stress testing to unmask impaired cardiopulmonary reserve remains controversial, and studies are ongoing to determine whether exercise stress testing has a role in the evaluation of suspected PAH in high-risk patients.

**Therapeutic Options**

**History**

Early descriptions of PAH include the first case of primary pulmonary hypertension, now called IPAH, more than 50 years ago. At that time, conventional therapies had little or no impact on outcomes and were mainly for symptomatic benefit, leading to a search for a specific therapy for PAH. Since then, therapeutic development for PAH has centered on three pathways: prostacyclin (prostaglandin I2, or PGI2), nitric oxide, and endothelin.

Patients with PAH have reduced levels of PGI2, contributing to an imbalance between pulmonary vasoconstrictor and vasodilator substances. This finding led to a search for a means to administer a PGI2 analog to patients with PAH. Because patients with PAH also have inadequate production of nitric oxide, development of therapies that stimulate nitric oxide synthesis or increase its activity has also been a focus of PAH drug development. The focus on the endothelin pathway in PAH is based on the rationale that endothelin levels are elevated and endothelin receptors are upregulated in PAH.

The first approved therapy for PAH was in 1995, more than 40 years after Dresdale’s description. Intra-venous (IV) epoprostenol, a synthetic PGI2, reached the market in the 1990s. However, the agent has a number of limitations: short half-life, need for continuous IV administration, complications related to use of a central venous catheter, and a substantial side effect profile that includes diarrhea, flushing, and headache.

Subsequently, a subcutaneous PGI2 analog, treprostinil, was developed and approved, following a successful multicenter clinical trial in patients with PAH. Almost simultaneously, the first oral endothelin receptor antagonist, bosentan, was approved for PAH.

More recently, oral sildenafil and oral tadalafil, which stimulate nitric oxide–mediated vasodilation, were approved for PAH, along with the oral endothelin-A receptor antagonist, ambrisentan, and inhaled formulations of synthetic PGI2, iloprost and treprostinil.

**Clinical Benefits**

The first evidence that a therapy could improve outcomes in PAH came from a relatively small (81 patients) randomized clinical trial comparing IV epoprostenol plus standard care versus standard care alone. The results showed a significant improvement in 6-minute walk distance for epoprostenol compared with a decrease in patients who received only standard care (P<0.002). More importantly, all of the patients in the epoprostenol group survived to the end of the study, whereas the standard care group had a 20% mortality rate.

A few years later, investigators replicated these findings with continuous IV epoprostenol in patients with SSC and PAH. Treatment with epoprostenol significantly improved 6-minute walk distance (P<0.002) and a variety of other functional outcomes in this study. Additionally, 38% (21 of 56) of the patients in the epoprostenol group had an improvement in New York Heart Association functional class compared with none of the patients randomized to standard care only. Importantly, about half of the patients remained alive after 4 years compared with an expected survival rate of 10% or less with conventional therapies.

Subsequently, other PGI2 analogs demonstrated improved outcomes in patients with PAH, as did endothelin receptor antagonists and drugs that stimulate nitric oxide–mediated vasodilation. A succession of approvals by the US Food and Drug Administration greatly expanded the list of effective treatment options for patients with PAH ('Table 2 on page 6).
of PAH. More recently, a comprehensive approach to the diagnosis and treatment published a consensus document outlining from the European Respiratory Society and European Society of Cardiology. In 2008, world experts convened an international consensus meeting and subsequently published a consensus document outlining an approach to the diagnosis and treatment of PAH. More recently, a comprehensive American Heart Association/American College of Cardiology guideline statement was published, with a treatment algorithm based on strength and weight of available medical evidence and, where applicable, expert consensus.

Current Treatment Strategies

Consensus Guidelines

In recent years, several consensus papers have been published on the diagnosis and management of PAH. These include statements from the American College of Chest Physicians and statements from the European Respiratory Society and European Society of Cardiology. In 2008, world experts convened an international consensus meeting and subsequently published a consensus document outlining an approach to the diagnosis and treatment of PAH. More recently, a comprehensive American Heart Association/American College of Cardiology guideline statement was published, with a treatment algorithm based on strength and weight of available medical evidence and, where applicable, expert consensus.

Conventional Therapy of PAH

In the PAH guideline documents, the authors recommend consideration of conventional treatments as needed, such as warfarin, diuretics, oxygen, and digoxin. In addition, recommendations on specific PAH treatments are provided.

Calcium Channel Blocker

Use and Vasoreactivity

It should be noted that, in the past, many clinicians have used calcium channel blockers for patients with PAH in addition to conventional treatments. This practice has often been empiric; however, the consensus statement advises against such empiric therapy and emphasizes that treatment with a calcium channel blocker should begin only if patients meet the definition of acute pulmonary vasoreactivity. Patients who are acutely vasoreactive may derive substantial benefit from treatment with a calcium channel blocker. However, most patients with PAH are not vasoreactive; in particular, it is rare for patients with CTD-associated PAH to be vasoreactive.

