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Editorial

In the Treatment of Pulmonary Arterial Hypertension, Less May Actually be Less … Less Beneficial

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EDITORIAL

Physicians have been warned about ordering too many tests, performing too many procedures and layering of medications on top of medications [1]. Whether it be for financial or patient safety considerations, we have been asked to adhere to the philosophy of "less is more" whenever possible. And in 1996, upon the commercial availability in the U.S. of IV Epoprostenol (FLOLAN) for the treatment of what had then been termed Primary Pulmonary Hypertension (PPH), monotherapy with Epoprostenol became the standard of care. Until Epoprostenol, for those diagnosed with this here to fore considered rare disease, their physicians viewed the diagnosis as a death sentence, if left treated only by the conventional medicines available at that time. Epoprostenol showed efficacy in terms of improved hemodynamics and survival [2].

Since those early years when physicians could provide only Epoprostenol for their patients, our understanding of Pulmonary Hypertension (PH) and particularly, Pulmonary Arterial Hypertension (PAH) has advanced greatly. And in 2015, the W.H.O. reclassified the disease states causing PAH into those primarily affecting the pulmonary arterioles - according to etiology of disease, histologic evidence of pulmonary arteriopathy and response to therapy. By today's reclassification, this comprises a much larger group of patients than those previously called PPH (1-2 cases per million) into what we now refer to as Group 1: PAH. The estimated worldwide prevalence ranges from 10 to 52 cases per million [3] and include those causes unknown and known, i.e. toxin exposure, connective tissue disorders, portal hypertension, HIV, congenital heart disease and schistosomiasis [4].

IV Epoprostenol and the later released parenterally-delivered longer-acting prostacyclin analogue Treprostinil (REMODULIN), despite their effectiveness in patients with W.H.O. Functional Class II-IV symptoms, carry with them the cumbersome baggage of a dedicated tunneled intravenous catheter and the associated risk of line infection, in addition to the inconvenience of regular and frequent mixing of the drug and priming and programming the drug delivery device for its continuous infusion. Though many alternatives to parenteral therapy have appeared since the advent of Epoprostenol and Treprostinil (inhaled and oral routes), treatment recommendations for these non-parenteral alternatives for those patients with W.H.O. Functional Class II or III symptoms had initially appeared to be based largely upon clinical trials that demonstrate their efficacy as monotherapy. And these alternative to parenteral forms of therapy, while shown to be beneficial, have generally been prescribed by physicians as monotherapy and only reluctantly, after failure of their patients to improve according to their clinical assessment, would they add an additional line of therapy in combination to the treatment regimen. Is such initial monotherapy with sequential combination therapy the right way to treat patients with PAH with W.H.O. Functional Class II-III symptoms? Let us bear in mind that PAH, through sustained high pulmonary vascular resistance over time, may lead to the development of right ventricular strain, and in turn to overt right heart failure and death [5]. Because of the dependence of right ventricular function on the pulmonary vasculature, all those who treat PAH must consider the potential cardiovascular ramifications of PAH. The importance of the right ventricle in PAH leads us to consider the way in which we treat PAH, but in the context of the practices and societal guidelines of our medical colleagues who treat other forms of cardiovascular disease.

For years, physicians treating systolic heart failure and essential hypertension have known that in many cases, medication prescribed early and in combination rather than as monotherapy may lead to better outcomes. ACE inhibitors or ARBs used in combination with beta blockers and aldosterone antagonists to treat systolic heart failure have been shown to reduced morbidity and mortality AHA [6]. The ESH/ESC Guidelines for the management of arterial hypertension suggest advantages of initiating with combination therapy namely, a more rapid blood pressure response in more patients, a greater probability of achieving the target blood pressure in patients with more difficulty-to-treat hypertension, and greater patient adherence due to less frequent treatment changes. Additionally, the authors posit that there may exist physiological and pharmacological interactions between different classes of agents that may lead to improved control of hypertension, possibly with a better adverse effect profile than those offered by a single agent [7].

