### Evidence Table 14. Pharmacologic Therapy: Leukotriene Receptor Antagonists—Monotherapy/Effectiveness Studies

**Abbreviations used in table:**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>BCD (or B)</td>
<td>beclomethasone dipropionate</td>
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<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
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<tr>
<td>ECP</td>
<td>eosinophil cationic protein</td>
</tr>
<tr>
<td>FEF_{25–75}%</td>
<td>forced midexpiratory flow</td>
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<tr>
<td>FEV_{1}</td>
<td>forced expiratory volume in 1 sec.</td>
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<tr>
<td>FP (or F)</td>
<td>fluticasone propionate</td>
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<tr>
<td>FVC</td>
<td>forced vital capacity</td>
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<tr>
<td>GINA</td>
<td>Global Initiative for Asthma Guidelines</td>
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<td>ICS</td>
<td>inhaled corticosteroid</td>
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<td>ITT</td>
<td>intent-to-treat</td>
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<tr>
<td>LTRA</td>
<td>leukotriene receptor antagonist</td>
</tr>
<tr>
<td>M</td>
<td>montelukast</td>
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<tr>
<td>PC_{20}</td>
<td>provocative concentration causing a 20% fall in FEV1</td>
</tr>
<tr>
<td>PEF</td>
<td>peak expiratory flow</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
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<tr>
<td>RFD</td>
<td>rescue-free days</td>
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<td>SAE</td>
<td>severe adverse event</td>
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* indicates primary outcome
<table>
<thead>
<tr>
<th>Citation (Editor)</th>
<th>Study Design</th>
<th>Purpose of Objective</th>
<th>Study N (Number Evaluated)</th>
<th>Asthma Severity at Baseline (if Reported)</th>
<th>Population Characteristics</th>
<th>Treatment</th>
<th>Dose</th>
<th>Duration of Active Treatment</th>
<th>Duration of Blind Treatment (if applicable)</th>
<th>Rescue Medication Use</th>
<th>Long Term</th>
<th>Exacerbations/Symptoms</th>
<th>Adverse Events</th>
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<tbody>
<tr>
<td>Malstrom et al. (for the Montelukast/Beclomethasone Study Group)</td>
<td>Oral montelukast, inhaled beclometasoned, and placebo for chronic asthma: a randomized, controlled trial. Ann Intern Med 1999;130(6): 487–495. (MERIT Research Laboratories)</td>
<td>To compare the clinical benefit of montelukast (M), placebo (P), and inhaled beclometasone (B)</td>
<td>895 (885; all patients at least 1 measurement after baseline)</td>
<td>Chronic asthma</td>
<td>Age 16–85 yr, median 35 yr Gender 40% male, 60% female Ethnicity Caucasian 52%, Hispanic 32%, Other 16%</td>
<td>Arm 1 M + placebo inhaler (n=387, 354 completers)</td>
<td>10 mg once daily in evening + 2 puffs from inhaler at bedtime and in morning 100 mcg/puff twice daily + placebo tablet</td>
<td>12 week trial after a 2-week, single blind placebo run-in period. Period 3 was a 3-week, double blind placebo washout period involving a subset of patients (approximately 40).</td>
<td>Mean difference between B treatment and M treatment for beta-agonist use was −0.67 puffs/day (95% CI −1.10 to −0.245 puffs/day)</td>
<td>% Mean difference between B and M treatment were 5.8% (95% CI 3.0% to 8.5%) for FEV1, 15.4 L/min (95% CI 8.1 to 22.5 L/min) for morning PEFR, and 11.2 L/min (95% CI 4.2 to 18.3 L/min) for evening PEFR. The M group had a larger and larger initial response than the B group, 7–10 days after initiation, effect of B treatment surpassed that of placebo. 22% of B group and 34% of M group did not show improvement in FEV1. No difference was found between B and M groups in decrease in peripheral blood eosinophil count.</td>
<td>Days with asthma exacerbations were less frequent, and asthma-control days were more frequent in B vs. M treatment (p &lt; 0.05).</td>
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<tr>
<td>Bisgaard and Nielsen Bronchoconstriction with a leukotriene receptor antagonist in asthmatic preschool children. Am J Respir Crit Care Med 2000;162(1): 187–190.</td>
<td>Randomized, placebo-controlled, crossover study. (Study was repeated with 6 original samples to evaluate consistency of treatment response.)</td>
<td>16 (13 in ITT analysis)</td>
<td>Hypermpermus to cold, dry air challenge Duration of asthma ≤42 months, mean = 39 months</td>
<td>Specific airway resistance, range 1.36–2.25, mean = 1.71 kPa % pred. range 103%–170%, mean = 129% 62% used inhaled budesonide, mean daily dose = 350 mcg</td>
<td>Arm 1 M 5 mg chewable tablet</td>
<td>Matching chewable tablet</td>
<td>Tablet was given between 8:00 and 9:00 a.m. daily for 2 days with cold, dry air challenge performed on 3rd day between 8:00 and 9:00 a.m. At least 1-week washout occurred between study periods. Terbutaline was used as rescue medication.</td>
<td>All children used terbutaline as rescue medication.</td>
<td>Specific airway resistance increased by 46% (95% CI 30% to 63%) after cold air challenge test with P treatment and by 17% (95% CI 3% to 31%) with M treatment (p&lt;0.01 for difference between P and M groups). During second round (n=6), specific airway resistance increased by 52% (95% CI 29% to 75%) with P treatment and by 20% (95% CI 8% to 32%) with M treatment (p=0.02 for difference between groups).</td>
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Multicenter, randomized, double-blind, double-dummy trial. To provide comparative data on important objective and subjective measures related to clinical efficacy of the lowest recommended dose of the ICS fluticasone propionate in patients compared with that of the recommended dose of oral zafirlukast (Z). 451 (ITT)

