Safety and tolerability—including treatment discontinuation—were similar between treatment groups.

"The activity of the rifapentine regimen was not superior to that of the rifampin regimen, based on the endpoint of culture status at the end of intensive-phase treatment," Dr. Dorman said in conclusion. "There was a trend toward rifapentine superiority in noncavitary pulmonary disease."

Pharmacokinetic studies showed relatively low exposure to rifapentine. Further studies are needed to determine the optimal dose of rifapentine and to define its role in the treatment of TB.

Asthma Exacerbations During Pregnancy Are Reduced By Inflammatory-Guided Asthma Management

Asthma exacerbations during pregnancy declined 50% in patients who were managed by a clinical algorithm that was guided by exhaled nitric oxide. Peter Gibson, MD, University of Newcastle, New South Wales, Australia, reported the results of the Managing Asthma in Pregnancy (MAP) trial.

The time to first exacerbation was significantly prolonged in patients who were managed by the fraction of exhaled nitric oxide (F_ENO) algorithm, associated with a hazard ratio of 0.565, compared with the control group. The proportion of patients who had at least one exacerbation was about 40% lower in the F_ENO group.

Unplanned or unscheduled clinic visits and use of oral corticosteroids also were significantly reduced by adherence to the F_ENO algorithm. More patients in the experimental arm received inhaled corticosteroids and long-acting beta agonists; however, inhaled corticosteroid dose requirements were significantly lower.

Asthma is the most common chronic illness in pregnancy, occurring in about 12% of cases. Asthma exacerbations are common during pregnancy and associated with significant maternal and fetal morbidity. Given the concern over medication use during pregnancy, a method to optimize the dosing of inhaled corticosteroids would be helpful in clinical management.

Treatment that is based on sputum eosinophil count has been shown to reduce asthma exacerbations, and F_ENO is a marker of airway eosinophilia and inflammation [Petsky H. *Cochrane Rev* 2008]. However, studies of F_ENO-guided management have yielded equivocal results, said Prof. Gibson. Continuing the evaluation of F_ENO-guided asthma management, investigators designed a randomized trial to assess the value of an algorithm in pregnancy. They enrolled asthmatic women between gestational weeks 12 and 20.

All patients on maintenance inhaled corticosteroids were switched to an equivalent dose of budesonide, and patients with unstable disease status began treatment with budesonide. Randomization occurred at the second clinic visit. Thereafter, patients in the F_ENO and control groups underwent the same evaluation at each clinic visit: F_ENO, spirometry, asthma control by Asthma Control Questionnaire (ACQ), and optimization of asthma self-management.

Patients in the control group were managed according to clinical guidelines. The remaining patients were managed by use of a validated algorithm, comprising F_ENO and ACQ [Gibson PG. *Clin Exp Allergy* 2009]. The algorithm was used to adjust the budesonide dose in response to changes in F_ENO, and a long-acting beta agonist (LABA) was used for symptom management in the absence of elevated F_ENO.

The algorithm comprises five steps:

1. F_ENO >29 parts-per-billion (ppb): Increase inhaled corticosteroid dose by one step
2. F_ENO 16–29 ppb, ACQ ≤1.5: No change
3. F_ENO 16–29 ppb, ACQ >1.5: Increase LABA dose by one step
4. F_ENO <16 ppb, ACQ >1.5: Decrease inhaled steroid dose by one step, increase LABA dose by one step
5. F_ENO <16, ACQ ≤1.5: Reduce inhaled steroid dose by one step

The study involved 220 patients, 203 of whom completed the trial. The two groups were similar with respect to baseline characteristics, including FEV_1 and use of inhaled corticosteroids. The primary outcome was the sum of moderate and severe asthma exacerbations during pregnancy. Exacerbations consisted of unscheduled visits to a doctor, visits to an emergency department, hospital admission, and oral steroid use for asthma control.

When the trial ended, the F_ENO group had an incidence rate ratio of 0.499 versus the control group (p=0.001). In the control group, 40% of patients had at least one asthma exacerbation during pregnancy, compared with 25% in the F_ENO group (p=0.011). The number-needed-to-treat was 6, meaning that for every 6 pregnant women with asthma

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