

# Once-daily oral controller therapy with low-dose theophylline or montelukast was not effective in poorly controlled asthma

The American Lung Association Asthma Clinical Research Centers. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. *Am J Respir Crit Care Med.* 2007;175:235-42.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆ Allerg & Immunol ★★★★★☆ Pulmonology ★★★★★☆

## QUESTION

In patients with poorly controlled asthma while taking medication, what is the effectiveness of adding once-daily oral controller therapy to low-dose theophylline or montelukast?

## METHODS

**Design:** Randomized placebo-controlled trial.

**Allocation:** {Concealed}†.\*

**Blinding:** Blinded (clinicians, patients, {data collectors, outcome assessors, and data safety and monitoring committee}†).\*

**Follow-up period:** 24 weeks.

**Setting:** 19 American Lung Association Asthma Clinical Research Centers (ALA-ACRC) in the United States.

**Patients:** 489 patients  $\geq 15$  years of age (mean age 40 y, 74% women, 61% white) who were diagnosed with asthma, were prescribed daily asthma medication for  $\geq 1$  year, had FEV<sub>1</sub>  $\geq 50\%$  of the predicted value, and had poor asthma control (score  $\geq 1.5$  on the Asthma Control Questionnaire [ACQ]). Patients continued their baseline medications. Exclusion criteria were use of oral corticosteroids, leukotriene antagonists, or theophylline within 4 weeks before randomization;  $\geq 20$  pack-years history of smoking; or significant illness.

**Intervention:** Theophylline, 300 mg/d ( $n = 161$ ); montelukast, 10 mg/d ( $n = 164$ ); or placebo ( $n = 164$ ).

**Outcomes:** Annualized rate of episodes of poor asthma control (EPAC) (composite

endpoint of  $> 30\%$  drop in PEF for  $\geq 2$  consecutive d, increased use of rescue medication by  $> 4$  metered-dose inhalations or 2 nebulizer treatments in 1 d, new use of oral corticosteroids, or unscheduled health care visit for asthma). Secondary outcomes were lung function (pre- and postbronchodilator [BD] FEV<sub>1</sub> and FVC), Asthma Symptom Utility Index (ASUI), Asthma Quality-of-Life Questionnaire (AQLQ), and ACQ scores; and adverse events. The study had 80% power to detect a 15% difference in the proportion of patients with  $\geq 1$  EPAC.

**Patient follow-up:** 90% (intention-to-treat analysis).

## MAIN RESULTS

Overall, groups did not differ in the proportion of patients with  $\geq 1$  EPAC (Table); unadjusted annualized rates of EPAC; pre- or post-BD FVC; or mean change in ASUI, AQLQ, or ACQ scores. Theophylline led to greater improvements than placebo in pre-BD FEV<sub>1</sub> ( $P = 0.006$  across all time points;

0.08 vs  $-0.01$  L at 24 wks) and post-BD FEV<sub>1</sub> ( $P = 0.005$  across all time points; 0.03 vs  $-0.02$  L at 24 wks); montelukast led to greater improvements in pre-BD FEV<sub>1</sub> ( $P = 0.003$  across all time points; 0.09 vs  $-0.01$  L at 24 wks) but did not differ from placebo for post-BD FEV<sub>1</sub>. At 4 weeks, there were more reports of nausea and nervousness with theophylline than with placebo or montelukast. Groups did not differ for any adverse event at 12 or 24 weeks.

## CONCLUSION

Once-daily oral controller therapy with low-dose theophylline or montelukast was not effective in poorly controlled asthma.

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\*See Glossary.

†Information provided by author.

## Theophylline or montelukast vs placebo in poorly controlled asthma at 4 to 24 weeks†

Outcome	Theophylline	Montelukast	Placebo	RRI (95% CI)	NNH
$\geq 1$ EPAC <sup>§</sup>	53% (80/151)	—	52% (81/154)	0.73% (−19 to 25)	Not significant
				RRR (CI)	NNT
	—	49% (79/160)	52% (81/154)	6.1% (−17 to 25)	Not significant

‡EPAC = episode of poor asthma control; other abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article.

§Composite endpoint of  $> 30\%$  drop in PEF (theophylline vs montelukast vs placebo = 17% vs 16% vs 19%), use of rescue medication (42% vs 40% vs 38%), new use of oral corticosteroids (19% vs 14% vs 16%), or unscheduled health care visit for asthma (18% vs 16% vs 13%).

## COMMENTARY

Inhaled corticosteroids (ICSs) are first-choice medications for initiating maintenance controller therapy in patients with mild persistent asthma (Step 2, Global Initiative for Asthma [GINA]) (1). Their effectiveness in improving asthma control and reducing exacerbations and asthma mortality are supported by clinical and epidemiologic studies over the past 3 decades. Adding long-acting  $\beta$ -agonists (LABAs) (Step 3, GINA) or leukotriene-receptor antagonists to ICSs improves clinical outcomes more than do ICSs alone (2).

The study by the ALA-ACRC compared the addition of oral montelukast, theophylline, or placebo to existing treatment regimens in patients with poorly controlled asthma. The results reinforce current guidelines showing little role for montelukast or theophylline in this setting. Most patients were white women, mean age of 40 years and asthma onset at mean age of 21 years. Of concern are the 18% of patients on LABA monotherapy without ICSs. Hence, generalizing these results to other populations should be done with caution.

Where does this leave montelukast and theophylline in overall asthma management? Montelukast is still first-line antiinflammatory controller therapy in children in whom oral or nonsteroidal medications are preferred. It is also effective for reducing rates of episodic viral-

induced asthma exacerbations in preschool children (3) and managing exercise-induced asthma in cases where ICSs are ineffective (4).

In some countries, theophyllines are a low-cost alternative to ICSs. A subgroup analysis in the study by the ALA-ACRC showed improved asthma control, symptoms, and lung function in patients taking theophylline without ICSs. However, it is not clear whether the reduced cost of theophylline in this setting may be offset by other direct (emergency presentation, hospitalization) or indirect (school or work absenteeism) costs of asthma and longer-term asthma outcomes in comparison with ICS therapy.

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