Age
12-68 yr, mean = 31 yr
Gender
50% male, 50% female
Ethnicity
Caucasian 83%, African American 8%, other 9%
Smoking
No use of tobacco within the previous yr or a smoking history of >10 pack-yr

Persistent asthma
Duration of asthma: 6 months
FEV1: mean = 2.5 L
PEF: mean = 362 L/min
Albuterol use, mean = 4.67 puffs/day
Symptom score, mean = 1.15

Arm 1
Inhaled FP aerosol
Arm 2
Oral Z
88 mcg twice daily
20 mcg twice daily

12 weeks after 8- to 14-day run-in period
Albuterol use was reduced by 2.39 puffs/day for FP treatment vs. 1.45 puffs/day for Z treatment (p < 0.001), with differences in favor of FP by week 1.

Treatment as compared to M treatment resulted in greater decrease in rescue albuterol use (3.10 vs. 2.31 puffs/day, p < 0.001) and percentage of RFDs (46.9 vs. 31.2, p < 0.001).


Multicenter, randomized, double-blind, double-dummy, parallel-group study (52 study sites, analyses adjusted for site). To compare the efficacy and safety of low dose fluticasone propionate (FP) and montelukast (M) as first-line maintenance therapy in symptomatic patients by using short-acting beta-agonists alone to treat persistent asthma. 533 (ITT analysis)

Age
15-83 yr, mean = 34.9 yr
Gender
44.8% male, 55.2% female
Ethnicity
83% White, 10% African American, 7% other

Persistent asthma
Duration of asthma: 6 months
FEV1: % pred., range = 65.5%
All used short-acting beta-agonist for 3 months before screening,
Symptom score, mean = 1.67 (0–5 range)

Arm 1
FP + placebo capsule (n=271, 194 completers)
Arm 2
Oral (M) + placebo inhaler (n=262, 187 completers)
88 mcg twice daily through metered-dose inhaler + placebo capsule in evening
10 mg in evening + 2 puffs of placebo twice daily through metered-dose inhaler

24 weeks after 8-14 day run-in period
Patients used inhaled albuterol as needed throughout study.

FP treatment as compared to M treatment resulted in greater improvement in asthma symptom scores (0.85 vs. 0.60, p < 0.001), percentage of symptom-free days (32.0 vs. 18.4, p < 0.001), and nighttime awakenings/night (1.64 vs. 0.48, p = 0.023).

Physician assessment and patient satisfaction favored FP over M treatment (p < 0.001).

No difference was found in exacerbations (4% of FP group and 8% of M group).

Incidence of AE was similar between groups, with 10% in each group having ≥1 drug-related AE. Two patients in the zafirlukast group had SAE resulting in withdrawal; no patient in the FP group had SAE resulting in withdrawal.

Multisite, randomized double-blind, double-dummy, parallel-group study (34 sites in the United States; analyses conducted for investigator alone) 338 (ITT analysis)
To assess the clinical benefits of an ICS and a leukotriene modifier as first-line treatment for persistent asthma in patients who were symptomatic when using short-acting beta-agonists alone 338

Age 12–75 yr
Gender 50% male, 50% female
Ethnicity Non-Hispanic White 86%, African American 10%, other 4%

Persistent asthma: majority had moderate asthma
Most had asthma diagnosed for \( \geq 10 \) yr.
FEV\(_1\), mean = 2.44 L
Morning PEF, mean = 349 L/min
Evening PEF, mean = 382 L/min
All had used short-acting beta-agonist at least 6 weeks.
Albuterol use, mean = 4.9 puffs/day
Albuterol-free days, mean = 2.8 days
Symptom score, mean = 1.36 (0–5 range)

Arm 1 Fluticasone propionate (FP) by inhaler + placebo capsule
(n=113)
88 mcg twice daily + placebo capsule twice daily
12 weeks after 8–14 day run-in period
Albuterol as needed for symptom relief or corticosteroids for asthma exacerbations were permitted during the study.

