Initial Combination Therapy Improves Hemodynamics and Function in Scleroderma PAH

Written by Mary Mosley

Patients with systemic sclerosis pulmonary arterial hypertension (SSc-PAH) have a worse prognosis than those with idiopathic PAH. Although the specific mechanisms are not known, it is thought to be related to persistent right ventricular (RV) dysfunction and pulmonary vascular remodeling despite guideline-directed management with a single agent for PAH. Dr. Mohamed A. Gashouta, MD, St. Luke's Hospital, Chesterfield, Missouri, USA, presented a 36-week, open-label, multicenter observational study evaluating upfront therapy with 2 drugs, tadalafil and ambrisentan, that target distinct pathways in treatment-naïve patients with SSc-PAH [NCT01178073; Gashouta MA et al. *Am J Respir Crit Care Med*].

The presenter reported findings for 17 of the 25 patients with SSc-PAH who had been treated with tadalafil 40 mg daily, a phosphodiesterase inhibitor, and ambrisentan 10 mg daily, an endothelin antagonist. The patients (mean age, 58.8 years) were predominantly female (88%), with limited (94%) as opposed to diffuse (6%) SSc-PAH disease. The mean baseline pulmonary arterial pressure (PAP) was 40 ± 16 mm Hg and pulmonary capillary wedge pressure (PCWP) was 9 ± 3.5 mm Hg.

The first primary end point, RV mass, as measured by computed magnetic resonance imaging, was significantly reduced over 36 weeks from 21.7 ± 10.6 g/m^2 to 18.0 ± 6.7 g/m^2 (p=0.04) with the combination therapy. The second primary end point, pulmonary vascular resistance (PVR), was also significantly reduced from baseline (8.1 ± 58 woods units) to 36 weeks (3.9 ± 3.5 woods units; p=0.0001).

Previous work by this group showed that pulmonary compliance (Pca; stroke volume over pulmonary pulse pressure) was an indicator of poor prognosis and survival in SSc-PAH [Campo A et al. *Am J Respir Crit Care Med* 2010]. The authors found that Pca, a secondary end point, was significantly improved from baseline (1.9 ± 1.2) to 36 weeks (2.9 ± 1.3; p=0.0007) with the combination therapy. There were also improvements in the secondary end points of ventricular mass index (VMI; 0.31 ± 0.11 at baseline to 0.27 ± 0.08 at 36 weeks; p=0.03) and 6-minute walking distance (6MWD; 361.3 ± 122.3 minutes at baseline to 405.5 ± 90 at 36 weeks; p=0.003). The combination treatment also significantly improved RV stroke volume (76.7 ± 16.5 mL to 94.6 ± 17.7 mL; p=0.007) and RV end systolic volume (RV ESV; 89.8 ± 28.3 mL to 73.1 ± 28.8 mL; p=0.02) over the 36 weeks.

These results suggest that treatment with tadafil and ambrisentan in treatment-naïve patients with SSc-PAH leads to improvement in a number of clinical (6MWD), functional (RV mass index, VMI, RV ESV), and hemodynamic (PVR, Pca, stroke volume) parameters. Additional larger, randomized studies are necessary to determine if combination therapy is superior to guideline-based therapy and whether it results in a survival benefit.

COPD Exacerbations Not Prevented With Simvastatin in STATSCOPE Study

Written by Mary Mosely

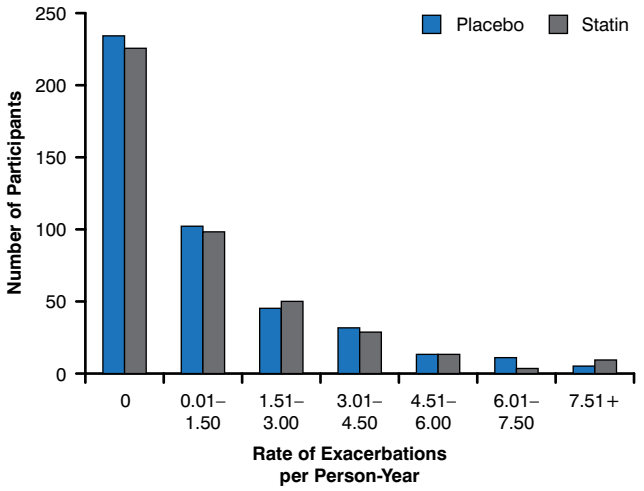
Simvastatin in addition to usual care did not reduce the rate of or time to exacerbations in patients with moderate to severe chronic obstructive pulmonary disease (COPD) in the Simvastatin Therapy for Moderate and Severe COPD study [STATCOPE; NCT01061671; Criner GJ et al. *N Engl J Med* 2014]. This multicenter study conducted in the United States and Canada and sponsored by respective federal agencies sought to validate benefits seen with statins, perhaps related to their anti-inflammatory effects, in retrospective studies of COPD, stated Gerard J. Criner, MD, Temple University, Philadelphia, Pennsylvania, USA. The study was terminated early for futility.

