Between 55% and 80% of ventilated ICU patients have delirium, with an estimated 65% unrecognized or untreated. Although limited evidence supports the use of haloperidol in delirium in critical patients, a survey of practitioners in the United Kingdom demonstrated that up to 95% and 80% of practitioners use haloperidol to treat hyperactive delirium and hypoactive delirium, respectively. The HOPE-ICU trial tested the hypothesis that early treatment of critically ill patients with haloperidol will increase the number of days alive without delirium or coma.

In the single-center, Phase 2, double-blind, placebo-controlled HOPE-ICU trial, 142 patients were randomized 1:1 to receive haloperidol 2.5 mg or intravenous saline every 8 hours for up to 14 days, at discharge, or until patient was delirium-free for 2 consecutive days. Patients were included if they required ventilation within 72 hours of ICU admission and were excluded for chronic antipsychotic use, Parkinson's disease, a QTC of greater than 500 msec, uncomplicated elective heart surgery, dementia, likelihood to leave or die within 48 hours, pregnancy, or readmission. Patients were assessed daily for delirium by the confusion assessment method-ICU.

The primary endpoint of the HOPE-ICU trial was the number of days alive free of delirium or coma at 14 days. The number of ventilator-free days at Day 14, delirium-free, coma-free, and mortality at 28 days, length of critical care, and length of hospital stay were considered secondary endpoints.

No significant difference was observed in delirium-free or coma-free days at Day 14 between patients that were treated with haloperidol or placebo. The trend of nonsignificance continued to Day 28. In addition, there was no significant difference between the haloperidol or placebo arms in the secondary endpoints of number of ventilator-free days at Day 14, delirium-free days and mortality at Day 28, length of ICU stay, and length of hospital stay.

The safety profiles were similar among the haloperidol and placebo arms. A QTC of >500 msec after electrolyte correction occurred in seven patients in the haloperidol arm and four patients in the placebo arm (p=0.29). Oversedation despite decreasing the dose by half occurred in eight patients in the haloperidol arm and five patients in the placebo arm (p=0.35). Extrapyramidal symptoms were not observed among patients in the haloperidol arm (after halving the dose) and in one patient in the placebo arm (p=0.57).

The data from HOPE-ICU indicates that treatment of ventilated ICU patients with haloperidol does not prevent or treat delirium. Prof. Page said that, in ICU patients with delirium, perhaps the target pathophysiology is actually neuroinflammation, rather than neurotransmitter imbalance.

Beraprost Plus Sildenafil Effective in Pulmonary Arterial Hypertension

Written by **Emma Hitt, PhD**

Combination treatment of beraprost and sildenafil results in improved 6-minute walk test (6MWT) distance and decreases N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and time to worsening in patients with pulmonary arterial hypertension (PAH). Zhi-Cheng Jing, MD, Fu Wai Hospital & National Center for Cardiovascular Disease, Beijing, China, presented data from the Beraprost Combined Therapy With Sildenafil for Pulmonary Arterial Hypertension study [BEST; ChiCTR-TCC-12002776].

Patients with PAH have poor long-term survival rates, highlighting a need for a first-line combination therapy. This is particularly important in China, where many novel targeted agents for the treatment of PAH are not available in typical daily practice. The hypothesis of the BEST study was that the addition of beraprost to sildenafil would improve efficacy in the treatment of PAH.

In the open-label BEST study, 60 patients with PAH receiving sildenafil monotherapy were randomized to receive beraprost in addition to sildenafil, or continue with sildenafil monotherapy. Patients aged 18 to 65 years who had World Health Organization functional class (WHO-FC) II to IV symptomatic PAH and a 6MWT of 150 to 450 meters at baseline who were receiving sildenafil monotherapy for 3 to 6 months were included in the study.

Follow-up at 12 weeks and 24 weeks included a 6MWT, WHO-FC assessment, and NT-proBNP analysis. The primary endpoint was improvement in the distance of the 6MWT. WHO-FC, NT-proBNP levels, hemodynamic parameters, and time to clinical worsening were the secondary endpoints.

At 12 weeks, patients treated with combination therapy demonstrated a mean 6MWT distance increase of 43.6 meters, as compared with 7.4 meters in the sildenafil monotherapy group (p=0.072). At 24 weeks, patients that received combination therapy had a mean 6MWT distance increase of 50.8 meters, as compared with 5.6 meters in the monotherapy arm (p=0.04).

A significant decrease in NT-proBNP levels was observed in the combination-therapy arm of 437 pg/mL at Week 12 and 399 pg/mL at Week 24, as compared with a 300-pg/mL increase at Week 12 (p<0.001) and a 46-pg/mL increase at Week 24 in the monotherapy arm (p<0.001). In addition, significantly more patients in the combination arm improved WHO-FC by at least one class, as compared with patients in the monotherapy arm (p=0.01). Event-free survival was significantly greater in the beraprost plus sildenafil group, as compared with the sildenafil monotherapy group (p=0.027).

