Developing Novel Therapies in Pulmonary Arterial Hypertension

Internal Medicine Grand Rounds
UT Southwestern Medical Center
May 10, 2013
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This is to acknowledge that Kelly Chin, MD has received funding for research and / or consulting work with commercial concerns related to this program. Dr. Chin will also be discussing off-label uses in her presentation.

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Purpose and Overview
The diagnosis and treatment of pulmonary arterial hypertension will be reviewed, and the design and conduct of clinical trials in this area will be discussed.

Objectives

At the conclusion of this activity, participants will be able to:

- Differentiate patients with pulmonary arterial hypertension (WHO group I) from other forms of pulmonary hypertension
- Determine which medical therapies (particularly oral vs. intravenous therapy) might be considered in the treatment of a patient with pulmonary arterial hypertension (PAH), based on PAH severity
- Identify endpoints that would meet the FDA's "feel, function, survive" criteria and would likely be acceptable as primary end-points in phase 3 clinical trials

Special Interests:
Dr. Chin completed medical school and residency at UT Southwestern, and completed her pulmonary and critical care fellowship at the University of San Diego, California. Her research interests include pulmonary hypertension medical therapies, prognostic markers in pulmonary hypertension, and the role for the serotonin and the serotonin transporter in idiopathic and drug-use associated pulmonary hypertension. She recently received a K23 award based on her preliminary work in this area. She is currently the director of the pulmonary hypertension program at UT Southwestern, and is currently serving on the steering committee for two pulmonary hypertension clinical trials.

Developing Novel Therapies in Pulmonary Arterial Hypertension: Contents

Definitions and abbreviations:

1. 5HT: serotonin
2. 6MWD: six minute walk distance.
3. CHD: congenital heart disease.
4. CTEPH: chronic thromboembolic pulmonary hypertension
5. PA: pulmonary artery
6. PAH: Pulmonary arterial hypertension: Synonymous with WHO group I PH (table 3. Refers to the specific subgroups of pulmonary hypertension with similar pathophysiology and response to treatment. It is diagnosed by a combination of hemodynamic findings plus exclusion of left heart disease, lung disease, chronic pulmonary emboli and other non-group I conditions.
7. PASMC: pulmonary artery smooth muscle cell
8. PH: Pulmonary hypertension: general term, defined as mean PA pressure >25 mmHg
9. RCT: randomized controlled trial

INTRODUCTION

Pulmonary hypertension in general has been defined as a mean pulmonary arterial pressure greater than 25 mmHg. This level was chosen to reflect "significant" pulmonary hypertension, as the upper limit of normal for mean pulmonary pressures is lower, approximately 20 mmHg. From a hemodynamic view, pulmonary hypertension occurs with any of the following: increased in left heart filling pressure, increased pulmonary vascular resistance, or increased flow, based on Poiseuille's law describing fluid dynamics.

$$\text{Cardiac output} = \frac{\text{PA pressure} - \text{LA pressure}}{\text{Pulmonary Vascular Resistance}}$$

What is now called idiopathic PAH was first described at autopsy by Romberg in 1891 (1). Rare cases were reported over the next 60 years (2), but it was not until the advent of right sided cardiac catheterization in the 1940s that pulmonary hypertension became more widely recognized (3,4).

Table 1: Landmark studies / advances in pulmonary hypertension

- 1891 Romberg describes case of idiopathic PAH (1)
- 1940s Right sided heart catheterization becomes possible
- 1951 Dresdale: 39 cases described
- 1958 Heath and Edwards: pathology of PH (CHD, N=67 and idiopathic, N=2) (5)
- 1958 Wood; PH classification paper, incorporating clinical, hemodynamic and pathological characteristics. Also describes vasodilator response (6)
- 1970 Wagenvoort and Wagenvoort: pathology series on idiopathic PAH (7)
- 1965-1968 Aminorex epidemic in Europe – multiple case series (8)
- 1973 1st WHO Consensus Conference
- 1980s NIH registry; survival equation based on hemodynamics(9,10)
- 1992 Rich: calcium channel blocker study (observational) (11)
- 1995 First prostacyclin (epoprostenol) approved
- 1996 Abenhaim - fenfluramine case-control study (12)
- 1998 2nd WHO Consensus Conference
- 2001 First endothelin-1 receptor antagonist (bosentan) approved
- 2005 First PDE-5 inhibitor (sildenafil) approved
- 2008 First (unequivocally) positive combination therapy study (13)

*"Idiopathic" PAH used for consistency; in earlier years, the term primary PH was used. Interestingly, Heath and Edwards in 1958 used the term idiopathic.

Demographics

Pulmonary hypertension in general (all types) is not at all rare, being diagnosed during more than 2% of all U.S. hospital admissions and in approximately 9% of echocardiograms (14,15). Left heart disease associated pulmonary hypertension is the most common form, particularly in a general community setting where it may account for 2/3 of all pulmonary hypertension diagnoses (15).

In contrast, idiopathic PAH is rare and a diagnosis of exclusion. It is considered when other causes of pulmonary hypertension have been excluded, including left heart disease, lung disease and chronic thromboembolic pulmonary hypertension. Idiopathic PAH is estimated to have an incidence of approximately 1 case per million, and a prevalence of 7 cases per million, based on national registries in countries with centralized care (16,17). Idiopathic PAH was initially described as a disease of young women. The NIH registry, conducted from 1981-1988, reported a mean age of 36 ± 15 with a female to male ratio of 1.7 to 1 (9). However, patients of both genders and of all ages are affected, and most registries in the modern era report a mean age closer to 50 years (17,18).

Untreated, survival averages around 3 years, and most deaths relate to the development of progressive right heart failure. With current PAH therapies, average survival has improved to approximately six years. Prognosis in other forms of PAH (WHO group 1) is similarly related to right heart function – but in general, connective tissue disease patients have a worse prognosis, while congenital heart disease patients have a better prognosis.

CLASSIFICATION

Wood in 1958 (6) divided pulmonary hypertension into six types (table 2). Mechanistically, these correspond to the three physiologic mechanisms discussed in the introduction: increased left heart filling pressures (passive), increased flow (hyperkinetic) and increased pulmonary vascular resistance, related to chronic PE (obstructive), structural changes in the vasculature (obliterative) or vasoconstriction (vasoconstrictive). Wood also hypothesized that widespread "obliterative" pulmonary vascular disease might potentially complicate virtually all varieties of long-standing, severe pulmonary hypertension, an idea now known to be true.