In total, 885 patients were randomized to simvastatin 40 mg/day (n=430) or placebo (n=329) on top of usual care for COPD; 74% of each group completed the 12-month follow-up, and 20% of the simvastatin and 18% of the placebo groups completed the 36-month follow-up. The patients (44% women) had a mean age of 62 years, a mean smoking history of 50.6 pack-years, and a mean forced expiratory volume in 1 second of 41.6% of the predicted value. Key exclusion criteria were the presence of diabetes or cardiovascular disease, need for statins according to the Adult Treatment Panel III criteria, and treatment with amlodipine, verapamil, diltiazem, or ranolazine.

The primary outcome, mean number of COPD exacerbations per patient per year, was similar: 1.36 with simvastatin (95% CI, 1.20–1.51) versus 1.39 with placebo (95% CI, 1.22–1.54; p=0.54). The number of exacerbations per person-year is shown in Figure 1. The median time to first exacerbation was 223 days with simvastatin (95% CI, 195–275 days), compared with 231 days with placebo (95% CI, 193–303 days; p=0.34). There was no

difference found in the severity of COPD exacerbations with simvastatin compared with placebo, with similar rates of mild, moderate, severe, and very severe exacerbations. No difference in the mean exacerbation rates was found with simvastatin compared with placebo for any prespecified subgroups, including smoking status, study center, gender, and race.

Figure 1. Mean Number of Exacerbations Per Person-Year



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There was no difference between simvastatin and placebo for the secondary endpoints of change in spirometric measures of lung function and quality of life, as assessed by the St. George's Respiratory Questionnaire. The rates of nonfatal serious adverse events (SAEs) were similar (0.63 and 0.62 per participant-year with simvastatin and placebo, respectively), but the overall number of SAEs was limited.

Simvastatin was associated with improvements in total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and high-density lipoprotein cholesterol (HDL-C). Baseline lipid levels were similar in study participants. LDL-C was decreased by 33.2 mg/dL with simvastatin and 6.6 mg/dL with placebo, and HDL-C was increased by 2.5 mg/dL and decreased by 0.5 mg/dL, respectively.

Study limitations included not using C-reactive protein level as an inclusion criterion and restriction of the patient population to those with moderate or severe COPD.

The STATCOPE trial did not demonstrate a therapeutic benefit, from a respiratory perspective, of statins in patients with moderate to severe COPD, stated Dr. Criner.

Nintedanib Is Safe and Effective in Patients With IPF: Results of the INPULSIS Trials

Written by Brian Hoyle

Nintedanib, a tyrosine kinase inhibitor that targets fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor, was shown to lessen the decline in lung function and decrease acute exacerbations in patients with idiopathic pulmonary fibrosis (IPF) in the Phase 2 TOMORROW study [Richeldi L et al. *N Engl J Med* 2011]. Luca Richedli, MD, PhD, University of Southampton, Southampton, United Kingdom, presented the primary results for two 52-week Phase 3 randomized, placebo-controlled trials (Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients [INPULSIS] I and II) [Richeldi L et al. *N Engl J Med* 2014].

In the INPULSIS trials, conducted at 205 sites in 24 countries globally, patients with IPF were randomly assigned in a 3:2 ratio to nintedanib 150 mg twice daily or placebo for 52 weeks. Key inclusion criteria were age ≥40 years, diagnosis of IPF within 5 years of randomization, chest high-resolution computed tomography (HRCT) performed within 12 months of screening, HRCT pattern and (if available) surgical lung biopsy pattern consistent with diagnosis of IPF as assessed centrally by 1 expert radiologist and 1 expert pathologist, forced vital capacity (FVC) ≥50% of predicted value, and carbon monoxide diffusing capacity 30% to 79% of predicted value. Key exclusion criteria included a ratio of forced expiratory volume in 1 second to FVC < 0.7 (prebronchodilator); treatment with N-acetylcysteine or prednisone >15 mg/day or equivalent within 2 weeks of screening; treatment with pirfenidone, azathioprine, cyclophosphamide, cyclosporine A, or any investigational drug within 8 weeks of screening; requirement for fibrinolysis, full-dose therapeutic anticoagulation, or high-dose antiplatelet therapy; and likelihood of undergoing lung transplantation during the study. The primary end point was the annual rate of decline in FVC. Key secondary end points were time to the first acute exacerbation and change in St. George's Respiratory Questionnaire total score over the 52 weeks.

Patient disposition is shown in Table 1. In total, 1066 patients were randomly assigned, with 25.2% and 17.6% medication discontinuation rates for nintedanib and placebo in INPULSIS-1 and 23.7% and 20.1% discontinuation rates, respectively, in INPULSIS-2 (Table 1).

Rates of study completion were similar, at 84.1% for nintedanib and 85.3% for placebo in INPULSUS-1 and 82.7% and 81.7%, respectively, in INPULSIS-2.