Original Article:

Szefler SJ, Murphy K, Harper T 3rd et al. A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma. J Allergy Clin Immunol. 2017 Feb 9. pii: S0091-6749(17)30218.

Review by: Gregory Metz, MD, AE-C

Despite aggressive management of comorbidities and adherence to medications, asthma can remain uncontrolled in some children. Prior studies in adolescents and adults with persistent, uncontrolled asthma have demonstrated clinical efficacy with the addition of tiotropium. Consequently, this study evaluated the efficacy and safety of adding on tiotropium to standard therapy in children aged 6-11 with severe symptomatic asthma.

Subjects were enrolled if they were aged 6-11, had pre-bronchodilator FEV1 of 60-90% predicted with significant reversibility, had uncontrolled asthma (based on Asthma Control Questionnaire/ACQ-IA scores) and were already being treated with high dose inhaled corticosteroid + $\geq$1 more controller therapies (LABA or LTRA) OR medium dose ICS + $\geq$2 or more controller therapies (LABA, LTRA and/or theophylline).

Four hundred and one subjects were randomized into the study. The control group received their standard asthma treatments. One intervention group received standard therapy with the addition of tiotropium 2.5mcg daily while the second intervention group received tiotropium 5mcg daily. Baseline demographics, asthma severity and asthma treatments were similar in all groups. The majority of subjects in all groups were male. The treatment period lasted 12 weeks and the primary end point was peak FEV_1 0-3 hours after dosing. Information was also obtained about tolerability and safety.

Add on tiotropium dosed at 5mcg daily resulted in significant improvement in FEV_1 (139mL) within 3 hours after dosing (95% CI, 75-203, P<.001). There were no significant differences in adverse events between the treatments groups and controls. It is important to note, however, that 8 subjects had serious adverse events in this study but none were attributed to the study intervention and 2 involved the control subjects.

A major strength of the study is the large number of participants especially since this was a pediatric intervention study. Limitations include short duration of intervention and lack of patient-centered clinical outcomes being evaluated. This study strengthens the mounting evidence for the safety and efficacy of add on therapy with tiotropium in those with persistent, uncontrolled asthma, even in children. Asthma educators counsel patients regarding adherence to their therapies and consequently need to be aware of all therapeutics agents currently in the arsenal to treat asthma.