FP treatment compared with placebo improved percentages of albuterol-free days (48.9% vs. 19.9%) and albuterol use (\( < 0.8 \) vs. \( > 1.3 \) puffs/day) (p = 0.006).
Z treatment compared with placebo improved percentage of albuterol-free days (37.5% vs. 19.6%) and albuterol use (\( < 1.9 \) vs. \( > 1.3 \) puffs/day).
FP treatment compared with Z treatment improved the percentage of albuterol-free days and albuterol use (p = 0.004).

Arm 2 Oral zafirlukast (Z) + placebo by inhaler
(n=111)
20 mg capsule twice daily + placebo by inhaler twice daily
Placbeo capsule + 2 puffs of placebo by inhaler twice daily


Multisite, randomized, double-blind, parallel-group study (25 centers in the United States; analyses adjusted for site) 294 (294)
To compare the effects of low-dose fluticasone (F) and zafirlukast (Z) on measures of clinical efficacy and safety over 4 weeks; in addition, the effect of switching patients from Z to F therapy was evaluated 294

Age 12–70 yr
Gender 44% male, 56% female
Ethnicity Caucasian 85%, African American 10%, other 5%

Persistent asthma: Morning predose FEV\(_1\), mean = 2.5 L
FEV\(_1\) % pred., mean = 88.5
Morning PEF, 352 L/min
Evening PEF, 389 L/min
Use of inhaled or oral short-acting beta-agonist for \( > 8 \) weeks.
Daily albuterol use, mean = 4.4 puffs/day

Arm 1 Inhaled F
(n=144; 139 completers)
2 puffs of 44 mcg morning and evening
26 mg morning and evening
4 weeks after 7–14 day screening period
A 4-week open-label treatment period followed. No other asthma medications were permitted during the study.

F treatment more than Z treatment reduced albuterol use (\( > 1.8 \) vs. \( < 1.1 \) puffs/day, p = 0.019).

Arm 2 Oral Z
(n=150; 138 completers)
28 mg morning and evening

After weeks 3 and 4, F treatment improved morning PEF more compared to treatment with Z (p = 0.033).
At endpoint, mean change in morning PEF was greater in the F group than in the Z group (3.1 L/min, 8.2% change vs. 18.3 L/min, 5.3% change; p = 0.02).
No difference in change occurred in evening PEF or morning PEF (p = 0.20).
During the open-label period, no difference in change occurred in percentage of symptom-free days.
During the double-blind period, no difference occurred in percentage of patients with exacerbations.

F treatment increased the percentage of symptom-free days compared to treatment with Z (19.8% vs. 11.6%, p=0.025).
No difference in change occurred in asthma symptom scores (p=0.085).
During the open-label period, no difference change occurred in percentage of symptom-free days.
During the double-blind period, no difference occurred in percentage of patients with exacerbations.

