Evolution in PH Care: 3 Decades of Milestones

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PRE-1990 PULMONARY HYPERTENSION: NO DRUGS, NO CARE, NO SOCIETIES, NO HOPE

At the first world symposium on pulmonary hypertension (PH) in 1973, at a time when knowledge of pulmonary vascular disease was limited, experts convened to review scientific information and to discuss epidemiology, pathophysiology, and clinical aspects of PH and reported their proceedings.[1] From this symposium came the first published attempt at classifying PH subtypes (Table 1). Without treatments for PH, however, knowing a patient had PH was merely academic. There was little that doctors could do for these patients, and little in the way of advocacy.

In the late 1980s, I was introduced to PH while training in internal medicine at a university hospital that specialized in surgical "cure" for patients suffering from PH due to chronic thromboemboli (chronic thromboembolic pulmonary hypertension, CTEPH). I was merely an observer of this masterful feat that exploits the expertise of highly skilled surgeons and genius pulmonologists to remove the bulk of organized blood clots that have been lodged in the pulmonary arteries for years,[2] but after seeing patients for their 1-year follow-up, I was very impressed to see that they had received their lives back.

1990s: PH IS ON THE MAP

After residency, I began my training in cardiology at Harbor-UCLA Medical Center in Torrance, California. It was the early 1990s, and I was again introduced to PH. This time, though, it was a rare and incurable form of PH, which at the time was called primary pulmonary hypertension (PPH).[3] While a classification scheme for "cor pulmonale" had been published more than 20 years prior, in particular describing diseases affecting the pulmonary vasculature, there were no approved treatment options.

I met many patients with PPH at Harbor, because our Chief of Cardiology, Bruce Brundage, MD, was recruiting them to participate in a clinical trial of a new, experimental treatment for PPH: continuously infused epoprostenol. In many instances, we were the last hope for these patients because their doctors had told them to "get your life in order," since there were no treatment options available, and no hope (this still happens, even today). Fortunately, some patients were beginning to find their way to a newly formed patient organization called the United Patients Association for Pulmonary Hypertension (UPAPH, Figure 1), now called the Pulmonary Hypertension Association (PHA).[4] This organization sought to not only attract PH patients in order to provide a place

Table 1. PH Classification. Reprinted from Hatano S, Strasser T. *Primary Pulmonary Hypertension: Report on a WHO Meeting, Geneva, 15-17 October 1973*. Annex 1, pages 38-39. Geneva: World Health Organization, 1975.

CLASSIFICATION OF CHRONIC COR PULMONALE ACCORDING TO CAUSATIVE DISEASES[a]

The diseases that may cause chronic pulmonary heart disease are listed below, classified into broad etiological groups.

1. Diseases primarily affecting air passages of the lung and the alveoli
   - 1.1 Chronic bronchitis with generalized airways obstruction with or without emphysema
   - 1.2 Bronchial asthma
   - 1.3 Emphysema without bronchitis or asthma
   - 1.4 Pulmonary fibrosis, with or without emphysema, due to:
     - (*a*) Tuberculosis
     - (*b*) Pneumoconiosis
     - (*c*) Bronchiectasis
     - (*d*) Other pulmonary infections
     - (*e*) Radiation
     - (*f*) Mucoviscidosis
   - 1.5 Pulmonary granulomata and infiltrations
     - (*a*) Sarcoidosis
     - (*b*) Chronic diffuse interstitial fibrosis
     - (*c*) Berylliosis
     - (*d*) Eosinophilic granuloma or histiocytosis
     - (*e*) Malignant infiltration
     - (*f*) Scleroderma
     - (*g*) Disseminated lupus erythematosus
     - (*h*) Dermatomyositis
     - (*i*) Alveolar microlithiasis
   - 1.6 Pulmonary resection
   - 1.7 Congenital cystic disease of the lungs
   - 1.8 High-altitude hypoxia

[a] From: WHO Technical Report Series, No. 213, 1961 (Report of the WHO Expert Committee on Chronic Cor Pulmonale), pp. 7-8.

