(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

region designed a randomized trial to compare the safety of interhospital transport of critically ill patients who were escorted by critical care nurses versus physicians. The trial tested the hypothesis that ground transport of selected patients who are escorted by critical care nurses is not inferior to physician-based ground transport.

The trial design excluded patients with a low oxygenation index (P/F ratio <100 mm Hg) that was associated with a positive expiratory pressure >15 cm H_2O; mean arterial pressure <60 mm Hg despite adequate fluid therapy; increased inotrope requirements (noradrenaline >0.35 µg/kg/min or dopamine >15 µg/kg/min); or the need for cardiac resuscitation or defibrillation within the previous 24 hours.

The primary outcome was the number of critical events, comprising:

- Technical events (loss of battery power, device malfunction)
- Increase or decrease in arterial pressure >20 mm Hg for more than 10 minutes
- Decline in O_2 saturation >10% for more than 10 minutes
- Temperature <36°C (96.8° F)

Monitoring equipment was linked to an electronic medical record system to ensure that every critical event was documented automatically.

Investigators randomized 307 patients to nurse or physician escort during interhospital ground transport. The patients were 60 to 65 years of age, women accounted for about 40% of the study population, APACHE II scores were 18 to 19, and the length of intensive care unit (ICU) stay before transport averaged 3 days. Transport distance averaged 17 miles, and transport time averaged 65 minutes.

Overall, 51 critical events occurred during the study—28 in the physician group and 23 in the nurse group. There were no significant differences in the percentages of technical or critical events between the two groups.

Analysis of secondary outcomes showed no significant differences in the average number of events by transport time, adjustments to ventilator settings, or adjustments in inotropic/vasoactive medications. Physicians were more likely to make adjustments to O_2 settings (16% of patients vs 12%; p=0.03) and to administer >1000 ml of fluid (11% vs 5%; p=0.002).

"Ground critical care transport by nurses seems safe," said Prof. van Lieshout. "The level of vasopressor, inotropic, and ventilator support could be tailored to the staffing of transport."

Prof. van Lieshout acknowledged several limitations of the study, including the lack of evaluation of air transport, enrollment of a selected patient population, and no standardization of ICU stabilization. He suggested that future studies should compare physician and nurse performance in the transport of sicker patients and should examine the potential role that telemedicine might play in the transport of critically ill patients.

Chronic Azithromycin Decreases the Frequency of COPD Exacerbations

One year of treatment with azithromycin significantly educed the rate of acute exacerbations of chronic obstructive pulmonary disease (COPD) and improved quality of life (QoL), according to results of a large randomized clinical trial, presented by Richard K. Albert, MD, Denver Health, University of Colorado, Denver, Colorado, USA.

Both the time to first acute exacerbation and the annualized rate of acute exacerbations were significantly lower in the azithromycin group (p<0.0001 and p=0.004, respectively). Scores on a QoL questionnaire that was specific for pulmonary disease showed significant improvement with azithromycin compared with placebo (p<0.006). The incidence of hearing decrement was increased by about 25% with active therapy versus placebo (p=0.002). The findings might help bring some clarity to the role of macrolide antibiotics in the management of COPD.

Although the trial addressed many of the shortcomings of previous studies [Banerjee D et al. *Respir Med* 2005; Suzuki T et al. *Chest* 2001; Seemungal TAR et al. *Am J Respir Crit Care Med* 2008; Yamaya M et al. *J Am Geriatr* Soc 2008; He Z et al. *Respiration* 2010], the impact of azithromycin on macrolide resistance in community bacterial flora remains unknown. Macrolide antibiotics have anti-inflammatory and immunomodulatory effects, in addition to antimicrobial properties. Chronic macrolide use has been shown to reduce the rate of exacerbations of cystic fibrosis and improve the status of patients with other types of airway disease, said Dr. Albert.

To examine the role of macrolides in COPD, investigators designed a randomized, placebo-controlled trial to evaluate azithromycin 250 mg/day, added to patients' existing COPD medications. Treatment and follow-up in the azithromycin and placebo groups continued for 1 year after randomization.

Eligible patients were aged >40 years, had moderate to severe COPD, and at least a 10 pack-year history of