who were managed by this algorithm, then 1 had an asthma exacerbation that was prevented.

Analysis of the individual types of exacerbations showed no difference in hospital admission or visits to an emergency department or labor ward. Patients in the control group had a significantly higher rate of unplanned or unscheduled clinic visits (p=0.002), and significantly more patients required oral steroids as compared with the $F_ENO$ group (p=0.04). The algorithm was associated with a significantly lower daily dose requirement of inhaled corticosteroids (p=0.043).

"Asthma exacerbations during pregnancy can be significantly reduced by the use of a validated $F_ENO$-based treatment algorithm," said Prof. Gibson. "Future work should investigate the application of this algorithm in routine antenatal care and other settings."

## TESRA Study Results

Results from the Treatment of Emphysema with a Selective Retinoid Agonist (TESRA; NCT00413205) study showed that emphysema patients had a mixed response to treatment with the retinoid agonist palovarotene. Treatment with palovarotene failed to meet the primary endpoint of improving lung function ($FEV_1$) in the overall analysis. However, the subset of patients with lower lobe emphysema had a significant reduction in the rate of decline in lung function.

A post hoc analysis in the lower lung suggested that palovarotene was associated with less worsening over time in most outcomes in patients with lower lung emphysema predominance. "These findings are very much post hoc and preliminary and require confirmation using a more detailed analysis of emphysema progression in different parts of the lung. However, the observations from this hypothesis-generating study do suggest that they need to be tested again but in a group of patients identified beforehand as having predominant lower lung emphysema," said Paul W. Jones, MD, PhD, St. George's University of London, London, United Kingdom.

TESRA was a Phase 2, double-blind, randomized, placebo-controlled, multicenter trial that involved investigators at 69 centers in 12 countries. Palovarotene is an oral retinoid agonist that is selective for the gamma receptor, which is thought to play a key role in alveolar formation. In preclinical models of emphysema, the drug reduced inflammation, promoted structural repair, and improved lung function.

TESRA involved ex-smokers who had computed tomography-documented emphysema, baseline postbronchodilator $FEV_1$ <70% of predicted, and baseline $TL_{CO}$ <70% of predicted. They were randomized 2:1 to palovarotene 5 mg/day or placebo, both in addition to optimized therapy for chronic obstructive pulmonary disease (COPD). Treatment and follow-up continued for 2 years. The primary outcome was the change in $FEV_1$ after 2 years.

When the trial ended, patients in the palovarotene arm had a 4.5-ml improvement in $FEV_1$ compared with the placebo group, a difference that failed to achieve statistical significance (p=0.86).

Four regions of interest had been identified in the lungs: upper quartile, upper half, lower half, and lowest quartile. Patients in the placebo arm had greater loss of lung function in the lower half and lowest quartile, compared with the upper half and upper quartile. A post hoc analysis of these regions of interest showed that in patients who were treated with placebo, the change in $FEV_1$ in the lower half of the lung averaged -56.7 ml at 12 months and -124.4 ml at 24 months and -56.2 ml at 12 months and -174.7 ml at 24 months in the lower quartile. In contrast, the rate of loss of $FEV_1$ in patients who were treated with paloverotene was less: lower half -33.0 ml and -40.9 ml at 12 and 24 months; lowest quartile: -56.2 ml and -46.0 ml at 12 and 24 months. A similar response pattern emerged with respect to $DL_{CO}$, 6-minute walk distance, and quality of life.

In addition to optimal COPD therapy, in patients with lower lung emphysema, palovarotene significantly reduced the decline in $DL_{CO}$ and $FEV_1$, which may be suggestive of a disease-modifying effect.

## Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus Trial

Lung function in lymphangioleiomyomatosis (LAM) stabilized and symptoms and quality-of-life (QoL) improved significantly during treatment with sirolimus, according to results of the Multicenter International LAM Efficacy of Sirolimus (MILES) Trial, reported Francis X. McCormack, MD, University of Cincinnati, Cincinnati, Ohio, USA, on behalf of the NIH Rare Lung Diseases Consortium.

$FEV_1$ increased by 1 ml in the sirolimus group compared with a 12-ml decrease with placebo (p<0.0001) over the course of the 1-year treatment period. Forced vital capacity

(FVC) also improved with sirolimus, but exercise tolerance and measures of gas exchange did not change. There was a 50% reduction in serum levels of vascular endothelial growth factor-D (VEGF-D), which stimulates pathological growth in LAM. Functional and symptomatic improvement lasted only so long as patients remained on sirolimus.