2. Diseases primarily affecting the movements of the thoracic cage
   - 2.1 Kyphoscoliosis and other thoracic deformities
   - 2.2 Thoracoplasty
   - 2.3 Pleural fibrosis
   - 2.4 Chronic neuromuscular weakness—e.g., poliomyelitis
   - 2.5 Obesity with alveolar hypoventilation
   - 2.6 Idiopathic alveolar hypoventilation
3. Diseases primarily affecting the pulmonary vasculature
   - 3.1 Primary affections of the arterial wall
     - (*a*) Primary pulmonary hypertension
     - (*b*) Polyarteritis nodosa
     - (*c*) Other arteritis
   - 3.2 Thrombotic disorders
     - (*a*) Primary pulmonary thrombosis
     - (*b*) Sickle cell anaemia
   - 3.3 Embolism
     - (*a*) Embolism from thrombosis outside the lungs
     - (*b*) Schistosomiasis (bilharziasis)
     - (*c*) Malignant embolism
     - (*d*) Other embolism
   - 3.4 Pressure on main pulmonary arteries and veins by mediastinal tumours, aneurysm, granuloma, or fibrosis.

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Table 2. Evolution of PAH Drug Treatments

Year	
1951	Dresdale describes PPH
1950-1990s	Controversy over embolic vs thrombotic
	National Institutes of Health registry shows natural history of PPH: poor outcome with conventional treatment
1980s	Epoprostenol development begins
1990s	Epoprostenol approved by FDA for PAH: intravenous infusion
2000-2005	Bosentan approved by FDA: the first oral PH treatment and the first endothelin antagonist
	Treprostinil approved by FDA: the first subcutaneous PAH treatment
	Sildenafil approved by FDA: the first PAH drug targeting the nitric oxide pathway
2005-2018	Newer drugs approved targeting the prostacyclin, endothelin, and nitric oxide pathways, ranging from oral to inhaled to parenteral formulations

for them to turn after they were diagnosed, but also to gather PH experts together to serve as advisors for PHA's mission: to find a cure for PH.

The First Drug for PH: Hope Springs

In 1995, the year I finished my cardiology training and became an attending cardiologist, epoprostenol received US Food and Drug Administration (FDA) approval and became the only medication available at that time specifically to treat PPH. Because of the extreme complexity of the drug and its specialized intravenous delivery system, treatment could only be initiated at a small number of medical centers across the country—those with the facilities and staff that knew how to treat it. This resulted in hospitals like ours receiving dozens of referrals for patients every month with suspected or proven PPH, because we were the only ones in town that could properly diagnose and treat it. The dawn of PH care had arrived.

By the late 1990s, experts from around the world with basic, translational, and clinical research backgrounds recognized the need to better understand PH and thus convened the next world meeting in 1998, the Second World Symposium on PH, in Evian, France.[5] At this meeting, an improved PH classification was proposed, which became the template for subsequent modifications that would take place at each subsequent world symposia, now slated to convene every 5 years. The newer classification was designed to stratify PH subtypes based mainly on clinical presentation, pathological findings, hemodynamic characteristics, and treatment strategy. The Evian classification and subsequent iterations would greatly influence decision-making in PH, and would become the reference standard for providing a framework upon which scientists, clinicians, pharmaceutical companies, regulatory bodies, and payers would base their understanding of PH.

With the new treatment, specific to PPH, came many questions: how long can patients last with this treatment? Who should prescribe it? How will it be paid for? How should PH patients be classified and diagnosed to determine appropriateness for this specific treatment, a continuous infusion of epoprostenol? On the other hand, it was fairly simple to decide on a treatment for PPH. Apart from the few (rare) patients who responded to a few pills a day of calcium channel blockers,[6] there was only one option: continuous intravenous epoprostenol—a medication that could only be delivered nonstop through a catheter connected on one end to a battery-powered pump and on the other end to the bloodstream. This was a life-saving medicine that made patients feel better, do more, and for many patients, live longer. Given the high mortality for patients without this treatment,[7] it was a "no-brainer" to prescribe epoprostenol—for most patients.

