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In this issue of *Advances*, section editors Jonathan Rich, MD, and Oksana Shlobin, MD, review findings from 2 recently published studies and discuss their implications on treatment of patients with pulmonary arterial hypertension.

Galiè VN, Barberà JA, Frost AE, et al; AMBITION Investigators. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med.* 2015;373(9):834-844.
Sitbon O, Channick R, Chin KM, et al; GRIPHON Investigators. Selexipag for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med.* 2015; 373(26):2522-2533.

The results of 2 studies were published at the end of 2015 in the *New England Journal of Medicine* that may impact the way patients with pulmonary arterial hypertension (PAH) are treated: AMBITION (a randomized, double-blind, multicenter study of first-line combination therapy with AMBrIsentan and Tadalafil in patients with pulmonary arterial hypertensION) and GRIPHON (Prostacyclin [PGI2] Receptor agonist In Pulmonary arterial HypertensiON).

Physicians who treat PAH have been combining drugs with different mechanisms of action for close to a decade, but with limited data to support its use—largely from add-on trials and case reports of sequential therapy. The use of combination therapy has been surrounded by a multitude of questions including when to start it, which combinations to use, and what treatment goals should be targeted.

The AMBITION trial was a multicenter, randomized, double-blind Phase 3 trial that evaluated 500 treatment-naïve (or incident) New York Heart Association (NYHA) functional class (FC) II and III patients in a 2:1:1 fashion to receive either a combination of ambrisentan and tadalafil (n=253), tadalafil monotherapy (n=121), or ambrisentan monotherapy (n=126). The mean duration of the study was 517 days (550 days for combination and 484 days for monotherapy groups, respectively). The total number of patients originally enrolled was 610; however, a final analysis was performed on the primary analysis set, with 110 deemed to have multiple risk factors for left diastolic dysfunction, thus excluded per a protocol amendment. The primary efficacy endpoint was time to first clinical failure (TTCF), defined as either death (all-cause mortality), hospitalization for worsening PAH, disease progression (>15% decline in 6-minute walk test [6MWT] from baseline with NYHA FC III and IV symptoms), or an unsatisfactory clinical response (NYHA FC III symptoms while in the study for at least 6 months with a decrease in 6MWT distance from baseline), with the latter 3 events all adjudicated.

The results of the AMBITION trial demonstrated for the first time that a strategy of up-front combination therapy in treatment-naïve NYHA FC II and III patients resulted in a significantly lower risk of clinical failure events in comparison with a monotherapy treatment approach. The hazard ratio (HR) for TTCF in combination therapy compared with the pooled monotherapy arm was 0.50 (confidence interval [CI] 0.35-0.72, $P<0.001$), with the primary endpoint event occurring in 18% of patients in the combination arm and 31% of patients in the pooled monotherapy arm. The difference in the composite endpoint was driven mainly by a marked reduction in hospitalization with combination therapy (12% vs 4% in combination vs pooled monotherapy groups, respectively); HR of 0.37 (CI 0.22-0.64, $P<0.001$). At 3 years, approximately 68% of patients in the combination arm vs 56% of patients in the pooled monotherapy group were event-free. The results were consistent across prespecified subgroup analyses of etiology, World Health Organization (WHO) FC, age, gender, and geographical area.

Among the secondary endpoints studied, 3 demonstrated outcomes in favor of the combination group. The change in 6MWT distance at 24 weeks was +49 meters in the combination group compared to +27 meters and +22 meters in the ambrisentan and tadalafil monotherapy arms, respectively. In addition, N-terminal pro-brain natriuretic peptide (NT-proBNP) was significantly reduced in the combination therapy compared to the monotherapy subgroups. Finally, a higher percentage of patients with a satisfactory clinical response was observed in the combination group (39% vs 29%, odds ratio [OR] 1.56, CI 1.05-2.32, $P=0.03$). There was no difference in the change in WHO FC or Borg dyspnea scale between the groups.

The combination therapy was generally well tolerated. However, in the combination group, a higher proportion of patients had peripheral edema (45% vs 30%), headaches (42% vs 34%), nasal congestion (21% vs 14%), and anemia (15 vs 9%).