LAM is a rare cystic lung disease that affects women. The condition arises from mutations in the tuberous sclerosis complex (TSC) genes that regulate mammalian target of rapamycin (mTOR) [Carsillo and Henske. *Proc Natl Acad Sci* 2000]. Additionally, lung lesions that are associated with LAM exhibit abnormal mTOR activation, providing a rationale to investigate treatment with sirolimus, which inhibits mTOR [Goncharova et al. *J Biol Chem* 2002].

In a small open-label trial, tumors that were associated with TSC or LAM shrunk by 50% during treatment with sirolimus, and lung function improved by as much as 13% [Bissler et al. *N Engl J Med* 2008].

The accumulation of clinical and preclinical evidence led to the multicenter trial, reported by Dr. McCormack. Investigators at 13 sites in the United States, Canada, and Japan randomized 89 patients with moderate lung impairment to sirolimus or placebo for 12 months, followed by an additional 12 months of follow-up. The primary endpoint was the change in $FEV_1$ from baseline to 12 months.

Baseline characteristics did not differ significantly between treatment groups. The patients had an $FEV_1$ of 49% of predicted, FVC of 80%, total lung capacity of 105%, functional residual capacity of 113%, residual volume of 141%, and carbon monoxide diffusion capacity of 43%, consistent with moderately severe obstructive lung impairment, air trapping, and reduced diffusing capacity.

Patients who were randomized to active therapy received sirolimus 2 mg. Sirolimus levels were measured at every visit after baseline, and the dose was adjusted to maintain a serum level of 5 to 15 ng/ml.

The observation period of the trial was truncated after a planned interim analysis in February 2010 showed that the stopping rule for efficacy had been met.

Among patients in the sirolimus arm, $FEV_1$ had stabilized or improved in 46% of patients compared with 12% in the placebo group ($p<0.001$). Moreover, the change in $FEV_1$ averaged -134 ml in the placebo group versus an increase of 19 ml with sirolimus, resulting in a between-group difference of 153 ml ($p<0.001$).

"The clinical relevance of an $FEV_1$ difference of 153 ml is important to consider," said Dr. McCormack. "It represents more than a 10% increase from baseline mean $FEV_1$ of 1.37 liters for these patients. It exceeds the estimated minimal clinically important difference in $FEV_1$ for COPD of 100 to 140 ml, which can be perceived by patients and is typical for bronchodilator response. Another reason that a 153-ml difference might be important is that in any patient with advanced disease, any stabilization that may delay transplantation and associated risk is of value."

The change in FVC averaged a decrease of 129 ml in the placebo group versus an increase of 97 ml in the sirolimus group. Sirolimus was associated with significant improvement in functional performance and QoL versus placebo ($p=0.03$). $FEV_1$ began to decrease soon after patients stopped treatment, although the mean value in the sirolimus group exceeded that of the placebo group through the end of the 12-month follow-up period.

Sirolimus was associated with a higher incidence of adverse events. The most common adverse events were stomatitis, diarrhea, nausea, hypercholesterolemia, acneiform rash, and lower-extremity edema.

"Therapy with sirolimus may be useful in selected LAM patients," concluded Dr. McCormack. "Longer-term studies are needed to determine if benefit can be sustained with continued therapy."

## Intensive Care Physician- Versus Qualified Nurse-Based Critical Care Transport

Qualified nurses can safely accompany selected critical care patients during ground transport, minimizing the need for physician assistance, suggest the results of a randomized controlled (IQ transport) trial, presented by Erik van Lieshout, MD, University of Amsterdam, Amsterdam, The Netherlands. Transport time and the incidence of clinical events were similar whether critical nurses or physicians accompanied patients during transport. Additionally, the frequency and magnitude of adjustments in inotropic or vasoactive medication did not differ between groups.

Regionalization of health care delivery has increased the need for interhospital transport of critically ill patients. The level of clinical expertise that is required to ensure safe ground transport of intensive care patients remains unclear, and the Society of Critical Care Medicine has provided no guidance on the issue [*Crit Care Med* 2004]. In an effort to resolve some of the uncertainty, participants in the Mobile Intensive Care Unit in the Amsterdam