Unfortunately for a few patients, they simply did not have the means to avail themselves of the opportunity epoprostenol offered them. Some lived alone and had nobody to help them prepare and administer the medicine, prepare and run the pump, maintain the central venous catheter, etc. Some were not adherent to their medications or were at risk for injecting illicit drugs into their infusion catheter. And others, particularly at public hospitals like where I practiced, could not afford the $100,000+ price tag of the medication and supplies.[8]

2000s: A DECADE OF RAPID EVOLUTION – A WAVE OF DRUG TRIALS BEGINS

While epoprostenol was a big breakthrough for PPH patients, and in 2000 was expanded for use in all PH patients, with all of its physical, emotional, and socioeconomic quirks, it was depressing for many patients to have to look forward to what could be a lifelong marriage to a pump, a catheter, and medication with side effects that almost always included nausea, diarrhea, rash, and jaw pain. Therefore, when a new drug for PH promising to be a safe and effective alternative to epoprostenol entered the patient testing phase, there was no shortage of patient volunteers to test the drug. In fact, not long after epoprostenol gained FDA approval, pharmaceutical companies began to recognize the unmet needs of PPH patients. A resulting wave of clinical trials soon began as drug development during the first half of the decade started to blossom.

Figure 1: UPAPH.

Several pharmaceutical companies began to design and implement randomized clinical trials that would eventually lead to the approval of a multitude of new PH drugs (Table 2). By this time, PPH and other forms of precapillary PH had been reclassified under a term to be known as pulmonary arterial hypertension (PAH),[9] and the target population for PAH medications was now a much larger group of patients that were potentially treatable with drugs like epoprostenol targeting the pulmonary circulation. Importantly, drugs targeting several pathophysiologic pathways were being developed. In addition to the prostanoid pathway, drugs targeting the endothelin and nitric oxide pathways became available, suggesting the possibility that a multitargeted approach could be additive, if not synergistic.

On a personal note, as a junior faculty at the time, being introduced to a growing group of experts in the field at various scientific congresses and investigator meetings was a true honor and pleasure. Those that preceded me had made seminal contributions to the PH space, and I was allowed in their "circle." It would soon be apparent to me that there weren't a lot of "us" out there—those that knew PH and PH therapies well and took care of PH patients so fervently. But at the same time, having ridden the "wave" of PH drug development, many of us would often wonder how long it would be before being "just a PH doc" was no longer a thing (I still often wonder about this today).

Genomics

Perhaps one of the greatest discoveries of modern times was the complete sequencing of the human genome. In the world of PH, the spectacular discovery in 2000 of the first known familial PPH (FPPH) genetic mutation (now known as hereditary PAH, HPAH), caused by mutations in BMPR2, encoding a TGF-beta type II receptor (BMPR-II)[10] promised greater understanding of PAH, with implications for treatment strategies aimed at improving the outcomes of patients with PAH. Since then, at least 7 more genetic mutations associated with PAH have been identified.[11] Unfortunately, to date there are still no approved PAH therapies that have resulted from the BMPR-II discovery nor from other, more recent genetic discoveries. Nevertheless, the time may soon come when individually targeted PAH therapies based on a patient's specific genetic makeup become available.

Standardization of PH Care: Raising the Bar

The world PH symposia were instrumental in proposing recommendations for clinical trial design in PH. Because change in 6-minute walk distance (6MWD) had been the primary endpoint in nearly all of the pivotal trials of PAH drugs during the first decade of PH drug development, there grew a desire and a need for better surrogate endpoints that could encompass long-term outcomes. Thus, at the Third World Symposium on PH in 2003, experts first proposed trial designs whose primary endpoint would be based on clinical outcome, with change in 6MWD as a supportive secondary endpoint.

The bar had been raised, and the implications for PH care were clear: while improvement in exercise capacity using 6MWD after treatment with PAH drugs was desirable, it was no longer satisfactory to base treatment just on exercise capacity. Experts at the third world symposium proposed reforms in clinical trial design and demanded that treatment strategies for those caring for PAH patients incorporate longer-term goals. This goal-directed therapy was based on several parameters of the patient encounter, including functional class, exercise capacity, and additional imaging and laboratory benchmarks that would drive decision-making.[12] In addition to defining long-term goals, the call for more meaningful and longer-term endpoints was also underway. Indeed, the first large-scale clinical trial of a PAH drug that was event-driven rather than time-driven and which demonstrated efficacy using composite endpoints for the primary outcome variable first began enrolling patients in 2009.[13]