Table 2: Paul Wood's 1958 Classification

- *Passive,* as seen with increased pulmonary venous pressure due to raised left atrial or ventricular pressure
- *Hyperkinetic,* caused by increased pulmonary blood flow
- *Obstructive,* resulting from pulmonary embolism or thrombosis
- *Obliterative,* manifested by a reduction of pulmonary vascular capacity
- *Vasoconstrictive,* brought about by functional and presumably reversible vasospasm
- *Polygenic,* arising in two or more of the preceding ways

The modern clinical classification system **(table 3)** focuses on the underlying disease, and it is not uncommon for multiple of Wood's proposed mechanisms to be present within one patient. For example, a patient with idiopathic PAH may have a combination of obliterative changes (vascular remodeling), vasoconstriction and obstructive changes (thrombi are common within the small pulmonary arteries, presumably formed *in situ*). Similarly, patients with heart failure and "passive" pulmonary hypertension may also have evidence of vascular remodeling ("obliterative" changes). Current pulmonary hypertension specific therapies are only approved for "WHO group I".

Table 3 Fourth World Symposium Diagnostic Classification of PH (2009)

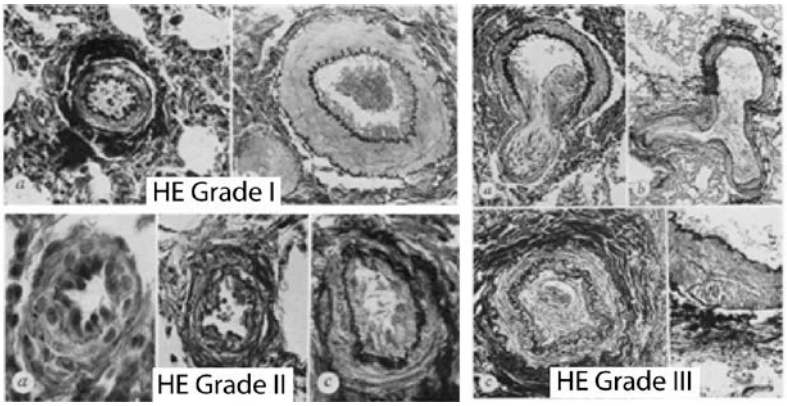
GROUP 1: PULMONARY ARTERIAL HYPERTENSION (PAH)
Idiopathic PAH
Heritable PAH: BMPR2, ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia),
    Unknown genes
Drug- and toxin-induced
Associated with:
    Connective tissue diseases
    HIV infection
    Portal hypertension
    Congenital heart disease
    Schistosomiasis
    Chronic hemolytic anemia*
Persistent pulmonary hypertension of the newborn
GROUP 1′: PULMONARY VENO-OCCLUSIVE DISEASE (PVOD) AND/OR PULMONARY CAPILLARY HEMANGIOMATOSIS (PCH)
GROUP 2: PH OWING TO LEFT HEART DISEASE
Systolic dysfunction
Diastolic dysfunction
Valvular disease

GROUP 3: PH OWING TO LUNG DISEASES AND/OR HYPOXEMIA
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
GROUP 4: CHRONIC THROMBOEMBOLIC PH (CTEPH)
GROUP 5: PH WITH UNCLEAR MULTIFACTORIAL MECHANISMS
Hematologic disorders: myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK1, activin-like kinase type 1; BMPR2, bone morphogenetic protein receptor type 2; HIV, human immunodeficiency virus. *Moving hemolytic anemia to Group 5 has been proposed

PATHOLOGY

In 1958, Heath and Edwards (5) documented the pathology of hypertensive pulmonary vascular disease in a study of 67 patients with congenital heart disease and 2 patients with idiopathic PAH, focusing on the muscular pulmonary arteries 100 to 1000 µm in size. They argued that the progression of lesions in these patients was so stereotyped as to allow division of the structural effects of PAH into six grades:



- **Grade 1**: medial hypertrophy without intimal changes
- **Grade 2**: medial hypertrophy with cellular intimal proliferation
- **Grade 3**: medial hypertrophy, intimal proliferation, and intimal fibrosis
- **Grade 4**: vascular dilation and occlusion by intimal fibrosis (**plexiform lesion)**
- **Grade 5**: appearance of dilation lesions, including vein like branches of occluded pulmonary arteries, complex plexiform lesions, angiomatoid lesions, and cavernous lesions
- **Grade 6**: necrotizing arteritis.

Heath and Edwards lumped the pathology of congenital heart disease and idiopathic PAH together, and large series of patients with the latter disorder were not available until 1970 (7). However, similar vascular changes are present in all forms of pulmonary arterial hypertension (WHO Goup I) (19,20), and histology does not allow differentiation of idiopathic vs. congenital heart disease PAH. Even connective tissue disease PAH cannot be *reliably* differentiated from idiopathic, though inflammatory parenchymal changes are more common. Plexiform lesions are more common in idiopathic PAH, found in 100% of idiopathic PAH and only 66% of connective tissue disease PAH in one recent series (21). Some degree of vascular remodeling also occurs in other forms of pulmonary hypertension (22-24), but the more severe arteriopathic changes (Heath-Edwards grades 4-6) are uncommon. Still, occasional patients with lung disease, left heart disease or chronic thromboembolic pulmonary hypertension have shown these advanced lesions (25). For this reason,

in addition to the risk of lung biopsy in patients with pulmonary hypertension, one rarely obtains pathologic tissue prior to lung transplant or death. Similarly, lung-biopsy in pulmonary hypertension due to congenital heart disease with to left to right shunting is also no longer common.

DIAGNOSIS

A thorough workup including right heart catheterization is required in all patients in whom idiopathic or other PAH (WHO group I) disease is suspected, because it is impossible to distinguish PAH from other forms of pulmonary hypertension on a clinical basis. A diagnostic algorithm has been developed, including basic tests which should be completed in all patients and optional tests to be performed if indicated (**table 4**). The suspicion of PAH (WHO group I) should be based on signs and /or symptoms such as unexplained dyspnea on exertion, chest pain or syncope, lower extremity edema and on the presence of any underlying predisposition: family history, presence of connective tissue disease, congenital heart disease and liver disease. Diet-pill or stimulant use may also raise suspicion, but even with the ~10-fold increased relative risk with these exposures, the *absolute* risk in an individual patient is low.

A similarly thorough work-up will be required in many patients felt to have pulmonary hypertension related to a WHO group II or III condition, but a more limited evaluation may be appropriate in *some* patients with borderline or mild pulmonary hypertension in the setting of known advanced left heart or lung disease and no plans to consider PAH specific therapies (and typically PASP <50 mmHg, normal RV size / function).

Most of the required tests focus on "ruling out" other forms of pulmonary hypertension, and can be remembered by classification system: echocardiogram and catheterization are required to exclude left heart disease; pulmonary function testing, CXR, and oximetry are to look for lung disease; and VQ scan (not CT angiogram) to exclude chronic thromboembolic disease. When specific diseases are suspected, additional tests may be required, such as high resolution CT scan for interstitial lung disease, or a pulmonary arteriogram for suspected chronic thromboembolic disease.