Adverse events such as headache, diarrhea, nausea, dizziness, and jaw pain occurred significantly more frequently in the combination arm, as compared with the monotherapy arm. Flushing and extremity pain occurred with similar frequency among both study groups.

Prof. Jing said that, in his opinion, the BEST Study suggests that adding beraprost to sildenafil therapy in the treatment of PAH is effective and well tolerated, but should be further evaluated in additional studies.

Dupilumab Is Safe and Effective for Controlling Asthma Attacks

Written by **Maria Vinall**

Dupilumab (SAR231893/REGN668) reduces symptoms and improves lung function with side effects similar to placebo in patients with moderate to severe, persistent asthma. Dupilumab, a fully human monoclonal interleukin (IL) antibody, is a potent inhibitor of both IL-4 and IL-13. Sally E. Wenzel, MD, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, presented the results of a Phase 2, randomized, double-blind study comparing the effect of dupilumab and placebo on the incidence of asthma exacerbations in patients with persistent moderate-to-severe eosinophilic asthma [NCT01312961].

Patients (n=52 in each group) with persistent (≥12 months) asthma defined as airway inflammation likely to be eosinophilic (≥300 cells/μL or sputum eosinophils ≥3%), with asthma partially controlled or uncontrolled on inhaled corticosteroid (ICS) plus long-acting β-agonist (LABA) therapy and on a stable dose of either fluticasone/salmeterol, budesonide/formoterol, or mometasone/formoterol combination therapy for ≥1 month prior to screening were enrolled in the study. The study consisted of a maximum 2-week screening period, followed by 12 weeks of treatment (or until asthma exacerbation), and 8 weeks of follow-up.

Patients were switched to fluticasone/salmeterol for 4 weeks at randomization, after which LABA was withdrawn. The primary outcome was the number of patients experiencing an asthma exacerbation after 12 weeks. Exacerbation was defined as ≥30% reduction from baseline in morning expiratory flow rate (PEF) on 2 consecutive days, ≥6 additional reliever inhalations per 24 hours on 2 consecutive days, or exacerbation of asthma requiring systemic glucocorticoid treatment, an increase in inhaled glucocorticoids of at least 4 times the most recent dose, or hospitalization for asthma, as determined by the investigator.

There were seven secondary outcomes including changes in forced expiratory volume in 1 second (FEV_1), morning/ evening PEF, reliever use, 5-item Asthma Control Questionnaire (ACQ5), asthma symptom scores, nocturnal awakenings, and the Sino-Nasal Outcome Test (SNOT-22). Tolerability measures included the proportions of patients with treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and discontinuations due to TEAEs. Dupilumab (300 mg) was administered subcutaneously QW for 12 weeks.

The percentage of predicted baseline FEV_1 values (~72%), ACQ scores (2.08), mean number of asthma exacerbations in the past 2 years (1.38), and percentage of prior ICS/LABA combination therapy doses were similar between the groups. At the end of treatment, 3 (6%) patients treated with dupilumab had an asthma exacerbation compared with 23 (44%) on placebo, corresponding to an 87% relative risk reduction (OR 0.08; 95% CI, 0.02 to 0.28; p<0.0001).

Time to asthma exacerbation was longer and risk of exacerbation reduced with dupilumab (Table 1). The cumulative exacerbation rate increased over the 12-week study period in the placebo group while remaining little changed in the dupilumab group. All secondary endpoint measures favored dupilumab (Table 1).

Table 1. Secondary Endpoints

Outcome	Difference, Dupilumab vs Placebo (95% CI)	p Value
KM estimate for asthma exacerbation probability at 12 weeks	0.10 (0.03 to 0.34)	<0.001
Change in FEV_1	0.27 (.011 to 0.42)	<0.001
Change in AM PEF	34.6 (10.6 to 58.5)	0.005
Change in PM PEF	22.7 (–0.7 to 46.0)	0.06
Change in ACQS	–0.73 (–1.15 to -0.30)	0.001
Change in AM symptom score	–0.7 (–0.9 to –0.4)	<0.001
Change in PM symptom score	–0.7 (–0.9 to –0.4)	<0.001
Change in number of nocturnal awakenings	–0.2 (–0.5 to 0.0)	0.05
Change in SNOT-22	–8.49 (–13.96 to –3.03)	0.003
Change in number of reliever inhalations	–0.2 (–2.9 to –1.2)	<0.001

TEAEs were observed in a similar proportion of patients in each group (81% of the dupilumab- and 77% of placebo-treated patients). The AEs were generally nonspecific and of mild-to-moderate intensity. Injection site reactions, nasopharyngitis, nausea and headache occurred more often in the dupilumab group. Upper respiratory tract infections were more common among placebo-treated patients. There were 4 SAEs (3 in the placebo group and 1 in the dupilumab group); none were considered to be related to the study drug. There were no deaths.

Dupilumab appears to be effective and safe for preventing and controlling protocol defined asthma exacerbations and improving lung function and asthma control both after addition to ICS/LABA and following ICS/LABA withdrawal in patients with moderate to severe, persistent asthma with elevated eosinophil levels.