Expanded PH Care

With the continued approval of new PAH drugs, particularly the oral medications, PH care began to spring from a much wider prescriber base, ranging from experts in high-volume academic PH centers to individual practitioners with little (and sometimes no) experience in PAH. In some respects, the FDA was generous in its labeling of PAH drugs. It did not mandate any particular expertise in PH for prescribers. And payers mainly screened for patient eligibility based on hemodynamic criteria and, for the most part, trusted prescriber judgment. Thus, while PAH was no longer a disease that always required a dedicated team of doctors and nurses with expertise in continuous prostacyclin infusions, some patients without PAH were starting to be treated with PAH drugs.[14]

Thus, while on the one hand some of our colleagues believed that their days as PH experts running PH clinics would be numbered, others saw the need to continue to push the envelope; better treatments, better markers of disease, and more awareness in the community were still needed.

Educating the World on PH Care

Along with raising the bar for PAH treatment expectations, and a passionate push for raising PH awareness by PHA and other patient advocacy organizations, it was recognized that the educational needs for disseminating optimal PH care strategies were of extreme importance to both the patient and medical communities. Efforts by the pharmaceutical industry, governmental agencies, patient advocacy groups, and independent continuing education companies resulted in the development of a rich repository of educational materials aimed at prescribers of PAH medications, primary care practitioners, and patients. These programs stressed the importance of early recognition and diagnosis of PH, differentiating types of PH, and proper use of PAH treatments.

2010s: THE NEXT 10 YEARS – EVOLUTION, REFINEMENT, AND CHALLENGES IN PH CARE

Treatment Choices

As more treatments for PAH have been introduced, more questions are arising about how to care for PAH patients. The era of one single treatment for PAH evolved to adopt a multipronged ap-

proach. However, with more treatment options available came more difficulty in choosing the optimal sequence or combination of PAH drugs. Initially, there was little evidence to support which particular PAH drug or combination of drugs to initiate at the time of diagnosis, and there was little guidance on when to add or even replace a drug. Once a drug strategy was shown to be beneficial, with so much for patients to lose if they tried something else, it became ethically and fundamentally quite difficult to rationalize an alternative strategy. Nevertheless, several approaches to treatment strategies arose.

The concept of goal-oriented treatment[15] suggested that certain milestones needed to be reached with PAH treatment, such as a 6MWD >380 meters, a distance previously shown to predict outcome. A "treater" was to initiate one PAH drug and if goals were not achieved, they were to add additional drugs targeting separate pathways in a stepwise fashion, until the goals were achieved; failures would then be referred for lung transplantation. While this exact strategy has not been propagated in expert guidelines for PAH, the concept was a sound one considering that most PAH patients can be expected to progress over a relatively short time, calling empirically for a more aggressive treatment approach. Many of the "treatment goals" had never been validated in clinical trials but were generated only by expert opinion.

More recent clinical trials have provided clear evidence to support the strategy of targeting more than one abnormal pathway in PAH patients. Results from the AMBITION trial support the use of 2 drugs at the time of initial diagnosis, almost regardless of severity.[16] Rather than waiting until patients deteriorate to add a second therapy, the earlier use of 2 drugs has now become common practice in the United States. Unfortunately, access to these expensive medications can be difficult, particularly in poorer nations. For these countries, access to even one PAH drug can be extremely difficult; practicing optimal treatment strategies therefore may be impossible.

Nonpharmacologic Treatments

While some nonpharmacologic treatments for PAH such as lung transplantation[17] and atrial septostomy[18] have existed for many years, they have been (and remain) reserved for patients with advanced disease who have not responded to conventional treatments. Unfortunately, although lung transplantation techniques and post-transplant care have enjoyed technical refinements over the years, patients with PH have not had as high a priority for transplantation as other patients with lung disease,[19] despite attempts to improve the system.[20]

In an effort to push the treatment envelope for stable patients beyond drug therapy, nonpharmacologic treatment modalities for PAH, such as rehabilitative exercise, were developed. At first considered by many as unsafe [personal communications from 19 PH physicians, 1999], experts eventually realized that moderate aerobic training was not only safe, but in fact salutary for patients able to exercise.[21] Adjunctive treatments such as rehabilitative exercise have in fact been included in PH treatment guidelines since 2009,[12] and since then, additional evidence[22] supports the use of exercise as an adjunctive treatment modality.[23] As a researcher and treater in PAH with an avid interest in exercise, these advances have crowned nearly 2 decades of efforts to further the integration of exercise in both the evaluation and treatment of PH.

