Evaluation of a Rifapentine-Containing Regimen for Intensive Phase Treatment of Pulmonary TB

Patients with sputum-positive tuberculosis (TB) had similar negative culture rates after 8 weeks of treatment with rifapentine or rifampin, according to results of the TBTC Study 29 (NCT00694629). By solid media analysis, 91.4% of the rifapentine group and 89.1% of the rifampin group had negative cultures. By liquid media, the negative-culture rates were 74.6% with rifapentine and 70.1% with rifampin, as presented by Susan E. Dorman, MD, Johns Hopkins University, Baltimore, Maryland, USA.

Rifamycins, including rifampin, form the key antibacterial component of current regimens for treating pulmonary TB but require continuous use for 6 months or longer.

The rifampin analog rifapentine demonstrated bacterial eradication after 3 months of daily treatment in a mouse model of TB [Rosenthal et al. *PLoS Medicine* 2007]. In healthy humans, rifapentine doses of as much as 10 mg/kg proved safe when administered once daily for a week [Keung et al. *Int J Tuberc Lung Dis* 1999].

Dr. Dorman reported findings from a Phase 2 study that compared rifampin 10 mg/kg and rifapentine 10 mg/kg, administered without food 5 times weekly for 8 weeks as a component of combination therapy with isoniazid, pyrazinamide, and ethambutol on behalf of the Tuberculosis Trials Consortium. The primary endpoint was the proportion of patients with negative cultures at the end of intensive-phase treatment. Secondary outcomes included safety, tolerability, and time to culture conversion.

Follow-up visits occurred at 2-week intervals and included sputum culture and assessment of safety and tolerability. The final analysis comprised 381 patients who were enrolled at sites in the United States, South America, Europe, Africa, and Asia. The study population had a median age of 33 years and a median body mass index of 20 kg/m^2. Between 50% and 55% of patients were enrolled in Africa, and women accounted for about a third of the study population. Ten percent to 12% of patients were HIV-positive, 70% had cavitation on chest x-ray, about 60% had smear grade 3 or 4 (high bacillary load), and the median duration of prior TB treatment was 2 days.

Per-protocol analysis showed that 128 of 179 patients (71.5%) in the rifampin arm and 152 of 202 (75.3%) in the rifapentine arm had negative sputum tests by liquid media at 8 weeks of treatment (p=0.48). By solid media, 152 of 171 patients (88.9%) in the rifampin group and 182 of 198 (91.9%) in the rifapentine group had negative sputum cultures (p=0.42).

Similar results emerged from an intention-to-treat analysis, as 72.2% of rifampin-treated patients and 76.4% of patients in the rifapentine arm had negative cultures by liquid media (p=0.39). Negative-culture rates by solid media were 88.2% and 92.1% in the rifampin and rifapentine groups, respectively (p=0.25).

A post hoc per-protocol analysis by cavitation status demonstrated a significantly higher negative-culture rate by solid media for patients with noncavitary disease who were treated with rifapentine (100% vs 89.3%; p=0.03). Otherwise, the analysis showed no significant differences between the groups.

A multivariate analysis of factors that were associated with negative sputum culture by liquid media confirmed that treatment assignment did not affect outcome. The analysis did identify four independent predictors of response, as defined by negative sputum culture: female sex (OR=2.78; p<0.01), high bacillary load (OR=0.34; p<0.01), fever (OR=0.37; p=0.01), and productive cough (OR=0.12; p<0.01).

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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