Adverse events were reported by 4% of patients, and 0.5% of patients had serious adverse events. Adverse events led to discontinuation in 2.8% of patients. No patients died during the study.

Prostacyclin Analog Shows Chemoprevention Potential

Treatment with an oral prostacyclin analog improved endobronchial dysplasia in former smokers in a randomized pilot study of lung cancer chemoprevention, presented by Robert Keith, MD, Denver VA Medical Center and the University of Colorado, Denver, CO.

All measures of dysplasia (airway damage) improved in patients who were treated with iloprost, whereas the same parameters worsened in patients who were randomized to placebo. Consistent with results from previous studies, only former smokers benefited from treatment, suggesting that smoking cessation is a necessary component of chemoprevention.

Clinical and preclinical evidence has suggested that regulation of prostaglandin production (PGI_2 and PGE_2) plays a major role in the risk, evolution, and progression of lung cancer. For example, manipulation of prostacyclin synthase (PGI) has been shown to prevent tumor formation in mouse models of lung cancer (Keith et al. *Cancer Res* 2002; Keith et al. *Cancer Res* 2004).

To test the chemopreventive potential of iloprost, investigators enrolled 152 current and former smokers with a smoking history of at least 20 pack years, no history of cancer, and sputum cytologic atypia. Study participants were randomized to placebo or to oral iloprost (not available in the United States) at a starting dose of 50 µg BID, increasing to a maximum dose of 150 µg BID.

Participants underwent bronchoscopy at baseline and after 6 months of treatment. The primary endpoint was the change from baseline in total dysplasia score at 6 months, based on bronchial biopsy samples that were obtained from six prespecified sites. The dysplasia score was derived from the 8-point World Health Organization classification system for preneoplasia (ranging from normal=1 to invasive cancer=8). Investigators employed three separate histological measures: average histology over all biopsies, worst histology, and dysplasia index, determined by the percentage of biopsies with dysplasia score ≥4 (moderate dysplasia).

The study population comprised 81 current smokers and 71 former smokers. At the 6-month evaluation, all three histological parameters favored iloprost in former smokers. On average, the worst-histology score in the iloprost group decreased from 4.25 at baseline to 3.85 at 6 months, whereas worst histology increased from 3.91 to 4.14 in the placebo group (p=0.038). In addition, twice as many participants in the iloprost group had at least a 1-point improvement in worst histology (40% vs 20%; p=0.014).

Each of the three measures of the primary outcome declined in former smokers who were randomized to iloprost but increased among former smokers in the placebo group. Between-group differences for all three parameters achieved statistical significance (p=0.010 to p=0.002). In contrast, none of the outcome measures differed significantly between current smokers who were treated with iloprost or placebo.

Investigators have begun planning another chemoprevention trial that will be limited to former smokers and will have lung cancer incidence as the primary outcome.

Assessing Young Children's Ability to Use a Novel Propellant-Free Inhaler

With parental assistance and use of a spacer, young children can correctly use a novel propellant-free metered-dose inhaler to treat respiratory conditions, German investigators reported.

Only one of 99 children aged younger than 5 years did not use the Respimat® Soft Mist™ inhaler correctly. Technical failure occurred as a result of the child's refusal to cooperate rather than an inability to use the inhaler, Wolfgang Kamin, MD, Children's Hospital, Hamm, Germany, and colleagues reported.

The Respimat® Soft Mist™ is a handheld, multidose, propellant-free inhalation device that generates a slow-moving cloud that contains a high, fine-particle medication dose. Because spray generation is independent of inspiratory flow, the device might afford opportunities to treat young children with respiratory disorders.

To assess the ability of young children to use the novel inhalation device, investigators at two centers in Germany recruited 99 pediatric patients with a variety of respiratory disorders. The children were grouped by age (<1, 1 to <2, 2 to <3, 3 to <4, and 4 to <5 years) and their inhaler usage skills were evaluated by direct observation of the investigators.

Dr. Kamin reported that all but one child aged younger than 3 years were able to use the Respimat® Soft Mist™

correctly with a spacer. Additionally, 23 of 27 (85%) children aged 4 to 5 years were able to use the device correctly without a spacer, but only 12 of 30 (40%) children aged 3 to 4 could use the Respimat® Soft Mist™ correctly without a spacer.

When paired with the spacer, all children in the 3 to 4 year and 4 to 5-year age groups could use the inhaler properly. Rates of correct usage decreased without parental assistance.