No difference occurred in possible drug-related AE (4% of the F group and 10% of the Z group).
No SAE occurred.
<table>
<thead>
<tr>
<th>Citation (Sponsor)</th>
<th>Study Design</th>
<th>Purpose Objective</th>
<th>Study N (Number Evaluated)</th>
<th>Population Characteristics</th>
<th>Asthma Severity at Baseline [if Required]</th>
<th>Treatment</th>
<th>Dose</th>
<th>Duration of Active Treatment; Duration of Placebo/Withdrawal OR Treatment Followup</th>
<th>Rescue Medication Use</th>
<th>Lung Function</th>
<th>Exacerbations/Symptoms</th>
<th>Adverse Events</th>
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<tr>
<td>Storms et al.</td>
<td>Clinical safety and tolerability of montelukast, a leukotriene receptor antagonist, in controlled clinical trials in patients aged &gt; or = 6 years. Clin Exp Allergy; 2001;31(1):77–87. (Merck and Co., Inc.)</td>
<td>Paired analysis from 11 multicenter, randomized, controlled Phase IIb and Phase III trials and 5 long-term extension studies</td>
<td>3,386 and 336 pediatric patients in trials; 2,031 adults and 257 children in extension studies</td>
<td>Trials: Adults &lt;0.01</td>
<td>Trials: Children</td>
<td>Treatment</td>
<td>Dose</td>
<td>Duration of Active Treatment; Duration of Placebo/Withdrawal OR Treatment Followup</td>
<td>Rescue Medication Use</td>
<td>Lung Function</td>
<td>Exacerbations/Symptoms</td>
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<td>To summarize safety data and describe the tolerability of montelukast derived from 11 placebo-controlled, double-blind Phase IIb and Phase III clinical trials in patients with chronic asthma and from 5 extension studies</td>
<td>Chronic asthma; mild, moderate, and severe persistent</td>
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<td>Phase IIb adult trials</td>
<td>2 Phase IIb adult trials</td>
<td>8 Phase II adult trials</td>
<td>1 Phase III pediatric trial</td>
<td>5 extension studies</td>
<td>0–200 mg/day</td>
<td>One 10 mg tablet/day</td>
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<tr>
<td>Brabant et al.</td>
<td>Efficacy and safety of low-dose fluticasone propionate compared with zafirlukast in patients with persistent asthma. Am J Med 2002;113(1):15–21. (GlaxoWellcome, Inc.)</td>
<td>Multicenter randomized double-blind, double-dummy trial (44 sites in the United States)</td>
<td>To compare the efficacy and safety of fluticasone (F) with zafirlukast (Z) in patients with persistent asthma who had been treated previously with low doses of ICS</td>
<td>Age = 12 yr, mean = 35.5 yr</td>
<td>Gender 37% male, 63% female</td>
<td>Stable persistent asthma</td>
<td>Fixed daily dose of inhaled BCD 168–336 mcg (mean = 263 mcg) or tramadol acetate nedol 400–800 mcg (mean = 602 mcg) 38% treated by primary care physician; 52% treated by specialist FEV1 % pred., mean = 73</td>
<td>Amn 1 F through metered-dose inhaler (n=224; 207 completers)</td>
<td>44 mcg morning and evening</td>
<td>6 weeks after 8-day run-in period</td>
<td>Abutrolıldı and used as needed for symptom relief.</td>
<td>20 mg</td>
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<tr>
<td>Citation (Sponsor)</td>
<td>Study Design</td>
<td>Purpose/Objective</td>
<td>Study N (Number Evaluable)</td>
<td>Population Characteristics</td>
<td>Asthma Severity at Baseline [If Repeated]</td>
<td>Treatment</td>
<td>Dose</td>
<td>Duration of Active Treatment; Duration of Postintervention (Off-Treatment Followup)</td>
<td>Rescue Medication Use</td>
<td>Lung Function</td>
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<tr>
<td>Israel et al. Effects of montelukast and beclomethasone on airway function and asthma control. J Allergy Clin Immunol 2002; 110(6): 847-854. (Merck and Co., Inc., Whitehouse Station, NJ; and USHII Merck and Co., Inc., West Point, PA)</td>
<td>Multicenter, double-blind, placebo-controlled, parallel-group study (64 canters in the United States)</td>
<td>To compare the effects of montelukast (M) and beclometasone (BCD), as judged by days of asthma control</td>
<td>782 (762: ITT)</td>
<td>Age 15-74 yr, mean = 33.2 yr</td>
<td>Gender 48% male, 52% female</td>
<td>Ethnicity Caucasian 85%, Black 6%, Hispanic 5%, other 4%</td>
<td>Smoking Nonsmoker for &gt;1 yr with smoking history ≤7 pack-yr</td>
<td>Persistent asthma Duration ≥1 yr, mean = 19 yr</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, mean = 2.5 L FEV&lt;sub&gt;1&lt;/sub&gt; % pred., mean = 66.7</td>
<td>Arm 1 Montelukast sodium (M) (n=339; 328 completers)</td>
<td>Arm 2 BCD (n=332; 318 completers)</td>
<td>Arm 3 Placebo (n=111; 106 completers)</td>
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<tr>
<td>Kanniesw et al. Montelukast versus fluticasone: effects on lung function, airway responsiveness and inflammation in moderate asthma. Eur Respir J 2002; 20(4): 853-858. (GlaxoSmithKline, Germany)</td>
<td>Randomized, double-blind, crossover design</td>
<td>To compare montelukast (M) with low-dose fluticasone</td>
<td>40 (40)</td>
<td>Age 18-60 yr, mean = 37 yr</td>
<td>Gender 60% male, 40% female</td>
<td>Ethnicity Not reported</td>
<td>Smoking 100% nonsmokers</td>
<td>Moderate, allergic bronchial asthma No ICS or systemic corticosteroids within 3 or 6 months of antihistamines or theophylline within 4 weeks</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, mean = 2.79 L FEV&lt;sub&gt;1&lt;/sub&gt; % pred., mean = 74.0</td>
<td>Arm 1 F = placebo tablet Arm 2 M = placebo inhaler</td>
<td>100 mcg twice daily</td>
<td>10 mg at nighttime</td>
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<tr>
<td>Citation (Sponsor)</td>
<td>Study Design</td>
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<td>Baumgartner et al. Distribution of therapeutic response in asthma control between oral montelukast and inhaled beclomethasone. Eur Respir J 2003;21(1):123–128.</td>
<td>Multcenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group study (16 centers in 8 countries)</td>
<td>To compare the effectiveness of montelukast (M) and inhaled beclomethasone (B) in the treatment of adult patients</td>
<td>730 (679;ITT for efficacy)</td>
<td>Age: 15 yr; Mean = 35.7 yr Gender: 34% male, 66% female Ethnicity: Not reported Smoking: Nonsmokers for ≥1 yr</td>
<td>Chronic asthma Duration ≥1 yr, mean = 18.6 yr FEV1, mean = 2.21 L FEV1 % pred., mean = 68 Beta-agonist use, mean = 5.2 puffs/day</td>
<td>Arm 1 Oral M (n=313; 219 completers) Arm 2 Inhaled B (n=314; 295 completers) Arm 3 Placebo (n=103; 93 completers)</td>
<td>10 mg once daily</td>
<td>200 mcg (4 puffs) twice daily</td>
<td>6 weeks after 2-week single-blind placebo run-in period Short-acting inhaled beta-agonist was used as needed throughout study.</td>
<td>Percent reduction in beta-agonist use was greater (p&lt;0.05) for patients taking B (45.7%) than for patients taking M (35.7%), with both greater than placebo (15.7%, p&lt;0.05).</td>
<td>Overlap in change in FEV1 between active treatment groups was 96%. No difference was found between change in M (12.1%) and B (13.9%) groups, with both greater than the placebo group (9.4%, p&lt;0.05).</td>
<td>Overlap in percentage of asthma-control days between active treatment groups was 89%. The mean in the M (50.7%) and B (57.9%) groups was greater than in the placebo group (40.0%, p&lt;0.05). Difference favored the B group over the M group (left 7.2; p&lt;0.05). Percent of patients with ≥1 asthma attack did not differ between M (6%) and B (4%) groups; both groups had fewer attacks than the placebo group (15%, p&lt;0.05).</td>
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<td>Bisgaard. A randomized trial of montelukast in respiratory syncytial virus post-bronchiolitis. Am J Respir Crit Care Med 2003; 167(3):379–385 (University Hospital of Copenhagen, Denmark)</td>
<td>Multcenter randomized, double-blind, placebo-controlled, parallel-group study (11 pediatric centers that were secondary referral centers)</td>
<td>To assess the effect of cyc-LT receptor antagonists on the post-infectious course of respiratory syncytial virus</td>
<td>130 (114 for treatment period, 87 for follow-up period)</td>
<td>Age: 3–36 months, mean = 9.5 months Gender: 48% male, 52% female Ethnicity: Not reported Tobacco exposure, 42% Pets at home, 43% Atopic heredity, 38%</td>
<td>Moderate-to-severe symptoms requiring hospital admission Admission 2–7 days, median 4.5 days Treatment: Δ, 29%; CPAP, 16%; beta-agonist, 81%</td>
<td>Arm 1 Montelukast (n=65; 55 completers) Arm 2 Placebo (n=65; 61 completers)</td>
<td>5 mg tablet in evening</td>
<td>28 days, beginning a median of 3 days after admission</td>
<td>ΔInfants given montelukast were free of daytime and nighttime symptoms 6 of 28 days vs. 1 of 28 days for infants given placebo (p=0.015). More infants reported ≥1 symptom-free day and night on active treatment (p=0.045). Daytime cough was reduced on active treatment vs. placebo (p=0.04). Exacerbations occurred in 4 infants given montelukast and 10 given placebo (p=0.08). Time to exacerbation was 8 vs. 23 days (p=0.044).</td>
<td>Three infants given montelukast were withdrawn due to symptom severity vs. 8 infants given placebo (p=0.11).</td>
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To compare the safety and efficacy of anti-leukotrienes and inhaled glucocorticoids as mono-therapy in people with asthma