Specific PAH Therapy

Following a negative vasoreactivity test, a consideration of the patient’s estimated risk of disease is recommended. Risk considerations are shown in Table 3. According to consensus guidelines, lower-risk patients can be treated with an endothelin-A receptor antagonist, a phosphodiesterase type 5 inhibitor (sildenafil or tadalafil), or an inhaled or subcutaneous PGI2 analog. For higher-risk patients, the therapeutic spectrum expands to include IV PGI2 analogs as the preferred initial agent.

Use of More Than One PAH-Specific Therapy

The availability of multiple therapeutic targets in PAH creates a potential for combination therapy. However, the safety and efficacy of combination therapy remains largely unproven, save for a few studies that have evaluated add-on therapy. Nonetheless, many patients with PAH do receive various drug combinations. An analysis of a large database of patients with PAH showed that 36% were being treated with two drugs and 9% with three drugs. It must be understood that the use of unproven drug combinations may pose a risk to patients and substantially increases the cost of therapy. Thus, experts strongly recommend adherence to guidelines when possible.

The list of treatment options for PAH will likely increase in the near future. Clinical trials have already begun with the endothelin receptor antagonist, macitentan; the soluble guanylate cyclase inhibitor, riociguat; the tyrosine kinase inhibitor, imatinib; the oral prostacyclins UT-15C and beraprost; and the prostacyclin, receptor agonist, slexipag. Additional trials for other novel agents may also begin in the near future.

Summary

Over the past few decades, PAH has evolved from a single concept into a complex disease spectrum encompassing five categories and more than two dozen subcategories, reflecting improved understanding of etiology and pathogenesis. Despite advances in clinical management, morbidity and mortality rates in patients with PAH remain high, owing in large part to the advanced stage at which most patients present and thus begin treatment. For reasons that remain unclear, PAH associated with SSc and other CTD has a worse prognosis than do other forms of PAH. Treatment options have continued to expand since the first PAH-specific drug received approval in the 1990s. Adherence to clinical recommendations offers the best assurance for providing safe and efficacious therapy for patients with PAH.

References


Table 3. Risk Stratification for Pulmonary Arterial Hypertension (PAH)*

<table>
<thead>
<tr>
<th>Determinants of Risk</th>
<th>Lower Risk (Good Prognosis)</th>
<th>Higher Risk (Poor Prognosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP†</td>
<td>Minimally elevated</td>
<td>Significantly elevated</td>
</tr>
<tr>
<td>Clinical evidence of RV failure</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CPET</td>
<td>Peak VO2 &gt;10.4 mL/kg/min</td>
<td>Peak VO2 &lt;10.4 mL/kg/min</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Minimal RV dysfunction</td>
<td>Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>RAP &lt;10 mm Hg, CI &gt;2.5 L/m²</td>
<td>RAP &gt;20 mm Hg, CI &lt;2.0 L/m²</td>
</tr>
<tr>
<td>6MW distance‡</td>
<td>Longer (&gt;400 m)</td>
<td>Shorter (&lt;300 m)</td>
</tr>
<tr>
<td>Progression of symptoms</td>
<td>Gradual</td>
<td>Rapid</td>
</tr>
<tr>
<td>WHO class§</td>
<td>II, III</td>
<td>IV</td>
</tr>
</tbody>
</table>

*Most data available pertain to idiopathic PAH. Few data are available for other forms of PAH. One should not rely on any single factor to make risk predictions. As there are currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP absolute numbers are not given for this variable. 6MW distance is also influenced by age, gender, and height. WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class. 6MW=6-minute walk, BNP=brain natriuretic peptide; CI=cardiac index; CPET=cardiopulmonary exercise testing; peak VO2=average peak oxygen uptake during exercise; RAP=right atrial pressure; RV=right ventricle; and WHO=World Health Organization.

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Lung Disease in Systemic Sclerosis

FVC <70% can define clinically significant disease requiring treatment. Treatment of scleroderma-related ILD remains challenging. Clinicians have no approved medications for the condition, and off-label therapies offer no more modest benefits, sometimes at a cost of significant toxicity. Commonly used therapies include cyclophosphamide, glucocorticoids, and azathioprine.

ILD confers an unfavorable prognosis for patients with systemic sclerosis. As a result, the current best hope for treatment is to initiate therapy as early as possible to slow disease progression.

Pulmonary Arterial Hypertension

Most types of PAH follow a similar pathway during disease progression, as described by Dr Oudiz elsewhere in this supplement. The pathogenesis of scleroderma-associated PAH differs in one key respect. The plexiform lesion that is almost universally associated with idiopathic PAH rarely occurs in patients with systemic sclerosis. That distinct difference in pathogenesis remains largely unexplained but could account for the worse prognosis of scleroderma-associated PAH.

