Successful Combination Therapies, Hospital Utilization Improvements Among Late-Breaking Clinical Trials

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MORTALITY INCREASES AND TRANSITION OF CARE

Mandated resident duty-hour restrictions have increased the total number of patient handoffs; however, little data exist as to how these transitions affect outcomes. Joshua L. Denson, MD, New York University School of Medicine, New York, New York, USA, presented data indicating there is a significant increase in all-cause hospital mortality the week following end-of-rotation handoffs.

This study investigated mortality rates during periods of resident handoff and whether these rates were affected by the Accreditation Council for Graduate Medical Education (ACGME) duty-hour rule amendments instituted in July 2011. This was a 2-year retrospective cohort study (July 2010 through June 2012) of 24 739 adult discharges from internal medical services at a public, university-affiliated hospital. The primary study outcome was unadjusted and adjusted mortality during the 7 days following a change in resident physician team (handoff) compared with the remaining 3 weeks of each 4-week rotation (control). The effect of the 2011 ACGME duty-hour changes on mortality was also evaluated.

Two diagnoses were significantly more common in the control group, anemia ($P = .003$) and other neurologic disorders ($P = .02$); otherwise the groups were similar. Over 2 years, both unadjusted and adjusted all-cause hospital mortality were significantly higher during the handoff period vs the control period, as well as for discharges occurring prior to implementation of the duty-hour adjustments. After duty-hour reform, the unadjusted hospital mortality rate remained higher during the handoff vs the control period (2.74% vs 2.32%; $P = .004$). The risk remained higher for all-cause mortality, pre-duty hour mortality, and post-duty hour mortality during the handoff period vs the control period, with odds ratios of 1.29 ($P = .013$), 1.42 ($P = .012$), and 1.15 ($P = .330$), respectively, adjusted for age, sex, length of stay, month, and Elixhauser Comorbidity Index.

Although improved by the 2011 ACGME duty-hour amendments, there remains a trend toward higher mortality during times of resident handoff.

INITIAL THERAPY WITH AMBRISENTAN PLUS TADALAFIL EFFECTIVE FOR PAH

Data presented by Lewis J. Rubin, MD, Gilead Sciences, Foster City, California, USA, demonstrated that initial combination therapy with ambrisentan + tadalafil may be beneficial across a variety of patients with pulmonary arterial hypertension (PAH).

AMBITION was a phase 3 trial [NCT01178073] showing that initial combination therapy with ambrisentan + tadalafil reduced the time to first clinical failure (TcF; all-cause death, hospitalization for worsening PAH, disease progression, and unsatisfactory long-term response) in treatment-naïve patients with PAH with World Health Organization (WHO) functional class (FC) II or III compared with initial monotherapy with ambrisentan or tadalafil. The primary analysis set comprised 500 patients with a median age of about 54 years and a median baseline 6-minute walk distance (6MWD) of about 360 meters. Dr Rubin presented the results of a prespecified subanalysis by disease etiology (idiopathic/heritable [I/HPAH] vs associated PAH [APAH]), FC (II vs III), and median age and baseline 6MWD vs the study population.

Initial treatment with combination therapy was associated with a significant 50% reduction in TcF compared with initial monotherapy. Initial combination of ambrisentan and tadalafil consistently outperformed pooled monotherapy on the end point of TcF across a variety of subgroups. There was a significant improvement of about 50 meters in 6MWD from baseline to week 24 with combination therapy compared with monotherapy. Patients with I/HPAH as well as those with APAH had similar and significant improvements in 6MWD compared with those randomized to

monotherapy. Similar results in favor of combination therapy were seen regardless of functional class, age vs the median age of the study population, and as a function of baseline 6MWD. More patients on initial combination therapy achieved a satisfactory clinical response at week 24. The safety profile was consistent with the known profiles of ambrisentan and tadalafil.

NONINVASIVE OPEN VENTILATION IMPROVES DYSPNEA AND RESPIRATORY SYMPTOMS

Noninvasive open ventilation (NIOV) has been shown to significantly improve respiratory muscle unloading, exercise tolerance, and dyspnea. Brian W. Carlin, MD, Allegheny General Hospital, Pittsburgh, Pennsylvania, USA, presented study results demonstrating that the use of NIOV in addition to standard medical therapy is associated with significant improvements in dyspnea and respiratory symptoms.

This was a retrospective study evaluating the impact of NIOV on the Modified Medical Research Council Dyspnea Scale (mMRC) and chronic obstructive pulmonary disease (COPD) assessment test (CAT) scores of patients with chronic lung disease, who remained symptomatic despite receiving optimal medical therapy. All patients completed the mMRC and received a CAT score prior to (average 14.6 months) and after (average 10.3 months) treatment. The decision to use NIOV was made by the care provider and patients were instructed to use it as needed.