13 trials, 5,109 subjects Sample sizes ranged from 20 to 666, with mean of 393

Age
- 1 pediatric trial with mean age = 10 yr, 12 adult trials with mean age ranging from 30 to 41 yr

Gender
- Males ranged from 35% to 65% in the various trials

Ethnicity
- Not reported

Smoking
- Not reported

Study Design
- Systematic review of randomized controlled trials (All were parallel group designs; 10 used double-blinding, while 3 were open label; 10 were of high methodological quality.)

Population Characteristics
- Asthma Severity at Baseline (if any)
- Treatment
- Dose
- Duration of Active Treatment
- Duration of Treatment/Off Treatment Follow-up
- Rescue Medication Use
- Lung Function
- Exacerbations/Symptoms
- Adverse Events

Arm 1
- Anti-leukotrienes: Montelukast (8 trials), zafirlukast (4 trials), or pranlukast (1 trial)
- 10 mg once daily (7 trials), 20 mg twice daily (4 trials), 5 mg once daily (1 trial), 450 mg once or pranlukast (1 trial)
- Ranged from 4 to 27 weeks

Arm 2
- ICS: Beclomethasone dipropionate (BCD) (8 trials), fluticasone propionate (5 trials), or budesonide (1 trial)
- One trial used two ICS arms.

Within 6 weeks, patients in the inhaled glucocorticoid group compared to the anti-leukotriene group experienced greater rescue use of beta2-agonists (p<0.01, 95% CI 0.55 to 1.00 puffs/day; 6 trials).

* Patients treated with LTRAs were 60% more likely to experience exacerbation requiring systematic glucocorticoids than those treated with inhaled glucocorticoids (RR 1.6, 95% CI 1.2 to 2.2; 11 trials). The magnitude of effect was not related to LTRA, inhaled glucocorticoid preparation, or baseline severity (all p >0.10).

Within 6 weeks, patients in the inhaled glucocorticoid group experienced fewer nocturnal awakenings per week (WMD = 0.56, 95% CI 0.28 to 0.77; 5 trials) and fewer days with symptoms <1%, 95% CI 5% to ~13%; 3 trials.