Table 4: Work-up of Suspected PAH

Required Tests	Contingent Tests
History, Physical, EKG	
Echocardiogram (with bubble study)	TEE
PFT and CXR	High resolution CT
Overnight Oximetry	Sleep study
VQ scan	Pulmonary angiogram
HIV, ANA, LFT	Other CTD tests
Catheterization	Shunt run

Additional tests that may be undertaken for *prognosis* rather than diagnosis include a six minute walk test or cardiopulmonary exercise test, and an NT-BNP level (26).

Echocardiogram is a key diagnostic test in the evaluation of PAH, providing an estimate of the pulmonary arterial systolic pressure and ruling out other cardiac conditions such as valvular heart disease and left ventricular systolic or diastolic dysfunction. Current guidelines recommend using echocardiography to estimate the *likelihood* of pulmonary hypertension, based on the Doppler derived peak tricuspid jet velocity (TR jet) and using the equation: right ventricular systolic pressure = [(TR jet velocity)^2 x 4] + estimated central venous pressure (27)

- Velocity <2.8 m.s-1: PASP <37 mmHg; PH unlikely
- Velocity 2.8 - 3.4 m.s-1: PASP 37-50; indeterminate

- Velocity >3.4 m.s-1: PASP>50; probable PH

Importantly, the accuracy and precision of echocardiographic measures have been limited in many studies, and in certain circumstances a decision to proceed with right heart catheterization may be appropriate even with a normal estimated pulmonary artery systolic pressure. It is also important to look for other echocardiographic findings suggestive of PAH. Suspicious findings include dilated right heart chambers, systolic flattening or diastolic bulging of the interventricular septum, and a short PA acceleration time, although in general these tend to be later findings (28).

Echocardiography is also used in estimating prognosis and tracking response to therapy, but importantly, this does *not* include estimated pulmonary arterial systolic pressure, which by itself does not have prognostic value in idiopathic PAH (though it *does* have value in other forms of pulmonary hypertension, where average pressures are lower and right heart failure is less common). Instead, echocardiographic measures suggesting right ventricular failure should be looked for, such as dilated right heart chambers, reduced right ventricular systolic function, significant tricuspid regurgitation, marked septal shift with a small left ventricular chamber, and a pericardial effusion (29).

In the evaluation of suspected idiopathic PAH, right heart catheterization is mandatory to document the presence and severity of pulmonary hypertension, rule out left heart disease, and to determine if there is acute pulmonary vasoreactivity using pharmacologic agents. Hemodynamic values, especially right atrial pressure and cardiac index, correlate closely with survival (10,30). Pulmonary arterial hypertension is defined hemodynamically as:

- Mean pulmonary arterial pressure $\geq$ 25 mmHg
- Pulmonary capillary wedge pressure $\leq$ 15 mmHg.
- $\pm$ Pulmonary vascular resistance (PVR) $\geq$ 3 Wood units

The PVR requirement has been included in some but not all definitions, but the vast majority of patients with PAH will easily meet this cutoff at diagnosis, with average a PVR in idiopathic PAH in the range of 12 Wood units or higher (18,22,31).

The measurement of the pulmonary capillary wedge pressure ("wedge" pressure) in pulmonary hypertension deserves extra attention, because a reading above 15 mmHg suggests a diagnosis of left sided heart disease rather than idiopathic PAH, and because accurate measurements can be difficult to obtain. The wedge pressure measurement is obtained by transiently occluding blood flow in the pulmonary artery using an inflated, balloon-tipped catheter. Problems can arise because of incomplete occlusion, resulting in a blunted PA pressure measurement rather than a true wedge pressure measurement, or because the catheter tip is not located centrally within the pulmonary artery. Visual inspection of the catheter location under fluoroscopy and ensuring that the resultant pressure tracings are consistent with an atrial pressure waveform help to ensure an accurate reading. In some cases, a better wave-form may be obtained by partially deflating the balloon and repositioning it and / or obtaining a reading in the opposite lung. Additionally, an accurate wedge pressure tracing is also more likely when highly oxygenated (capillary) blood can be aspirated through the catheter. Because this measurement is so critical to the diagnosis, some centers routinely perform left ventricular end diastolic pressure measurement during all diagnostic right heart catheterizations.

TREATMENT

Idiopathic and other forms of PAH are now treatable diseases. Clear-cut short- and long-term benefits are seen with currently available therapies (32). Therapy for idiopathic PAH may be subdivided into "supportive" or "conventional" therapies, defined as empirical treatments or recommendations for which there is no prospective, randomized, controlled data, and "specific" or "targeted" therapies, which have been tested and approved by regulatory authorities for the treatment of PAH.

Supportive Therapies

Exercise and Physical Activity

There is no evidence-based guidance regarding physical activity or exercise in PAH. Consensus guidelines permit exercise, recommending only that patients should avoid activities that lead to undue symptoms such as severe dyspnea, chest pain, light-headedness, or syncope. Low- to moderate-levels of exercise to prevent deconditioning and improve mental outlook are appropriate, and small studies (N=22 to 30) suggest supervised exercise training can lead to measurable improvements in 6-minute walk distance and peak oxygen consumption vs. controls (33,34). No significant changes in echocardiographic measures of right heart function or in brain natriuretic peptide levels were identified during these studies.

Avoidance of Altitude and Oxygen

Hypobaric hypoxia causes pulmonary vasoconstriction and, thus, can worsen pulmonary hypertension and lead to symptomatic worsening in PAH patients. It is generally recommended that patients flying on commercial airliners (pressurized to 1500–2400 m) or traveling to elevation above 5000 feet be evaluated for supplemental oxygen (35). Patients with severe PAH residing at high elevations may improve if they move to sea level. The benefits of supplemental oxygen in PAH patients, unlike patients with pulmonary hypertension associated with lung diseases such as chronic obstructive pulmonary disease (COPD) (36,37), are not clear. However, the consensus is that if arterial P_{O_2} is less than 60 mm Hg or systemic arterial O_2 saturation is less than 90% at rest, supplemental oxygen is indicated. One exception to this approach is in patients with Eisenmenger's syndrome, with hypoxemia due to right-to-left shunting. In this group, the use of supplemental oxygen remains controversial (38,39). There is also no general agreement about whether exercise-only systemic arterial O_2 desaturation warrants oxygen supplementation.

Avoidance of Pregnancy

Pregnancy and especially delivery are extremely risky in patients with PAH (40). Although there are case reports of patients managed with epoprostenol and undergoing successful pregnancies and deliveries (41,42), it is strongly recommended that women of childbearing potential use appropriate methods of birth control to avoid pregnancy.