A total of 21 patients (mean age, 70.2 years; range, 56 to 93 years) were included in the study. Nineteen patients had COPD, 1 had pulmonary hypertension, and 1 had bronchiolitis obliterans. The mean time from diagnosis to initiation of therapy was 16.8 months.

Prior to initiating NIOV, patients had an mMRC score of 3.38 ± 0.80 (range, 2 to 4) and a CAT score of 26.71 ± 7.22 (range, 10 to 37). At the end of therapy the mMRC score declined to 1.43 ± 1.08 (range, 0 to 4) and the CAT score decreased to 12.33 ± 7.16 (range, 4 to 27).

By reducing symptoms, patients may ultimately be able to enhance general exercise tolerance, increase ability to participate in pulmonary rehabilitation, increase ability to engage in activities of daily living, and improve overall health-related quality of life.

NEW HEALTH MANAGEMENT SYSTEM REDUCES COST FOR PATIENTS WITH CHRONIC RESPIRATORY FAILURE

Patients with chronic respiratory failure have a hospital utilization rate that is among the highest in the nation. Dov Hirsch, MA, Alana HealthCare, Nashville, Tennessee, USA, discussed the Comprehensive Respiratory Outcome Management (CROM) program, a new health management program that has decreased hospital utilization among patients with COPD and chronic respiratory failure.

The home-based program consisted of visits by a respiratory therapist to perform clinical assessments, intensive education, behavior modification, skill training, smoking cessation, and training in management and mitigation of exacerbations. Respiratory therapists also conducted scheduled and unscheduled phone interviews.

Eligible patients had COPD (GOLD Stage III to IV) and chronic respiratory failure requiring supplementary oxygen (2-4 L) and noninvasive positive pressure ventilation (NIPPV). A total of 459 patients (average age 66 years; 64% women) were enrolled. Of these, 211 (46%) had experienced ≥ 1 hospital admission in the 12 months prior to enrollment and 61 (13%) had experienced ≥ 1 30-day hospital readmission during that period.

After participating in the program, patients experienced a 51% reduction (483 days to 236 days) in hospital admissions, a 56% reduction in total days spent in the hospital, and a 48% reduction in 30-day hospital readmissions.

Dr Hirsch concluded that additional research is needed to determine whether the therapy or the program provides the benefits, who is best equipped to deliver the program (eg, nurse, respiratory therapist, care coordinator), the actual cost of home- vs hospital-based therapy (not just clinical outcomes), and how long patients should stay in the program.

COMBINATION THERAPY SAFE AND EFFECTIVE IN MODERATE-TO-VERY-SEVERE COPD

Umeclidinium (UMEC) is a long-acting muscarinic antagonist approved for maintenance treatment of COPD. Fluticasone furoate/vilanterol (FF/VI; combination inhaled corticosteroid + long-acting β_2 agonist) is indicated for long-term, once-daily maintenance treatment of airflow obstruction in COPD. Thomas Siler, MD, Midwest Chest Consultants, St Charles, Missouri, USA, presented data from 2 phase 3 randomized controlled studies [NCT01957163; NCT02119286], which found combination therapy with UMEC + FF/VI to be a safe and effective treatment for moderate-to-very-severe COPD, compared with placebo + FF/VI.

These were 12-week, parallel-group studies comprising patients (n = 1238) aged ≥ 40 years diagnosed with COPD. Patients were required to be current or former cigarette smokers with a pre- and post-albuterol forced expiratory volume at 1 second (FEV_1)/forced vital capacity (FVC) ratio < 0.7 and $FEV_1 \leq 70\%$ predicted. Treatment with inhaled corticosteroids was permitted prior to the

first study visit. At the end of the 4-week run-in period during which they received FF/VI 100/25 mcg once daily, patients were randomized 1:1:1 to once-daily UMEC 62.5 mcg, UMEC 125 mcg, or placebo, and open-label FF/VI for 12 weeks. All patients were followed for an additional week. The primary end point was trough FEV_1 on day 85. Other end points included weighted mean FEV_1 over 0 to 6 hours on day 84, serial FEV_1, rescue use, and St George's Respiratory Questionnaire (SGRQ) score. Safety was measured by on-treatment adverse events (AEs) and serious AEs.

Both doses of UMEC + FF/VI in both studies produced statistically significant and clinically meaningful improvements in trough FEV_1 at day 85 ($P \leq .001$) and 0 to 6-hour weighted mean FEV_1 at day 84 ($P \leq .001$).