Anti-leukotriene was associated with increased risk of withdrawal due to poor asthma control (RR 2.5, 95% CI 1.8 to 3.5; 12 trials).

Jayaram et al. Steroid naive eosinophilic asthma: anti-inflammatory effects of fluticasone and montelukast. Thorax 2005;60(2): 100–105. (Faxon/Wellcome Inc.)

To compare the magnitude of anti-inflammatory effects of montelukast with fluticasone in subjects with asthma and sputum eosinophilia

Study Design
- Multicenter, randomized, double-blind, parallel group placebo and active controlled trial (14 centers)

Population Characteristics
- Age
- Gender
- Ethnicity
- Smoking

50 (49)

- 34.7 yr
- 41% male, 59% female
- Not reported
- 10% current smoker, 14% ex-smoker, 76% non-smoker

Persistent symptomatic asthma

Arm 1
- Fluticasone (F) by inhaler + placebo tablet (n=18; 17 completers) (18 analyzed)
- Montelukast (M) + placebo inhaler (n=19; 18 completers; 19 analyzed)

Within 6 weeks, patients in the inhaled glucocorticoid group compared to the anti-leukotriene group experienced greater improvement in FEV1 (WMD 100 mL, 95% CI 80 mL to 170 mL; 8 trials) and morning PEF (WMD 19 L/min, 95% CI 14 L to 25 L; 7 trials).

* If resulted in greater reduction in sputum eosinophils (geometric mean = 11.9–1.7) vs. M (10.7–6.9; p=0.04) or Placebo (15.4–7.8; p=0.002) treatment. Mean difference for F vs. M treatment was -3.3%, 95% CI -5.2 to 0.1% and for F vs. Placebo treatment was -4.9% (95% CI -10.2 to 0.4).

Median reduction in sputum eosinophilia after F on day 7 was 72.7% vs. 56.2% with M and 34.9% with Placebo.

F treatment resulted in greater improvement in FEV1 (475 mL; 2.6–3.0 L) vs. M (156 mL; 2.8–2.8 L; p=0.02) and vs. Placebo treatment (125 mL; 2.4–2.4L; p=0.01). Mean difference between F and M treatment was 373 mL (95% CI 26 to 729 mL; p=0.03) and between F and Placebo was 458 mL (95% CI 73 to 842; p<0.02).

If exacerbation occurred, F (125 mcg, 2 puffs/day) was added to treatment.

* No difference occurred in the number of patients who experienced any AE (RR 1.0, 95% CI 0.9 to 1.1; 11 trials).

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### Jenkins et al.  

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<th>Study Design</th>
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<tbody>
<tr>
<td></td>
<td>Randomized double-blind, dummy crossover design</td>
<td>To examine the relationship between clinical and subjective variables in the assessment of response to treatment with 3 different classes of medication</td>
<td>58 (53)</td>
<td>Age 16–70 yr, mean = 38.5 yr</td>
<td>Gender 60% male, 40% female</td>
<td>Ethnicity Not reported</td>
<td>Smoking 19% former smokers</td>
<td>Mild-to-moderate persistent, suboptimally controlled asthma 67% taking ICS prior to enrollment FEV1 % pred., mean = 76.1 FEV1/FVC ratio, mean = 0.72</td>
<td>Arm 1 Encapsulated montelukast plus placebo Turbuhaler  10 mg once 2-week run-in period; two 6-week treatment periods separated by 1-week washout periods</td>
<td>Arm 2 Etorfotrol plus placebo capsules 12 mcg b.i.d. Reliever salbutamol was permitted throughout the study.</td>
<td><em>Mean morning PEF was significantly higher with eflornitrol (452 L/min) and with fluticasone (468 L/min) than with montelukast (428 L/min; both p&lt;0.001). No difference was found between eflornitrol and fluticasone. No difference in clinic FEV1 % pred. was found between montelukast and eflornitrol, with the effect of fluticasone better than both. Fluticasone &gt;etorfoformol for lung function factor derived from PCA.</em></td>
<td><em>Median nighttime symptom score was lower with eflornitrol and with fluticasone compared with montelukast (p&lt;0.001 and p=0.01, respectively). No difference was found in daytime symptom scores between eflornitrol and fluticasone compared with montelukast (p=0.054 and p=0.06, respectively). Better asthma control occurred with both eflornitrol and fluticasone than with montelukast. Mean absolute improvement in QoL scores with eflornitrol and fluticasone was not clinically important. Eflornitrol &gt;fluticasone for symptom/relievers use factor and equivalent for patient-centered factor derived from PCA.</em></td>
<td>Five severe exacerbations occurred (n=3 with montelukast; n=1 with eflornitrol; n=1 with washout after eflornitrol), and 11 moderate exacerbations occurred (n=8 with run-in, n=2 with eflornitrol, n=1 with fluticasone).</td>
</tr>
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</table>