Warfarin and Aspirin

There is strong *rationale* for the use of anticoagulants in PAH, but no clinical trial evidence of benefit. Many of the endothelial cell abnormalities that predispose patients to pulmonary arteriopathy also increase thrombosis. In addition, microscopic thrombotic lesions are seen in the pulmonary vasculature. Warfarin is the anticoagulant most frequently used in patients with PAH. In PAH clinical trials registries, about 50% to 85% of patients are on anticoagulants at study entry (43). However, anticoagulation has risks (i.e., bleeding). Eight studies have examined the effects of warfarin in idiopathic PAH. None were randomized or controlled, few were conducted in the

modern era of PAH therapies, and many did not attempt to control for PH severity (44,45). Overall, better survival was seen in patients on warfarin in 5 of 8 studies. However, one of the larger and more recent papers found the opposite, though this increased risk disappeared after adjusting for baseline severity (45). Despite the serious limitations in the existing data, published guidelines recommend that patients with idiopathic PAH be treated with warfarin (26,27), and suggest that anticoagulation may be considered in other forms of PAH. Given the limitations in the data, our own practice is to have a discussion of the potential risks and benefits. Aspirin has also been considered potentially beneficial in PAH, based on evidence of platelet activation in PAH and on evidence of improved outcomes in animal models (46). However, its use did not lead to improved outcomes in a randomized controlled clinical trial in PAH and it is therefore not recommended for the treatment of PAH (47).

Diuretics

Diuretics have long been a mainstay of therapy for heart failure, including right ventricular failure. Both total-body and intravascular volume overload are common in PAH patients. In pivotal trials of PAH drugs, the majority of patients entered the studies on chronic diuretic therapy (48,49). Despite the perceived benefits of diuretics in PAH patients, there are no controlled studies to guide the clinician in using these agents.

Calcium Channel Antagonists

In 1958, Paul Wood (3) first defined the clinical entity of pulmonary hypertension with reference to the "vasoconstrictive factor." It is not surprising, then, that a search for pulmonary vasodilators as effective therapies ensued, with a wide variety of agents evaluated in generally uncontrolled, observational studies. Out of the myriad of oral antihypertensive agents emerged calcium channel blockers. In a highly quoted paper, Rich and associates (11) described favorable survival in a subgroup of idiopathic PAH patients with a positive vasodilator response (20% fall in PA mean) who were treated with either diltiazem or nifedipine. This study, although seminal, likely led to overuse of calcium channel blockers, not only for idiopathic PAH but for other forms of PAH as well. Calcium channel blockers are not selective pulmonary vasodilators, and in the patient with minimal or no acute pulmonary vasoreactivity, the negative effects of calcium channel blockers can become predominant, with potential for catastrophic consequences. **A subsequent retrospective study (50) has further narrowed the role of calcium channel blockers: they can be considered in *idiopathic PAH* patients with a vasodilator response consisting of a ≥ 10 mmHg drop in PA mean pressure, a final PA mean pressure <40 mmHg, and no drop in cardiac output**. This more strict definition of a "responder" is based on a high failure rate in their study using the Rich et al definition, with better outcomes among those who met the more stringent definition. Independent validation has not been completed, but current evidence-based guidelines (27,51) have utilized this definition. The method for performing acute pulmonary vasoreactivity testing varies among pulmonary hypertension centers, but inhaled nitric oxide is preferred due to is established track record and absence of systemic effects.

Treatment: PAH Specific Therapies

PAH-specific therapies have been available since 1995, when intravenous epoprostenol was approved by the U.S. Food and Drug Administration (FDA), based on the first phase 3 prospective randomized, controlled trial done in PAH. Since then, an additional eight therapies have been approved for PAH: prostacyclin analogs (subcutaneous, intravenous and inhaled treprostinil, inhaled iloprost), endothelin-1 receptor antagonists (bosentan, ambrisentan), and phosphodiesterase-5 inhibitors (sildenafil, tadalafil). These therapies were developed to offset the imbalance in

endothelial derived mediators seen in PAH: excessive endothelin-1 production, deficient prostacyclin, and abnormal nitric oxide production.

Table 5: Medical Therapy for Pulmonary Arterial Hypertension	
Medication	**Dose (per package insert)**
Bosentan (Tracleer) ERA	Start 62.5 mg po bid. Increase to 125 mg po bid after 4 weeks
Ambrisentan (Letairis) ERA	Start 5 mg po qAM; consider increasing to 10 mg
Sildenafil (Revatio) PDE5i	20 mg by mouth three times daily. Up to 80 tid studied
Tadalafil (Adcirca) PDE5i	40 mg daily
Iloprost (Ventavis) inhaled. PGI2 analog	2.5 μg Inhaled 6 to 9 times daily; if tolerated increase to 5 μg 6 to 9 times daily
Treprostinil (Tyvaso) inhaled. PGI2 analog	Up to 9 inh Qid
Epoprostenol (Flolan / Veletri) iv. PGI2	Initiate at 2 ng/kg/min. Can increase every 15 minutes until dose limiting side effects occur†, though most go slower.
Treprostinil (Remodulin) iv / sc. PGI2 analog	Package insert: start at 1.25 ng/kg/min and increase by no more than 1.25 ng/kg/min weekly. Faster is common, however

†Intravenous epoprostenol and treprostinil dosing varies. ERA: endothelin receptor antagonist

Initial therapy decisions are based on a patient's overall mortality risk. Survival rates are known to be lower in patients with more advanced functional class (III/IV), clinical signs of right heart failure, more severe impairment in exercise capacity, and catheterization findings of poor cardiac function, including high right atrial pressure, low cardiac output, and low SVO2. Higher risk patients are usually started on iv therapy, while lower risk patients are started on oral therapy. Combination therapy is considered when response is inadequate, though guidelines are somewhat vague as to how this should be determined. Finally, for patients with persistent right heart failure, lung transplantation is considered.

DEVELOPING NOVEL THERAPIES

Early Phase Studies

The development of novel therapies involves four phases. Phase 1 clinical trials look at pharmacokinetics and safety, and are often conducted in healthy volunteers. Phase 2 involves testing for efficacy, but in a small-scale, preliminary way. It is also often an opportunity to test a protocol prior to the larger and more expensive phase 3 study, but the primary endpoint may be a surrogate measure and a control group may or may not be utilized. Phase 3 studies involve larger numbers and are intended to establish efficacy, while phase 4 studies are post-approval studies.

However, early pulmonary hypertension "studies" were much less formal, and randomized, controlled clinical trials are actually a relatively recent phenomenon in this field: studies in the 1980s were typically open label acute hemodynamic or open label observational studies of medications, often ones that were already approved for other uses. Most were vasodilators, and the list of agents that were studied is long: phentolamine, tolazine, captopril, hydralazine, calcium channel blockers, ketanserin (a serotonin 2A receptor antagonist), and others, and then eventually, intravenous epoprostenol.