Based on the results of this trial, the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines now recommend up-front combination therapy with tadalafil and ambrisentan for all treatment-naïve Group 1 PAH patients with NYHA FC II or III symptoms as the

first-line therapy (the only class I recommendation with level B evidence). This trial, however—while encouraging and an important contributor to the PAH field—generates additional questions that must be evaluated:

1. Can these results be attributed to a specific drug effect or class effect?
2. Is it possible that receiving 2 drugs vs 1 simply increased the chance that the patient would respond to *one* drug but not necessarily the combination?
3. What should be done with the patients currently on monotherapy who are doing well clinically?
4. Is it not still most logical to initiate a strategy of monotherapy and ensure efficacy and tolerability with a plan to *rapidly* add on another agent if a favorable response to the first drug is achieved?
5. Finally, what should be done to manage patients who received up-front combination therapy but do not show a satisfactory clinical response? Should we actually be layering on yet another drug to a regimen that is not working, or stop the drugs altogether and start over?

GRIPHON was a Phase 3, multicenter, double-blinded trial to investigate the safety and efficacy of selexipag in patients with Group 1 PAH who were treatment-naïve, and in those who were already receiving 1 or 2 therapies with a phosphodiesterase type 5 (PDE5) inhibitor and/or an endothelin receptor antagonist (ERA) (and deemed clinically stable for at least 3 months) at the time of enrollment. GRIPHON is the largest trial to date, enrolling a total of 1156 patients randomly assigned to selexipag (574 patients) or placebo (582 patients), with a median duration of 70.7 weeks for those in the selexipag group. The study had a 12-week dose-adjustment phase, during which the drug was initiated at 200 micrograms twice a day and increased weekly in twice-daily increments of 200 micrograms until unmanageable prostacyclin-related side effects occurred, with the maximum dose of 1600 micrograms twice daily. The largest tolerated dose was considered the maximal tolerated dose for that particular individual.

The study enrolled Group 1 PAH patients with a stringent pulmonary vascular resistance criterion of at least 5 Wood units. The primary endpoint in a time-to-event analysis was a composite of death or a complication related to PAH (whichever occurred first), up to the end of treatment. Complications related to PAH included disease progression or worsening of PAH that resulted in hospitalization, initiation of parenteral prostanoid therapy, or the need for lung transplantation or balloon septostomy. Disease progression was defined as a decrease of 6MWT distance by at least 15%, accompanied by a worsening of WHO FC or the need for additional treatment. One exploratory (change in NT-proBNP) and 4 secondary endpoints were also analyzed.

Most enrolled patients had NYHA FC class II (45.8%) and III (52.5%) symptoms. One-third of the patients were on dual background therapy, one-third on a PDE5 inhibitor, 15% on an ERA, and 20% on no treatment: ie, ~80% of the patients constituted a prevalent PAH cohort. Overall, 41.6% of patients in the placebo group compared with 27.0% in the selexipag group had a primary endpoint event with HR 0.60 (CI 0.46-0.78, $P<0.001$), with disease progression and hospitalization accounting for 81.9% of the events. The treatment effect was consistent across different treatment doses, as well as prespecified subgroups, including those on no background therapy and treatment with 1 or 2 medications as well as baseline NYHA FC, race, geography, and etiology of PAH. Secondary endpoints included a modest 12-meter treatment effect in 6MWT distance at Week 26, with 21.6% of the values imputed to a value of -10 meters. Death due to PAH or disease worsening occurred in 23.5% for placebo and 17.8% for selexipag groups, respectively (HR of 0.70, CI 0.54-0.91, $P=0.003$), with hospitalizations accounting for 87.4% of these events. By the end of the study, no difference in death from any cause was observed between the groups (in 18.0% for those receiving placebo and 17.4% in the selexipag group). At Week 26, NT-proBNP levels were significantly lower in the selexipag group. Selexipag was reasonably well tolerated, with a 7.2% difference in discontinuation between the 2 groups. The most frequent adverse effects that occurred more frequently in the selexipag group were consistent with known prostacyclin side effects, including headache, diarrhea, nausea, jaw pain, myalgias, extremity pain, and flushing. It will be interesting to see how well tolerated selexipag is in a nonclinical trial setting given the long history of intolerability of oral prostanoid therapy in general.

In summary, this study demonstrated that the primary endpoint of death or a complication related to PAH was lower among those who received selexipag in comparison to the placebo group, with the treatment effect driven by difference in disease progression and hospitalization with consistent outcomes in all prespecified groups. Based on these results, selexipag appears to provide yet another treatment option for patients with PAH.