Pharmaceutical companies have followed suit, producing tablets comprised of two drugs with different pharmacologic actions to treat these diseases. Why then have physicians treating PAH only recently been able to conclude that two drugs may be prescribed initially in combination to treat PAH with greater benefit than monotherapy alone? After all, even with the development of PAH-specific medications over the past twenty years or so, morbidity and mortality remain high in PAH. Of the 55 US Centers reporting between 2006 and 2009, mortality from the time of confirmatory right heart catheterization measured nearly 1 in 3 patients at year three and nearly 1 in 2 at year five [8-11].

The answer may lie in the limited success of earlier clinical trials studying combination therapy for PAH. Historically, physicians treating PAH began with monotherapy and after a period of time, sequentially added a second or third line medication based upon an assessment of response to therapy. Moreover, the REVEAL Registry showed that US physicians wait too long to make the diagnosis of PAH and that delayed diagnosis leads to more advanced state of disease at time of diagnosis. Problematically, studies showed no benefit when treating early in combination i.e., COMPASS-2, FREEDOM-C [10] and FREEDOM-C2 [11]) and this lead to physicians questioning the benefit of such an early and aggressive prescribing approach to PAH. Part of the problem in convincing physicians to treat PAH more aggressively lay in the clinical endpoints chosen in the earlier studies. Most of these clinical endpoints included assessment of distance walked or hemodynamic responses over a relatively short period of time studied, usually 12-16 weeks. While these endpoints satisfied the US FDA and allowed many to come to market, physicians treating PAH wondered about the sustainability of these pharmacologic effects and what might be their relevance in the longer term and upon examination of more clinically relevant endpoints. Longer-term studies using combined clinical endpoints have more recently been published and have begun to change the minds of physicians regarding the goals in PAH treatment. The SERAPHIN trial [12] brought us the clinical endpoint of "time to clinical worsening" - a combined endpoint of the time from the initiation of treatment to the first occurrence of a composite end point of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids or worsening of pulmonary arterial hypertension. Outcomes were analyzed over approximately two years. The AMBITION study [13] brought the combined endpoint of "time to clinical failure" - the time from the initiation of treatment to the first occurrence of a composite endpoint of death, hospitalization for worsening PAH, disease progression or unsatisfactory long-term response. Outcomes were analyzed over a similar period of time as SERAPHIN. Both studies showed that combination therapy (Macitentan added to a PDE-V inhibitor or rarely, a non-parenterally-delivered prostanoid – SERAPHIN or Ambrisentan taken upfront with Tadalafil - AMBITION) yielded sustainable and clinically relevant outcomes, thereby helping to convince physicians treating PAH that we may do better for our patients by treating them more aggressively with combination therapy.

Treatment of PAH has come a long way from the early days of IV Epoprostenol. In addition to better designed drug trials, we now have more objective ways in which to assess risk for disease progression in PAH [14,15]. The REVEAL Registry Risk Score shows us that by weighing algorithmically the relative importance of W.H.O. Group I Subgroup, W.H.O. functional class, demographics and co-morbidities, vital signs, distance walked in 6 minute walk test, BNP, presence of pericardial effusion on echocardiogram, severity of impairment of gas exchange on PFTs and hemodynamic evidence by right heart catheterization of right heart failure and high PVR, one can arrive at a Risk Score to help predict survival [15]. With our current enhanced ability to risk stratify our PAH patients and the more recent knowledge that in many cases combination therapy, when chosen according to the results of scientific outcomes of particular studies leading to meaningful long term outcomes, our PAH patients merit a more proactive treatment approach.

Treatment of PAH has progressed greatly since the advent of Epoprostenol. We recognized there exists a delay in PAH diagnosis due to the difficulty in differentiating PAH from other more common causes of our patients' signs and symptoms like obstructive lung disease, deconditioning or heart disease. With our current knowledge, let us not delay in making the diagnosis of what is now a very treatable disease. And let us treat according to our current medical knowledge; treatment with more than one drug early on in the clinical course may achieve better outcomes for our patients than the watch and wait approach of the earlier days. In the case of the treatment of PAH, less may actually be less - less beneficial.

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