Finally in the late 1980s, more controlled investigations began to be performed. One of the earliest was a randomized but open label study of epoprostenol involving 20 patients with idiopathic PAH.

This study looked at both acute hemodynamics and hemodynamics and 6MWD after 2 months, showing improvement (tested vs. baseline, interestingly) in both but with little correlation between hemodynamic improvement and 6MWD improvement (52).

Subsequently, phase 2 PAH trials have often been conducted in a similar manner, utilizing hemodynamics + walk distance as endpoints. Some but not all phase 2 studies have included a control group. A few medications were developed without a true phase 2 study - typically second in class medications. Although this did work out in several cases, in others tolerability and other dosing issues were not identified until the large phase 3 study was conducted.

Prior to making it to this stage of investigation, promising agents need to be identified based on pre-clinical studies. Identifying potentially efficacious medications in PAH has been difficult, though not for lack of candidates – there are many candidate drugs – but because:

1. The common animal models (hypoxia, monocrotaline) don't replicate idiopathic PAH very well, and are not particularly discriminatory
2. More recent animal models have not yet been adequately vetted. They *look* under the microscope more like idiopathic PAH. But we still are not sure what that means
3. In some settings, receptors vary across species – see serotonin example below.

***Serotonin signaling as an example*:**

Altering serotonin signaling has long been of interest in the PAH field, based on the identification of serotonergic effects of the aminorex and fenfluramine diet-pills. The receptors were the first object of interest, as fenfluramine increases circulating serotonin levels and increases serotonin receptor signaling. Two drugs have been studied: ketanserin, a serotonin 2A receptor antagonist, and terguride, a serotonin 2A / 2B receptor antagonist. Interestingly, although serotonin 2A antagonists are effective in animal models, this receptor only causes vasoconstriction in *human* lungs when serotonin levels reach >100 nM. In contrast, the serotonin 1B receptor is active at 10-fold lower levels. This of course was not known at the time of the ketanserin studies, though the results (greater systemic effects, significant hypotension, modest reduction in PVR) could have been predicted by what we *now* know about the human serotonin 2A receptor signaling, including its greater effects on the systemic circulation.

The decision recently to proceed with studying terguride, a 2A/2B antagonist study is a little more puzzling: the serotonin 2B receptor is present in human lungs, and is upregulated in hypoxia – but its function has only been studied in other species. Further, while the 2B receptor causes vasoconstriction in *most* species, it has counter-regulatory effects through endothelial signaling in some. In any case, terguride was ineffective in humans in a moderate sized study in PAH.

Because the global effect of serotonin signaling in the lungs is vasoconstriction in every species studied to date, there continues to be interest in this area. Potential targets include the serotonin 1B receptor, the serotonin transporter, involved in pulmonary artery smooth muscle cell growth, and the synthesis of serotonin in the periphery.

Fluoxetine in the treatment of PAH

Selective serotonin reuptake inhibitor (SSRI) antidepressants such as fluoxetine block the cell surface serotonin transporter, reducing serotonin uptake into multiple cell types including nerves, neuroendocrine cells, pulmonary artery smooth muscle cells (PASMC) and platelets. By blocking uptake into PASMCs, SSRIs reduce pulmonary artery smooth muscle cell proliferation *in vitro*,

reduce pulmonary vascular remodeling in both hypoxic and monocrotaline pulmonary hypertension, and long-term, lower pulmonary arterial pressures on animals. Observational studies in human subjects with pulmonary hypertension are mixed - SSRI use may have a beneficial effect on survival in adults (hazard ratios for mortality of 0.53 (95% CI 0.07-3.9) and 0.35 (95% CI 0.14-0.87) in two studies), but may increase risk of pulmonary hypertension in neonates; randomized controlled clinical trials are lacking.

In order to further evaluate the hemodynamic effects of fluoxetine, and using a pilot award from UTSW, I performed an open label study of fluoxetine in PAH (N=5) with hemodynamics before and after 3 months of fluoxetine. Pulmonary vascular resistance fell 16% (p=NS) and cardiac index increased 19% ($p<0.05$), while six minute walk distance results and QIDS-SR depression scale results showed no significant change. Overall, it remains unclear whether manipulation of serotonin signaling will be beneficial in PAH, and additional studies are needed. Interestingly, there is cross-talk between receptors and transporters – so a global approach, though more complicated, may be required.

Table 6: Serotonin Studies in Animals and Humans

	Human PA *in vitro* data:	Human *in vivo* data	Other / animal
1B receptor	Vasoconstriction at [5HT] ≥10 nM	Naratriptan (1B agonist) increases PAP 25% in normals; no antagonist studies	Mixed results in hypoxia, no monocrotaline studies. Combination with SSRI: greater improvement in PH in animals.
2A receptor	PA Vasoconstriction at [5HT] ≥100 nM. ++ systemic effects	Ketanserin (2A antag) lowered PVR ~10%; caused hypotension	More important *pulmonary* vasoconstrictor in other species. Ineffective in hypoxia models; prevents but does not reverse monocrotaline PH
2B receptor	Function unclear. *Loss* of function mutation found in one PAH patient	Terguride (2A/2B antagonist) was ineffective in a 12 week PAH trial	Promotes growth in *animal* PASMC / counter-reg. endothelial receptors seen in some species. Prevented PH in hypoxia model.
5HT Trans-porter	Promotes growth in human PASMC	No published data for SSRI; circulating serotonin levels do *not* stay elevated	Over-expression in animals causes PH / SSRI treats PH in both hypoxia, monocrotaline models

Phase 3 and 4 Studies

Following the small phase 2 study of epoprostenol that was published in 1990, a larger study was undertaken where 81 patients with idiopathic PAH and NYHA class III or IV symptoms, despite treatment with conventional therapy, were randomized to either continuous intravenous epoprostenol plus conventional therapy or conventional therapy alone for 12 weeks (48,52). The primary end point was change in 6-minute walk distance (6MWD). At 12 weeks, 6MWD had improved in the continuous intravenous epoprostenol group by 32 m and decreased by 15 m in the conventional therapy group ($p<0.05$). There were also significant improvements in the epoprostenol group in hemodynamics, quality of life and NYHA functional class. Eight patients died during the 12-week study and all were in the conventional treatment arm. Notably, this is the only PAH trial ever to show, compared with a control group, a beneficial effect on survival. Despite what looks like a very positive study (vs. other PAH trials), there was serious consideration about rejecting the application, based mainly on whether the benefit in 6MWD, the primary endpoint, met usual criteria for a phase 3 clinical trial (see endpoint section, page 15). Ultimately the drug *was* approved – and almost all subsequent phase 3 clinical trials in PAH have utilized 6MWD as the primary endpoint.