Defining Expertise in PH

With the recognition that PH, and particularly PAH, was a challenging diagnosis as well as a tenacious disease to treat came a desire to develop a network of national experts in the field. In 2014, a PHA-sponsored program known as the PH Care Center (PHCC) initiative began accrediting qualified expert PH centers with proven expertise in PH care. This program—the first of its kind in PH—has now grown to 57 expert US PH centers, with additional centers coming online in the next few years. This network promises to raise the level of care for PH patients, improve access to experts in the field, streamline diagnosis and prompt treatment, and increase collaboration between experts for optimizing clinical care as well as coordinating research.

Focus on the Patient

The concept of "feel, function, and survive" has been a tenet of the FDA's drug development program[24] for years. They define a drug's effectiveness as: "An essential component of the basis for marketing approval of a drug; drugs must be safe and effective to justify approval. Effectiveness is defined as a benefit to patients in how they feel, function, or survive due to treatment with the drug." Reading the medical literature covering PH care, it is evident that efforts have focused mostly on diagnostic and therapeutic advances, with "function and survive" endpoints that have included exercise capacity, disease severity, and albeit to a lesser extent, survival; there has been a decidedly minor focus on patient-related "feel" outcomes.

In 2010, Congress established the Patient-Centered Outcomes Research Institute (PCORI).[25] In their words, "PCORI was established to fund research that can help patients and those who care for them make better-informed decisions about the health care choices they face every day, guided by those who will use that information." Despite this initiative, since 2010, a paucity of PAH therapy clinical trial reports contain patient-centered outcome results, and none have had a patient-centered outcome as their primary endpoint. Quality of life in PAH, first reported in 2004,[26] is thus a metric that has unfortunately taken a backseat in clinical trial design; while PH care has evolved over 3 decades, our focus on how the patient feels has not advanced to any great degree.

Ongoing Challenges in PH Care

Despite the approval of more than a dozen drugs to treat PAH, many challenges remain.

- After decades of awareness and community education, delays in PH diagnosis have remained unacceptably long. In 2011, after 3 world PH symposia during the preceding 13 years and valiant attempts to educate the medical and patient communities, Brown et al reported that over 20% of patients

diagnosed with PAH had symptoms for more than 2 years.[27]

- With more treatments now than ever, the optimal sequence and/or combination of PAH drugs is still unclear. Addressing this problem has proven extremely difficult. Barriers to designing clinical trials comparing multiple strategies with multiple agents include financial concerns, industry buy-in, and (because of the rarity of PAH) the arduous challenge of applying a relatively small pool of eligible patient volunteers to meeting statistical power requirements in clinical trials.
- Most patients with PH do not have PAH,[28] and thus most do not have many treatment options, if any. Despite decades of research on PAH, only one drug has been approved to treat PH that is not PAH: riociguat for CTEPH (Group 4 PH). There are no drugs approved for PH Groups 2, 3, and 5.
- There are not enough PAH experts to go around. Despite the development of the PHCC initiative, particularly for patients living in smaller cities, it is not uncommon for PAH patients to have to travel hundreds of miles to see their PAH expert.

CONCLUSION

The diagnosis and treatment of PH have evolved tremendously over the last 3 decades. Refined diagnostic and treatment algorithms, multimodality treatments, and advances in the genomics of PH have driven the field in ways that were not imagined only a few years ago. The PH community has evolved from a small group of experts that had little to offer their patients to a growing list of international experts with treatments that have changed the outlook for many from grim to hopeful. While obstacles remain, it is hoped that the future of PH will continue to enjoy the benefits of increasingly innovative technologies and partnerships that will further advance PH care.

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