Both doses of UMEC + FF/VI increased the percentage of rescue-free days vs baseline (range, 5.9% to 14.2%) vs placebo (2.3% and 3.8%). There was a significant reduction in puffs per day in both studies for UMEC 62.5 mcg + FF/VI dose and for the UMEC 125 mcg + FF/VI in study 1 (but not study 2). SGRQ scores at day 84 were significantly improved with UMEC 62.5 mcg + FF/VI. The incidence of on-treatment AEs was similar across all groups in both studies (30% to 39%).

Compared with placebo + FF/VI in patients with COPD, once-daily UMEC (62.5 or 125 mcg) added to once-daily FF/VI resulted in improvements in lung function and rescue use, with consistent safety profiles across all treatment groups.

New Bronchodilation Treatments for COPD

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The muscarinic antagonist tiotropium when combined with the β-2 agonist olodaterol provided significant bronchodilation above that achieved with tiotropium alone in patients with chronic obstructive pulmonary disease (COPD). Richard ZuWallack, MD, St. Francis Hospital and Medical Center, Hartford, Connecticut, USA, presented the results of ANHELTO 1 [NCT01694771] and 2 [NCT01696058], studies that evaluated the effectiveness of tiotropium (18 µg QD administered with HandiHaler) + olodaterol (5 µg QD administered with Respimat) in clinically stable patients with COPD.

Both were double-blind, randomized, 12-week studies carried out in 184 centers. Patients with post-bronchodilator forced expiratory volume at 1 second (FEV_1) ≥ 30% and < 80% of predicted normal, with post-bronchodilator FEV_1/forced vital capacity (FVC) < 70%, ≥ 40 years of age, and who are current or ex-smokers with a smoking history of > 10 pack-years were included in the studies. Primary end points were the changes from baseline to 12 weeks in FEV_1 area under the curve from 0 to 3 hours (AUC_{0-3}) and trough FEV_1 response. Secondary end points included St. George's Respiratory Questionnaire (SGRQ) score, peak FEV_1, FVC AUC_{0-3}, peak and trough FVC responses, and rescue medication use.

The mean ages of the 1132 patients enrolled in the studies were 64.6 (study 1) and 64.1 years (study 2); 49.8% and 53.6%, respectively, were men. The mean duration of COPD diagnosis ranged from 7.1 to 8.5 years.

Compared with tiotropium plus placebo, the combined treatment produced significant improvement in FEV_1 AUC_{0-3} response at treatment days 1, 29, and 85 in both studies ($P < .0001$).

Trough FEV_1 response to treatment was also significantly improved by combination therapy compared with tiotropium alone in both studies ($P < .01$). Significant improvements with combined treatment were noted in all secondary end points. Combining olodaterol and tiotropium provided significant improvements in lung function compared with tiotropium + placebo after 12 weeks.

SUN-101 is a long-acting muscarinic antagonist formulation of glycopyrrolate delivered by the eFlow vibrating mesh nebulizer, and it was shown to be as safe and effective as once-daily dosing in patients with moderate-to-severe COPD [GOLDEN-1; NCT01426009]. Edward Kerwin, MD, Sunovion Pharmaceuticals Inc., Marlborough, Massachusetts, USA, presented the results of a recent study [GOLDEN-2; NCT01706536] that evaluated the efficacy and safety of twice-daily treatment.

GOLDEN-2 was a 28-day, randomized, double-blind, placebo-controlled, parallel-arm study that included 282 patients with COPD aged 35 to 75 years, with baseline FEV_1 ≥ 30% and ≤ 70% of predicted, and ≥ 10 pack-year smoking history. Patients were randomized to SUN-101 (12.5 mcg, n = 55; 25 mcg, n = 54; 50 mcg, n = 57; or 100 mcg, n = 59) or placebo (n = 57) twice daily. Inhaled corticosteroids and roflumilast were permitted throughout the study. The primary end point was change from baseline in morning trough FEV_1 on day 28. The main secondary end point was change from baseline in AUC_{0-12} FEV_1 on day 28. Safety was assessed by adverse events (AEs).

All doses of SUN-101 were associated with significant increases in trough FEV_1 on day 28 ($P < .005$). After each dosing, there was rapid onset of bronchodilation, which persisted throughout the dosing interval.

Significant improvements were also seen in FEV_1 AUC_{0-12} on day 28 for all doses versus placebo ($P < .0001$). All doses of SUN-101 were well tolerated, with no deaths and a low incidence of serious AEs. The most