A later study in scleroderma PAH found a significant improvement in 6MWD, functional class and exercise capacity in these patients as well (53). Long-term follow-up studies suggest sustained benefits, including improved functional class and improved survival at 1, 2 and 3 years compared with historical controls. Five-year survival of approximately 60% has been seen in treated patients in two series (30,54). Despite its benefits, chronic use of epoprostenol is complex and requires an indwelling central venous catheter, continuous-infusion pump, and daily preparation of the medication. In addition numerous side effects including jaw pain, leg and foot pain, diarrhea, rash, and weight loss occasionally with ascites occur.

Table 7: Randomized Controlled Clinical Trials in PAH – Approved Drugs

	N	Wks	Back-ground Rx (%)	Δ6MWD , vs. placebo (m)		FC	QOL	Cath	CW	NT-BNP
Prostacyclins										
'96 Epoprostenol IV	81	12	-	60	Y♦	Y	Y	Y	Y	
'00 Epoprostenol IV	111	12	-	108	Y♦	Y		Y		
'02 Treprostinil SC	469	12	-	16	Y♦		Y	Y		
'02 Iloprost Inh	203	12	-	36	Y*		Y	Y	N	
'10 Tre INH / TRIUMPH1	235	12	100	20	Y♦	N	Y		N	Y
Endothelin receptor antag										
'01 Bosentan	32	12	-	76	Y♦	Y		Y	Y	
'02 Bosentan	190	16	-	44	Y♦	N			Y	
'08 Ambrisentan-1	202	12	-	5mg 31 10mg 51	Y♦	Y	N		N	Y
'08 Ambrisentan-2	192	12	-	5mg 59	Y♦	N	Y		Y	Y
PDE-5 Inhibitors										
'05 Sildenafil	278	12	-	45	Y♦	Y		Y	N	
'09 Tadalafil	405	16	53	33	Y♦	N	Y	Y	Y	
Non-approved drugs + phase IV bosentan										
'06 Bosentan, congen	54			53	Y	?		Y♦		
'08 Bosentan, FC II	185	24	16	19	N♦	Y	Y	Y♦	Y	Y
'13 Tre po /FREEDOM M*	349	12	-	23	Y♦	N			N	
'13 Tre po /FREEDOM C*	350	16	100	16	N♦	N			N	

Y: p<0.05; N: p=NS; ♦ 1° endpoint; N Number ; Wks: weeks; Rx: Treatment; FC: functional class. QOL: quality of life. CW: clinical worsening / mortality. ? Measured, but no statistical test reported

Overall results

Subsequent phase 3 studies have shown benefit for nine medications across three classes (table 7): intravenous prostacyclins (n=2), subcutaneous prostacyclins (n=1), inhaled prostacyclins (n=2), oral endothelin antagonists (n=2), and oral phosphodiesterase-5 inhibitors (n=2). As shown in the chart above, all three classes of PAH medications have been shown to improve exercise capacity, functional class, quality of life, hemodynamics and possibly time to clinical worsening at 12-16 weeks of therapy. Overall:

- Survival has improved vs. historical controls (30)
- Survival in RCTs is better in the treatment arm, based on meta-analysis (32)
- Survival in functional class III patients treated with an "oral therapy first" approach has similar survival to that of an iv only approach – based on historical data (55)
- Improvements in exercise capacity seem to be sustained over ~two years follow-up, at least for the ~80% of patients who remain on drug

As a result, PAH treatment is now recommended for all patients with WHO group I pulmonary hypertension.

Drug Development – Combination Therapy Studies

There has also been a great interest in combining two or more therapies, based on other fields (HIV, cancer), animal data, and the limited response to one drug. These studies were initially conducted as phase 4 studies (post-approval studies). As time has gone on, phase 3 studies have more often allowed background therapy, both for ethical and practical reasons.

Results suggest that combination therapy does work well, at least from a hemodynamic standpoint: all but one placebo controlled study that has looked at combination therapy has shown greater improvement ($p<0.05$) in hemodynamics, usually PVR ± cardiac output, PA mean etc. Further, the one that failed from a statistical standpoint still showed a trend toward greater improvement in PVR with combination therapy (-36% vs. -23%, p=0.08). Translating this into *clinical* evidence of benefit, however, has been more variable. Although walk distance has consistently favored the treatment group in all moderately large or larger studies (>50 patients), the effect size is smaller than what is seen in treatment naïve studies. Improvement in secondary endpoints has also been weaker. At some point one begins to question the *meaning*, from a clinical perspective, of very small amounts of improvement in 6MWD. Notably, one medication (oral treprostinil) was recently rejected after showing a modest but significant improvement in 6MWD in a treatment naïve study and an even smaller and non-significant increase in 6MWD in combination studies. Similarly, an application for a second medication (imatinib) was withdrawn after meeting its primary endpoint (6MWD) but with a concerning safety signal. As a result, use of alternative endpoints has recently been a very hot topic of discussion in this field.

Table 8: Combination Therapy Studies

Trial (phase)	N	Wks	Back-ground Rx (%)	Intervention	6MWD (m), vs placebo		FC	QOL /DFI	Cath	CW	NT-BNP
Phase 4 Studies											
'04 BREATHE2	33	16	-	Epo ± bosentan	-6	N	N		T♦		
'06 STEP	67	12	100	±Iloprost inh	26	T♦	Y		Y	Y	
'06 COMBI	40	12	100	±Iloprost inh	-10	N♦	N	N		N	
'08 PACES	267	16	100	±Sildenafil	29	Y♦		Y	Y	Y	
XX SR-PASS3 (stopped early)	131	~21	Varied by SRPASS1 status; Study: sitaxentan ± sildenafil		31	Y	N	Y		N♦	
Phase 2 and 3 Studies											
'10 TRIUMPH1	235	12	100	± treprostinil inh	20	Y♦	N	Y		N	Y
'11 PHIRST(ERA-sub)	216	16	100	± Tadalafil	23	T♦	N	?		N	
'12 Selexipag (phase 2)	43	17	100	± Selexipag	24	N	N		Y♦		N
'13 FREEDOMC	350	16	100	±treprostinil po	16	T♦	N	Y		N	
'13 IMPRES	202	24	100	± Imatinib	32	Y♦	N	?	Y	N	?
XX SERAPHIN	742	~105	64	± Macitentan	15	Y				Y♦	

Y: p<0.05; N: p=NS; T: trend (p=0.05-0.1); ♦ 1° endpoint; N Number ; Wks: weeks; Rx: Treatment; FC: functional class. QOL: quality of life. CW: clinical worsening / mortality. ? Measured, but no statistical test reported CW: clinical worsening

ALTERNATIVE ENDPOINTS

Guidelines on drug approvals in the US are based on a 1962 amendment to the food, drug and cosmetics act stating that medications are to be evaluated in "adequate and well-controlled trials" showing "substantial evidence" of effectiveness. While this is often interpreted to mean "survival"

or at least a composite based on serious events like "survival or myocardial infarction or stroke", the FDA's own guidelines suggest that this should be interpreted as requiring evidence of benefit to the patient in how they **feel, function or survive**. In other-words, improvement in shortness of breath (feel), exercise capacity (function), or survival might all be considered as candidate end-points for a phase 3, pivotal trial of a novel therapeutic, assuming they also meet requirements of being **measurable, interpretable and sensitive** – but hemodynamics, HIV viral load, BNP levels, troponin levels, right ventricular systolic function, and tumor size on imaging could not be used as endpoints, at least not in trials following the *regular* approval process.