### Straub et al.  

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<tr>
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<td></td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>To investigate the therapeutic effect of montelukast (M) in a well defined group of very young children with recurrent wheeze and a positive family history of asthma and allergy</td>
<td>24 (24)</td>
<td>Age Mean = 18.3 months</td>
<td>Gender 54% male, 46% female</td>
<td>Ethnicity Not reported</td>
<td>Mild disease activity FEV1 %, mean 175 mL Symptom score, range 0–9; median = 4.5 (possible range, 0–18) Fractional exhaled nitric oxide, mean = 31.6 ppb Sensitive only to food allergens, 66.7%; sensitive only to aeroallergens 16.7%; sensitive to both food and aeroallergens, 16.7% All had history of recurrent wheeze. All had positive family history of asthma.</td>
<td>Arm 1 M (n=12) 4 mg daily 1 placebo tablet daily 4 weeks</td>
<td>Arm 2 Placebo (n=12)</td>
<td>Mean FEV1 % improved in the M group (189.0 to 214.4 mL; p=0.038) but not in the placebo group (161.0 to 166.8 mL; p=0.026). Fractional exhaled nitric oxide decreased in the M group (29.8 to 19.0 ppb, p=0.01) but not in the placebo group (33.4 to 34.5 ppb, p=0.25). Difference in change between the groups was significant (p=0.04).</td>
<td>Median score in the M group improved from 5.5 to 1.5 (p=0.04) but not in the placebo group (3.0 to 4.0, p=0.35).</td>
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### Citation (Sponsor) and Study Design

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<tr>
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<tr>
<td>Garcia-Garcia et al. Montelukast, compared with flixofluconic, for control of asthma among 6- to 14-year-old patients with mild asthma the MODIASC study. Pediatrics 2005;116(6): 360–369. (Merck and Co.,)</td>
<td>Multicenter, randomized, double-blind, double-dummy, parallel-group design (104 sites in 24 countries)</td>
<td>994 (966; ITT analysis)</td>
<td>Age 5–15 yr, median 9 yr</td>
<td>Gender 62% male, 38% female</td>
<td>Ethnicity 63.6% White, 21.2% Hispanic, 5.9% Asian, 6.0% Black, 7.2% multiracial, 1.5% other</td>
<td>Weight 186–181 kg, median 136 kg</td>
<td>Height 186–181 cm, median 135 cm</td>
<td>Mild persistent at step 2 of GINA guidelines</td>
<td>5 mg tablet once at bedtime (10 mg if patient turned 15 during study)</td>
<td>12 months after 4-week run-in period</td>
<td>Percentage of days with beta-receptor agonist use was 15.4% in the M group and 12.8% in the F group (p=0.003), a decrease of 22.7% in the M group and 25.4% in the F group. The percentage of patients with additional asthma rescue medication was 20.7% in the M group vs. 13.5% in the F group (RR=1.56, 95% CI 1.17–2.06).</td>
</tr>
<tr>
<td>Ostrom et al. Comparative efficacy and safety of low-dose flixofluconic propionate and montelukast in children with persistent asthma. J Pediatr 2005;147(2): 213–220. (GlaxoSmithKline Inc.)</td>
<td>Multisite randomized, double-blind, double-dummy, parallel-group study (43 clinical centers in the United States; investigator controlled in analysis)</td>
<td>342 (ITT analysis)</td>
<td>Age 5–12 yr, mean = 9.3 yr</td>
<td>Gender 65% male, 35% female</td>
<td>Persistent asthma Duration ≥ 6 months PEV, % pred., range 60%–85%, mean = 75.9%</td>
<td>Mean height of 145 cm</td>
<td>Mean of 1.65 mL</td>
<td>Per cent of days &gt; 30% change in FEV1</td>
<td>50 mg twice daily through multidose powder inhaler + placebo capsule once daily</td>
<td>12 weeks after 8- to 14-day run-in period</td>
<td>Patients used inhaled albuterol as needed through the study.</td>
</tr>
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Randomized crossover study 144 (126)

Age 6–17 yr
Gender Not reported
Ethnicity Not reported

Mild-to-moderate asthma Improvement in FEV1, of 12% or greater after maximal bronchodilator or methacholine PC20 of 12.5 mg/mL or less
No corticosteroid treatment within 4 weeks, no leukotriene-modifying agents within 2 weeks, no history of respiratory tract infection within 4 weeks
Asthma symptoms or rescue bronchodilator use, on average, 3 or more days/week during previous 4 weeks

Arm 1 Fluticasone propionate + placebo tablet (FP)
Arm 2 Montelukast + placebo inhaler (M)
Study n=144; 127 completers

100 mcg per pimhalation; 1 inhalation twice daily
1 tablet at night; 5 mg for those 5–14 yr of age and 10 mg for those 15–18 yr of age

Two 8-week periods after a 5–to-10-day characterization period First 4 weeks of 2nd treatment period were considered sufficient for washout of medication used in first period.

Agreement in responses to 2 medications at end of 6-week period; concordance correlation of 0.65 (95% CI 0.43 to 0.65; n=126)
Mean FEV1 improvement was 6.8% for FP and 1.9% for M treatment groups (mean diff 4.9%, p<0.001).