Unexplained dyspnea or other pulmonary symptoms should raise suspicion of PAH or ILD in patients with systemic sclerosis. Physical examination can identify suggestive clues to pulmonary involvement, but imaging—both chest x-ray and echocardiography—provides more definitive information. Right heart catheterization remains the gold standard for diagnosis of PAH.

Early Diagnosis and Treatment: Keys to Better Outcomes

As reviewed by Dr Oudiz, the number and types of therapeutic options for PAH have increased dramatically in recent years. The options include almost a half-dozen drugs that affect prostacyclin, two that stimulate nitric oxide—mediated vasodilation via phosphodiesterase type 5 inhibition, and three agents that affect the endothelin pathway. As much as any recent developments in the field of PAH, the increased availability of effective therapies offers the most reason for optimism about the potential to improve survival and quality of life in affected patients.

Optimizing the use of available therapies requires early diagnosis, which remains the major obstacle to improved outcomes for PAH. Most patients continue to be diagnosed in late stages of the disease process. Earlier diagnosis begins with clinical suspicion. PAH does not occur with sufficient frequency to warrant routine screening. However, screening is warranted in patients at high risk, such as those with systemic sclerosis or a positive family history of PAH.

References

CME QUESTIONS

Instructions: For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate response.

1. What is the origin of scleroderma?
   A. Viral infection
   B. Birth trauma
   C. Autoimmune disorder
   D. Enzyme deficiency

2. What major organ system is most often involved in scleroderma?
   A. Lungs
   B. Kidneys
   C. Heart
   D. Liver

3. What are the two principal types of lung disease associated with scleroderma?
   A. Emphysema and chronic obstructive pulmonary disease (COPD)
   B. COPD and lung cancer
   C. Chronic bronchitis and emphysema
   D. Interstitial lung disease and pulmonary arterial hypertension

4. Which of the following was not mentioned as a commonly used therapy for interstitial lung disease?
   A. Cyclophosphamide
   B. Beta-blockers
   C. Glucocorticoids
   D. Azathioprine

5. As compared with idiopathic pulmonary hypertension, connective tissue disease-associated pulmonary hypertension:
   A. Has a more favorable prognosis
   B. Is more often controlled with medication
   C. Has a worse prognosis
   D. Has similar outcomes

6. Which of the following was not mentioned as a pathway for therapeutic development in pulmonary arterial hypertension?
   A. Nitric oxide
   B. Prostacyclin
   C. Leukotrienes
   D. Endothelin

7. Which of the following has/have approval for treatment of pulmonary arterial hypertension?
   A. Sildenafil
   B. Bosentan
   C. Synthetic PGI2
   D. All of the above

8. What is the most common type of lung disease associated with scleroderma?
   A. Intestinal lung disease
   B. Asthma
   C. Pulmonary arterial hypertension
   D. A & B

EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for other activities of this type. All information is confidential. Please print.

Name:

Specialty:

Degree:  MD  DO  PharmD  NP  RN  BS  PA
   □ Other

Affiliation:

Address:    City:    State:    ZIP:

Telephone:    Fax:    E-mail:

Signature:

CME CREDIT VERIFICATION

I verify that I have spent _____ hour(s)/_____ minutes of actual time working on this CME activity. No more than 1.0 CME credit will be issued for this activity.

COURSE EVALUATION: GAPS

This activity was created to address the professional practice gaps listed below. Please respond regarding how much you agree or disagree that the following gaps were met:

- Medical literature reveals that the understanding of which antibodies cause systemic sclerosis is relatively recent and still evolving.
- There is a high mortality rate associated with most patients with systemic sclerosis because of complications from pulmonary hypertension and pulmonary fibrosis.
- Physician experts on systemic scleroderma report that patients with this disease who are regularly screened for pulmonary function show improved survival rates and delayed rates of internal organ involvement.
- To avoid irreversible tissue and organ damage, it would be helpful for clinicians treating systemic sclerosis to be able to recognize early organ involvement and institute effective therapy.

Did participating in this educational activity improve your COMPETENCE in the professional practice gaps that are listed above?

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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</tbody>
</table>

Please elaborate on your answer.

Did participating in this educational activity improve your PERFORMANCE in the professional practice gaps that are listed on the left?

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
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</table>

Please elaborate on your answer.

Please identify a change that you will implement into practice as a result of participating in this educational activity (new protocols, different medications, etc.).

How certain are you that you will implement this change?

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
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</table>

What topics do you want to hear more about, and what issue(s) in your practice will they address?

Were the patient recommendations based on acceptable practices in medicine?

☐ Yes  ☐ No

If no, please explain which recommendation(s) were not based on acceptable practices in medicine.

Do you think the articles were without commercial bias?

☐ Yes  ☐ No

If no, please list the article(s) that was/were biased.

The University of Louisville thanks you for your participation in this CME activity. All information provided improves the scope and purpose of our programs and your patients' care.