Table 9: Definitions Related to Clinical Trial Endpoints (56,57)

1. **Clinical endpoint**: Measurement providing information on how a patient **feels, functions, survives.** Should also be measurable / interpretable, and sensitive.
2. **Biomarker:** A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. *Should be able to be measured accurately and reproducibly.*
3. **Surrogate endpoint:** Measurement providing early and accurate prediction of both a clinical end point, and the effects of treatment on this end point. *Frequently useful clinically because it can be measured earlier, more conveniently, or more frequently than the endpoint of interest*
4. **Validation of a surrogate (definitions vary):** Confirmation by robust statistical methods that a candidate prognostic biomarker, predictive biomarkers or surrogate end point fulfills a set of conditions that is necessary and sufficient for its use. *Requires many studies showing that the surrogate predicts the clinical endpoint, that treatment has a significant effect on both the surrogate and the endpoint, and that the treatment effect on the surrogate should capture the full effect of the treatment on the clinical endpoint – though the latter requirement is frequently lessened to "the effect of the surrogate on the intervention is sufficiently correlated with the effect on the true end-point"*
5. **Minimally important difference (MID) –** the smallest difference that patients perceive as beneficial and that would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management. *Determination of the "MID" has received considerable attention in recent years, particularly with regard to patient reported outcomes. Such a determination isn't needed with easy to understand endpoints such as mortality. Instead, results are put into perspective by calculating relative risk reduction, absolute risk reduction, and number needed to treat. When dealing with other difficult to interpret outcomes, calculation of the MID can be helpful, using either defined statistical methods that depend on the variability in the measure that occurs within a given individual, or with "anchor"-based methods that look to an external outcome that is clinically important.*

The latter are all biomarkers (and in some cases surrogates), and the use of surrogate end-points in clinical trials is not allowed by the FDA unless it is considered a validated surrogate (table 9). In occasional circumstances, an exception is made and a surrogate that is "reasonably likely" to predict the ultimate clinical outcome is allowed instead. This exception can be granted in life threatening conditions where there are no approved therapies, if the FDA agrees to allow the less stringent level of evidence. Typically this is for drugs being evaluated in an accelerated approval program. This has applied predominantly to cancer and to HIV, and even in these settings, post-approval clinical trials are still required later in order to more unequivocally show benefit.

For pulmonary hypertension, walk distance does not even seem to meet the "reasonably likely" definition, at least based on what we currently know. Interestingly, based on conversations with some of the participants, it seems that the initial choice of walk distance in the epoprostenol pivotal

trial (vs. hemodynamics) was because 6MWD is not *completely* a biomarker / surrogate. It does have value as a semi-direct measure of "function", i.e. exercise capacity.
Six minute walk distance (the absolute value) correlates moderately well with quality of life and functional class, and predicts survival (58). However, the meaning of any given *change* in 6MWD is not obvious, and until recently had not been explored in any depth. Two recent studies put the meaning of changes in 6MWD into better perspective:

- Mathai et al found a "minimally important difference" (see table 9) for 6MWD in PAH of around 33 meters, using anchor based methods with the SF-36 physical score. Similar results were found using distributional measures (59).
- Seperately, Gabler et al reported that a cutoff of 41 meters predicted a reduction in short-term clinical events, based on a meta-regression analysis of 10 randomized controlled clinical trials (60). Other results:
    - PAH therapies reduce clinical events (OR 0.43 (95% CI 0.31-0.59)
    - PAH therapies have an effect on 6MWD: mean 22.4 m, $p<0.05$
    - The proportion of the reduction in clinical events *accounted* for by the Δ6MWD was modest: 22%.

Consistent with this poor correlation between 6MWD change and clinical events, a recent large morbidity and mortality study found only a 15 meter improvement in 6MWD at 6 months, but long-term clinical worsening fell by an impressive 45%, even with a majority of patients on background therapy (see Seraphin study below).

The response within the pulmonary community to these reports on 6MWD has sometimes been a bit simplistic "See, walk distance is stupid. It's a "soft" endpoint and we should use "hard" endpoints like (insert favorite biomarker) – hemodynamics, RV function, etc". But the answer is not that easy – as noted above, these are surrogates – and even with a supposedly validated surrogate (which these are not), you will still never be certain that a novel drug class won't have completely other off-target effects that will not be identified if looking only at the surrogate.

Potential Alternative Endpoints
Identifying endpoints in PAH that are clinically relevant, sensitive to treatment effect, measurable and interpretable, *and* can be utilized in a rare disease where clinical trial size is limited has been difficult. Large changes in six minute walk distance meet some of these criteria, but small changes may not, based on both "minimally important difference" estimates, and probably from the standpoint of just "does this make sense" – there is *some* measure of 6MWD below which we should reject outright as a positive finding. Alternatives that have been proposed include

- Composite endpoints related to clinical worsening
- Alternative measure of exercise capacity (CPX based measures usually)
- Quality of life measures, as reported by the patient such as the SF-36 or a PH specific instrument
- Functional assessment by the physician, such as with functional class

Functional class (New York Heart Association functional class): The inhaled iloprost pivotal trial set a primary endpoint of a 15% improvement in walk distance + improvement in functional class. This worked, and on some level makes more sense than walk distance alone. But it does not seem to be particularly sensitivity to change, particularly in patients already on background therapy.

Almost no class II patients improve to class I, simply because even when we normalize PA pressures (which is uncommon) – patients still have symptoms with exertion, even when they feel much better. And patients who improve from "late class III" to "early class III" (using semi-official but not studied in PAH 3a and 3b terminology) seem quite different in their satisfaction with their disease state. Finally, it's not very reliable, with poor inter-observer reliability scores.