"The majority of subjects aged 4 to 5 can handle the Respimat® Soft Mist™ inhaler without a spacer but with considerable variability in technique," Dr. Kamin concluded. "Thus, to ensure standardized dosing, children below 5 years of age are recommended to use the Respimat® Soft Mist™ inhaler with a spacer."

In general, patient and parental satisfaction with the Respimat® Soft Mist™ inhaler was high, with or without the spacer. Satisfaction rates for reliability, instructions, ease of use, and overall ability to use the inhaler were 90% or higher, declining to 75% when children were handling the device alone. The Respimat® Soft Mist™ inhaler plus spacer had satisfaction rates that ranged from 83% to 97% for all components of use.

Comparing Combination Therapies for COPD Maintenance

Combination therapy with tiotropium and salmeterol led to greater improvement in lung function parameters in patients with chronic obstructive pulmonary disease (COPD) than did the combination of fluticasone and salmeterol, reported Helgo Magnussen, MD, PhD, Hospital Grosshansdorf, Grosshansdorf, Germany.

Thoracic gas volume (TGV) improved significantly after 8 weeks of therapy with tiotropium+salmeterol ($p<0.05$), and exercise endurance time (EET) also improved.

The findings come from a randomized, crossover clinical trial to provide information about the relative effects of different combination maintenance therapies for COPD. Current clinical guidelines recommend combination therapy when response to single-agent therapy is suboptimal.

The study involved 309 patients whose mean age was 61 years and who had a mean baseline postbronchodilator forced expiratory volume at one second (FEV_1) of 1.36 L (47% of predicted), TGV of 5.42 L (165% of predicted), and EET of 458 seconds. The trial lasted 16 weeks, during which time patients were randomized to 8 weeks of therapy with tiotropium+salmeterol or fluticasone+salmeterol and then crossed over to the opposite therapy for an additional 8 weeks of treatment.

The co-primary endpoints were TGV and EET at 8 weeks. The tiotropium+salmeterol combination led to significantly greater improvement in TGV compared with fluticasone+salmeterol, averaging 87 mL after 8 weeks ($p=0.0482$). The difference between groups emerged early and averaged 182 mL after 4 weeks ($p<0.0001$).

Improvement in EET did not differ significantly between groups, averaging 15 seconds more with tiotropium+salmeterol after 8 weeks. The difference averaged 26 seconds for patients who reported dyspnea and 12.5 seconds for patients who reported dyspnea and leg discomfort.

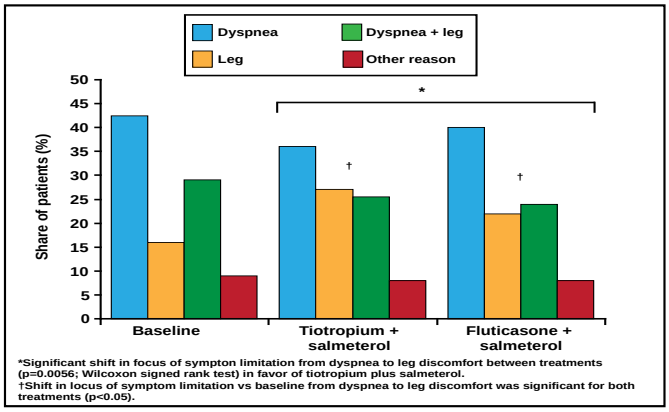
Several other parameters of lung function improved significantly during treatment with tiotropium+salmeterol. Postbronchodilator differences at 8 weeks were:

- FEV_1, 71 mL; $p<0.0001$
- Forced vital capacity, 154 mL; $p<0.0001$
- Inspiratory capacity, 115 mL; $p=0.0005$
- Residual volume, -154 mL; $p=0.0011$

The change from baseline in the Borg dyspnea score at exercise isotime favored tiotropium+salmeterol (-0.21; $p=0.07$) and was significantly greater after 4 weeks (-0.23; $p<0.05$).

The results demonstrated a significant shift in the locus of exercise-limiting symptoms from breathing discomfort (-20 patients) to leg discomfort (+35 patients) after treatment with tiotropium+salmeterol compared with fluticasone+salmeterol (-1, +19 patients; $p=0.0056$ between groups; Figure 1).

Figure 1. Exercise-Limiting Symptoms.



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