Defining response as FEV1 >7.0%, 17% responded to both FP and M, 23% responded to FP only; 5% responded to M only; and 55% responded to neither.

Difference in response (PP – M) was associated with lower prednisolone FEV1/FVC ratio, %predicted and FEV1/FVC ratio lower methacholine PC20 value, higher bronchodilator use, higher FEV1 response to bronchodilator, elevated nitric oxide level, higher ECP level, and nonmorbidity race.

Multivariable regression model for difference in response (PP – M) included baseline prednisolone FEV1/FVC ratio, baseline log, ECP value, body mass index, and log, PC20 value.


Multicenter, randomized, 12-part, parallel-group trial (39 sites) Mild Asthma Montelukast versus Inhaled Corticosteroid (NAM) study 400 (176 in JT analysis for double-blind period; 224 for open-label period)

Age 18–65 yr, mean = 37.2 yr
Gender 31% male, 69% female
Ethnicity 50.0% White, 7.9% Black, 2.6% Asian, 9.7% other

Mild persistent asthma Age at first treatment, mean = 20.9 yr
Atopy, 89%
FEV1, mean = 3.3 L
FEV1% pred, mean = 94
Abdomen use, mean = 3.5 days/week
Daytime asthma symptoms, mean = 3.6 days/week
Nighttime awakenings, 65.5% ≥2/month, 34.5% ≥2/month
PC20s, mean = 68.1% of days in run-in period

Arm 1 Inhaled F (n=191); 173 completed double-blind therapy; 177 entered open-label period; 151 completers
Arm 2 Montelukast (M) (n=189); 177 completed double-blind therapy; 173 entered open-label period; 138 completers

2 pills of 44 mcg twice daily + placebo tablet
10-week double-blind period and 36-week open-label period (10% of participants switched to therapies to preserve masking in preceding period), 3-week placebo run-in period

M was as effective treatment as F with respect to mean percentage of RFDs during the 12-week double-blind period Mean percentage of asthma RFDs days was 7.4% for F group and 7.3% for M group (diff 0.1%, 95% CI -0.2% to 0.3%, p=0.7).

During double-blind period, those in lowest quartile of FEV1 (<70%) had more RFDs with F than with M treatment.

During open-label period, mean percentage of RFDs was greater for F group vs. M group (77.2% vs. 71.1%; diff 6.2%, 95% CI 0.6% to 11.7%).

Those in the highest quartile of days of abutus use at baseline (5–6 days/week) had more RFDs with F than with M during the open-label period whereas those in the lower 3 quartiles (≤2 days/week) F and M groups were comparable across the 8-week study period.

No difference was found between F and M groups in increase in morning PEF during either period.

During the 12-week double-blind period, no difference was found between F and M groups in change in asthma symptoms score (p=0.09), asthma control score (p=0.05), or asthma-specific QOL score (p=0.01).

During the open-label period, F vs. M treatment group showed improved asthma symptom score score (p=0.2, 95% CI -0.3 to 0.8, p=0.02), with no difference in change in control score (p=0.1, 95% CI 0.2 to 0.01) or asthma-specific QOL score (p=0.1, 95% CI 0.0 to 0.3, p=0.11).
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<tr>
<td>Zieger et al.</td>
<td>Multicenter, double-blind, randomized, crossover trial (Stratified by clinical center, age, and FEV, percent predicted)</td>
<td>To determine intrapulmonary and interindividual response profiles and predictors of response to an ICS and an LTRA</td>
<td>144 (127)</td>
<td>Age 6–17 yr with 33% 6–9-y</td>
<td>Mild-to-moderate persistent asthma Absence of late asthmatic reaction use within 2 weeks</td>
<td>Arm 1</td>
<td>Fluticasone propionate (FP)</td>
<td>100 mcg/ inhalation; 1 inhalation twice daily</td>
<td>1 tablet at night; 5 mg for those 6–12 yr of age and 10 mg for those 10–18 yr of age</td>
<td>5–10 day run-in period; 16-week trial, with two 6-week treatment periods First 4 weeks of second treatment period was washout period for the first treatment. Subjects received an active drug and a matching placebo for the alternative drug.</td>
<td>Greater improvement occurred after FP vs. M treatment in prebronchodilator FEV1/FVC (0.2 vs. 0.0; p &lt; 0.0001), FEV1 variability (7.5 vs. 8.5; p &lt; 0.03), morning PEF (334.2 vs. 334.8; p = 0.002), R5 (0.60 vs. 0.63; p = 0.003), and area of reactance (1.25 vs. 1.53; p &lt; 0.0003). Decrease occurred in exhaled nitric oxide after both FP and M treatment (56.6 and 35.9; p &lt; 0.001), with the decrease greater after FP (p &lt; 0.0002). Higher exhaled nitric oxide levels at baseline discriminated asthma control day response to treatments, with greater responses to FP than to M treatment (p = 0.011).</td>
</tr>
</tbody>
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