Other measures of exercise capacity seem unlikely to be the best option either. A few studies have used a cardiopulmonary stress test (CPX) endpoint, and found it did not perform as well as 6MWD even in the US. Performance was better at centers that regularly performed CPX in PAH prior to the clinical trial – but phase III PAH studies are now usually world-wide efforts – making this a poor option except perhaps in small early phase studies. Even aside from the technical aspects, exercise capacity alone does not seem to fully capture the patient experience. This is supported by the finding that 6MWD accounted for only a small portion of the improvement in time to clinical worsening seen in the meta-analysis described earlier.

Patient reported outcomes

Another option that has been discussed is the use of patient reported outcomes (PRO). PROs are any report of the status of a patient's health that comes directly from the patient. The FDA has provided some guidance recently (2009) on the use of PROs in clinical trials (61). This area of research probably comes across as a bit foreign to the average clinical investigator, as one can't intuitively know what a 2 point improvement on an arbitrary scale means. Nevertheless, if done well, it does get to the heart of what matters to patients. However, disease specific measures are preferred, but there are currently no disease specific instruments that were developed utilizing the FDA recommended process (though one is under development).

Table 10: Terminology in Patient Reported Outcomes Studies

	Definition and Comments (italics)
Instrument	The questionnaire plus the documentation that supports its use
Reliability	
Test retest reliability	Stability of scores over time when no change is expected. *Most informative when the time interval is long enough to minimize memory effects. Proving test-retest reliability can be difficult for remitting and relapsing diseases. On the other hand, flaws in reliability tend to increase type II errors, and false positive results are unlikely.*
Internal consistency	Extent to which items representing a scale measure the same concept.
Validity	
Face validity	Test "looks like" it measures what it is supposed to measure
Content validity	Evidence that the instrument measures the concept of interest including that the items are appropriate and comprehensive. Evidence to support this includes qualitative studies showing that the items and domains of the instrument are appropriate and comprehensive relative to its intended use. *Typically means item generation includes input from the target population, all aspects of the concept that are important to patients are covered, and saturation was reached during qualitative interviews*
Construct validity	Evidence that relationships among items, domains and concepts conform to *a priori* hypotheses concerning logical relationships that should exist with other measures or characteristics of patients or patient groups. *Major component of PRO "validation", as gold standards are rare (see criterion validity below)*
Criterion validity	Extent to which the scores on a PRO instrument are related to a known *gold standard* of the same concept. *Often not available – example would be comparing a sleep scale as a measure of obstructive sleep apnea, vs. formal polysomnography*

Developing a PRO is an iterative process that starts with figuring out what is important – a general framework of symptoms and limitations may be developed by the clinicians, but ultimately patient interviews, focus groups and qualitative cognitive interviews are undertaken to develop a more complete understanding. Occasionally the result will be a single item of interest (pain intensity), but usually multiple items will be identified. During the confirmatory process, items are tested and may be rejected for lack of relevance, clarity, limited response range, poor reproducibility or inability to detect change, among others. Currently available PROs have been used in PAH as a secondary endpoint, including the SF-36, EURO-QOL, St. George's Respiratory Questionnaire, Minnesota Living with Heart Failure Questionnaire, and CAMPHOR, a PH specific questionnaire.

Composite Endpoints:

Finally, composite endpoints have been utilized in one completed and two ongoing trials. These trials are larger (one over 1000 patients), longer, expensive, and more complicated, both from a conduct standpoint (dropouts become a problem) and from a choice of endpoint / analysis standpoint. When utilizing a composite endpoint in a clinical trial, guidelines suggest that each component should itself be clinically meaningful, and ideally, each component should be approximately *equally* meaningful. When not equally meaningful, "success" should not be concluded if driven by a less meaningful component if there is evidence of a therapeutic disadvantage on a more meaningful component.

Seraphin (N=742), the recently completed study, looked at macitentan, a novel endothelin-1 antagonist, in PAH. The definition for clinical worsening used in this study included:

- All cause death
- Atrial septostomy
- Lung transplantation
- Initiation of iv therapy
- Other worsening PAH, to include *all* of the following
    - 15% decline in 6MWD
    - Increased FC or new signs of RV failure
    - Need for new PAH therapy

Overall results were positive: Improvement in 6MWD at 6 months (a secondary endpoint) was only 15 meters, but a 45% decline in clinical worsening was seen. A significant reduction on a separate composite "death or hospitalization for PAH" (a secondary endpoint) was also seen, suggesting that whatever benefit the drug has is not trivial.

Moving forward, concerns that have already been noted include (1) With this composite, most events will be driven by the relatively less important endpoint: "other worsening PAH", (2) PAH studies in general have not been following patients who drop out in a very comprehensive way (essentially violating intention to treat principles).

Improving the dropout rate and subsequent problems from an intention to treat standpoint will require that patients who quit taking the study medication be followed, rather than simply allowed to exit the study and marked as a "withdrawal of consent". And the usual ability to cross-over into active treatment may need to be reconsidered. For some ongoing studies, the follow-up modification has been made midway through (not perfect, but will still yield better data), and in the future greater care will clearly need to be taken.

For the definitions and make-up of the composite itself, future studies will need to consider this carefully. Are we happy with "other worsening PAH" including its reliance on 6MWD and functional class? Or can we do better? Without some type of "other worsening" criteria, studies may be underpowered – though substituting hospitalization might work in some cases, particularly for more advanced disease patients. Potential "other worsening" definitions might also make use of quality of life measures, alone or in combination with 6MWD, particularly if better validated instruments become available.

Conclusion

The latest consensus algorithm on treatment was published in 2009, a point at which combination therapy was becoming increasing likely. These guidelines recommend that lower risk patients be initiated on oral therapy, higher risk on intravenous or subcutaneous therapy, and those failing to respond "adequately" be considered for combination therapy. At our own PAH center, we currently have a lower threshold for adding a second agent in persistently symptomatic patients (which is really almost everyone), based on the growing number of clinical trials including particularly time to clinical worsening studies showing add-on therapy can be beneficial. For future studies in PAH, there seems to be a growing awareness of the areas we can improve in (dropouts, endpoints), and a hopefully overall improvement in the quality of clinical trials in this area.

For Non-WHO group I patients, trials are limited and therapy is much less certain. These patients have recently been included in a few clinical trials, with an inoperable chronic thromboembolic disease study the only unequivocally positive study. Riociguat, a direct guanylyl cyclase activator, had positive results in studies in both PAH and CTEPH, and will go before the FDA this fall. For groups 2 and 3, there is very little data to support PH therapies - there is one positive single center study with sildenafil in heart failure with preserved ejection fraction that included patients with advanced RV failure, but a negative multicenter study followed, including patients with mild (or no) pulmonary hypertension, based on their mean echo PASP of 40 mmHg. Similarly, sildenafil was ineffective in idiopathic pulmonary fibrosis (non-PH study), but in a post-hoc analysis, those with evidence of RV failure seemed to benefit. For the moment, therapy is not recommended.

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