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UPLIFT: New Data Reinforces a Maintenance Algorithm

San Diego - Late last year, a large multinational study found that a maintenance pharmacologic therapy with improved outcomes in chronic obstructive pulmonary disease (COPD) over four years. It was the first study to substantiate the hypothesis that effective and sustained bronchodilation can alter the long-term disease course. Newly completed analyses of this same study further reinforce a correlation over the long term between major measures of disease control, including preservation of lung function, protection against exacerbations, and a reduction in the rate of decline of QoL. In addition, the new data confirm that benefits extend to a broad array of subgroups, including COPD patients who have not been treated previously and those who continue to smoke. By providing an evidence base for first-line maintenance, the data move the debate in COPD toward the timing and types of combinations with the potential to offer the next step in further delay of disease progression.

Despite an array of therapies that reduce symptoms in patients with COPD, symptomatic benefits were not linked to objective improvements in long-term outcome until completion of the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial last year (Tashkin et al. *N Engl J Med* 2008;359:1543-54). The study confirmed that maintenance anticholinergic therapy can improve an array of clinically relevant outcomes, including lung function and quality of life (QoL), over a period of at least four years.

Findings from the Treatment-naïve Population

A subgroup analysis in patients treatment-naïve at study entry further defined the anticholinergic as first-line because of parallel benefits to those achieved in the total study population. "When used for maintenance, we now have the evidence that [the anticholinergic tiotropium] is something that makes patients better in the long run," reported Dr. Thierry Troosters, Department of Rehabilitation Services, Catholic University of Leuven, Belgium. In his presentation of data from a subgroup analysis in patients who entered the study without previous treatment, Dr. Troosters explained that this particular population further strengthens evidence that the anticholinergic is a first-line. Similar to benefits observed in the study as a whole, treatment-naïve patients randomized to the anticholinergic had better lung function and QoL at the end of four years even though patients in the opposite study arm were permitted any medication other than an anticholinergic as needed to control symptoms.

The 810 patients in the treatment-naïve group represented about 14% of the 5993 patients randomized overall in UPLIFT. The active treatment (403 patients randomized to tiotropium 18 µg q.d.) and control groups (407 patients randomized to placebo) were of similar size. There were no

significant differences for baseline characteristics which, despite the fact that these patients had not been previously treated, were remarkably similar to the UPLIFT study population overall. At entry, patients had a forced expiratory volume at one minute (FEV₁) of 53%. Approximately 40% were active smokers. Although the majority of patients in the treatment-naïve cohort was in GOLD stage II with a smaller number in GOLD III, there was even some representation in GOLDIV.

The goal of this analysis was to determine whether tiotropium was an effective initial choice for maintenance even in those previously untreated. The results showed benefits that were comparable to those observed in the total study population for both the objective measures and QoL outcomes. Over the course of four years, the decline in FEV₁ was 42 mL/year among those randomized to tiotropium vs. 53 mL/year in those randomized to placebo ($P=0.026$). There was a similar difference in the rate of decline in vital capacity favoring tiotropium over placebo at the end of treatment. At the end of the trial, the trough FEV₁ was 134 ml greater in the tiotropium vs. the placebo group.

Protection Against Respiratory Function Decline

The protection against decline in respiratory function was reflected in measures of lung function with the St. George's Respiratory Questionnaire (SGRQ) total score and in measures of QoL. On the SGRQ, for which a clinically significant advantage is considered to be 4.0 units, the advantage of tiotropium remained significant from the second year onwards with the difference of 4.6 units at four years ($P<0.001$). On QoL, the greatest relative advantage of active treatment over placebo was in activity, which is arguably the most important measure of drug benefit. Like SGRQ, a graph of QoL shows a

separation of the curves early with a gradual but steadily increasing advantage for tiotropium over placebo over time. At the end of four years, the differences in QoL were highly significant for impact of disease ($P=0.004$) and activity ($P<0.001$)

The risk of exacerbations was reduced 15% over the course of follow-up, but the difference fell short of statistical significance ($P=0.07$). However, there was a 23% relative reduction in the risk of hospitalized exacerbations for the active treatment group relative to placebo ($P=0.012$).

In addition, the risk of being placed on an additional therapy, such as a long-acting beta agonist or an inhaled corticosteroid, was reduced by 28% ($P<0.01$). This was a finding considered to be especially pertinent in treatment-naïve patients.

“The reduction in the risk of being put on another maintenance therapy is for me an important outcome of this study,” Dr. Troosters remarked. In the context of the advantages of tiotropium over the course of follow-up, “it reinforces the evidence that tiotropium is effective first line.”

As in the published study, Dr. Troosters was cautious in declaring a mortality benefit for tiotropium. In the overall UPLIFT results, the hazard ratio (HR) for all cause mortality was 0.89 (95% CI 0.79 – 1.02) overall when including a post-randomization analysis at 30 days during which time both groups received 40 µg ipratropium q.i.d (a design choice made to confirm sustained differences in lung function off tiotropium). When mortality was compared at the end of the randomization, the 13% reduction (HR 0.87; 95% CI, 0.76 – 0.99; $P<0.05$) did reach statistical significance. In the treatment naïve patient sub-group presented here, a similar trend was observed for a reduction in mortality (HR 0.74; 95% CI, 0.50 – 1.10).

Benefits in Smoking Subgroup

The sustained improvement in lung function and the improvements in QoL also extended to smokers in another subgroup analysis from the UPLIFT study. In a report from Dr. Donald P. Tashkin, Emeritus Professor of medicine, Medical Director, Division of Pulmonary and Critical Care, David Geffen School of Medicine, University of California, Los Angeles, treatment effects were assessed in the 846 patients who reported continued smoking and the 3534 who reported sustained abstinence (intermittent smokers were excluded from the analysis). Not surprisingly, the rate of decline in

FEV1 was substantially greater in continued smokers (59 mL/year vs. 36 mL/year), but there was a significantly milder slope of decline among those taking tiotropium when compared to placebo in both.

“The benefit of tiotropium relative to placebo was very similar in smokers as it was in non-smokers, including sustained improvement in lung function and in health-related QoL. We also saw protection from tiotropium relative to placebo against the risk of an exacerbation in smokers as well as sustained ex-smokers,” Dr. Tashkin reported.

Both Drs. Tashkin and Dr. Troosters emphasized that the size and scope of the study has provided the type of data essential to an evidence-based approach to selecting a first-line maintenance therapy for management of COPD. In discussions after both presentations, the question emerged whether other bronchodilators, particularly a long-acting beta agonist, may be capable of the same types of benefits. They and others, including Dr. Bartolome R. Celli, Chief of the Division of Pulmonary, Critical Care Medicine and Sleep Medicine, Elizabeth’s Medical Center, Professor of medicine, Tufts University School of Medicine, Boston, Massachusetts, cautioned that there is no answer without comparable data.

He told delegates, “The UPLIFT study demonstrates that once daily tiotropium management alters the natural history of COPD. This is important new information that we did not have before, and I think it will guide us for patient treatment,” Dr. Celli indicated.

Summary

New data from the UPLIFT study has reinforced the initial findings. Over a period of at least four years, once daily tiotropium reduces decline in lung function and QoL, and lowers the risk of exacerbations in the total study population and in patients who had not had previous treatment. The favourable but non-significant trend toward a reduction in the rate of mortality contributes to the evidence that the symptomatic relief with this agent changes important measures of long-term outcome. The results of UPLIFT confer tiotropium with the first evidence-based support for a maintenance therapy and set the stage for studies to determine which additional agents might be added to further reduce progression as symptoms advance. □

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