

Original article

Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial

Background: The Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy (COMPACT) trial demonstrated that montelukast added to budesonide (MNT + BD) was as efficacious as double the dose of budesonide (dBD) in improving morning peak expiratory flow (AM PEF) in adult asthmatics. Recent studies have demonstrated that montelukast is also effective in treating daytime and nighttime allergic rhinitis (AR) symptoms in asthmatic patients. This analysis was designed to examine whether asthmatic patients with comorbid AR respond differently than patients without comorbid AR in terms of asthma control (lung function).

Methods: There were 216 asthmatic patients in the MNT + BD group and 184 patients in the dBD group with AR. Treatment differences in the change from baseline in AM PEF were compared. Least square (LS) mean and 95% confidence interval (CI) were derived from an ANOVA model adjusting for baseline and study site.

Results: There was a 9.2% increase in AM PEF from baseline in the MNT + BD group compared with a 6% increase in the dBD group. The LS mean difference [(MNT + BD) – dBD] was 14.2 l/min ($P = 0.028$). Other secondary endpoints were similar between groups.

Conclusion: In the subgroup of asthmatic patients with AR, a combined treatment approach that included montelukast and budesonide provided significantly greater efficacy in reducing airflow obstruction compared with doubling the dose of budesonide. These results support recommendations by the Allergic Rhinitis and its Impact on Asthma initiative that suggest a unified approach aimed at treating the airway inflammation common to both diseases is beneficial for the large proportion of asthmatics who also suffer from AR.

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Asthma and allergic rhinitis (AR) are highly prevalent diseases that frequently occur as comorbid conditions (1). Clinical symptoms of asthma and AR may represent local manifestations of a single inflammatory disorder as both diseases share a common pathology and are characterized by similar inflammatory cell infiltrates (2–4). The degree of inflammation in asthma highly correlates with the level of inflammation in the nose, and allergen challenge to the nose leads to hyper-responsiveness in the lungs (5, 6). Similarly, allergen challenge to the lung leads to inflammation in the nose (7).

Functional relationships between the two diseases demonstrate that comorbid AR significantly worsens asthma. A retrospective analysis of nine clinical trials showed significantly increased asthma symptoms score and need for β -agonist rescue medication in the patients with comorbid conditions compared with patients with asthma alone (8). Asthmatics with AR were more than twice as likely to suffer an asthma attack (9). Similarly, an analysis of patients in a UK General Practice database

found that comorbid AR increased the risk of hospitalizations for asthma (10).

Treatment guidelines have recognized that asthma and AR are linked conditions of ‘one airway’ and recommend that asthmatic patients be routinely evaluated on how AR affects their asthma (11, 12). These guidelines support a combined approach to treating both conditions to maximize therapeutic benefit and minimize medication load if possible.

Cysteinyl leukotrienes, key drivers of symptoms in both asthma and the early and late phase AR response, are not blocked by steroids or antihistamines. Montelukast has proven to be efficacious in the treatment of both asthma and AR (13–18) and is the only drug therapy approved to treat both conditions in a single formulation. Recent studies have demonstrated that montelukast provides benefit for both asthma and AR in patients with comorbid conditions (19–21). The Clinical Outcomes with Montelukast as a Partner Agent to Corticosteroid Therapy (COMPACT) study was a randomized

double-blind trial including 889 asthmatic adults whose asthma symptoms persisted despite use of inhaled corticosteroids (ICS) (22). The objective of the present analysis was to investigate whether patients with asthma and AR taking montelukast added to budesonide (MNT + BD) in the COMPACT study had increased benefit in controlling symptoms of asthma compared with patients taking double the dose of budesonide (dBD).

Methods

Study design

The original study design has been previously described (22). Briefly, during a 1-month run-in period, adult patients whose asthma was not optimally controlled with ICS were switched from their current medication to 800 µg/day of inhaled budesonide (Turbohaler™ 200 µg, two puffs daily; AstraZeneca UK Ltd, Luton, UK). Inadequate control of asthma was determined by investigators for their patients who were taking regular prescriptions for 600–1200 µg/day of budesonide, beclomethasone, triamcinolone, or flunisolide or 300–800 µg/day of fluticasone. After the run-in period, patients were randomized to receive either once daily oral montelukast 10 mg added to 800 µg/day of inhaled budesonide or inhaled budesonide 1600 µg/day (800 µg twice daily) for 12 weeks to compare the treatment regimens. Patients had to have had a forced expiratory volume in 1 s (FEV₁) of ≥50% of predicted, ≥12% improvement in FEV₁ after β-agonist administration and to have required at least 1 puff/day of β-agonist for asthma symptoms during the last 2 weeks of the run-in period. The Price et al. (22) study was approved by the appropriate ethical review committees and each patient gave written informed consent.

Patient selection

For this *post hoc* analysis, patients were identified who had a positive history of both asthma and AR. Allergic rhinitis was defined by patient self-report and was confirmed by their physician. Allergic rhinitis could occur all year long with or without seasonal flares or only during certain seasons. Because of the study design, there was no means of identifying when patients had active symptoms during the 12 weeks. Patients taking allergy medications while on study was used as a surrogate for identifying patients with active symptoms and were evaluated separately. This subgroup of asthmatic patients was currently taking intranasal steroids, antihistamines, and other medications to control allergy symptoms. This medication could have been continued or stopped during the study.

Study endpoints

The primary efficacy endpoint was morning peak expiratory flow (AM PEF) measured in the morning and in the evening immediately before taking any medication. Other endpoints evaluated for this study were β-agonist use, asthma-free days (any day free of oral corticosteroid use, emergency care, nocturnal awakenings, with use of ≥2 puffs β-agonist), and nocturnal awakenings. Patients recorded nocturnal awakenings and overnight β-agonist use on a validated asthma diary card (23). The proportion of patients who achieved control of their asthma using the guidelines outlined by the Gaining Optimal Asthma Control (GOAL) study were assessed (24). These endpoints of control included AM PEF ≥ 80% each day of the week, daytime asthma symptoms score > 1 on no more than

2 days/week, and no more than 2 days of β-agonist use per week at 4, 8, and 12 weeks of therapy.

Statistical analysis

Statistical tests for each endpoint were performed using an ANCOVA model, with treatment and study site as factors and the appropriate baseline value as covariate. The AM PEF was calculated as the on-treatment average for the last 10 weeks of the 12-week double-blind period of the study. Analysis for asthma-free days and nocturnal awakenings were performed using the normalized ranks. The proportion of patients achieving asthma control reaching AM PEF ≥ 80% each day of the week, daytime asthma symptoms score > 1 on no more than 2 days/week, and no more than 2 days of β-agonist use per week at 4, 8, and 12 weeks of therapy were determined using the Mantel–Haenszel chi-square test.

Results

Patients

There were 410 patients (46.1%) from the Price et al. (22) study, who had asthma and AR by self-report and confirmed by a physician, and 479 patients without AR (Table 1). There were no clinically meaningful differences between the treatment groups in baseline characteristics (Table 2). Of the patients with asthma and AR, 136 (33.2%) had rhinitis all year long without seasonal flares, 127 (31%) had rhinitis all year long with seasonal flares,

Table 1. Demographics and baseline characteristics of patients with asthma and allergic rhinitis (asthma/AR+) and without AR (asthma/AR–)

Baseline parameters	Number of patients (%)	
	Asthma/AR+	Asthma/AR–
Patients	410 (100.0)	479 (100.0)
Patient-reported allergic rhinitis	410 (100.0)	99 (20.7)
Physician-diagnosed allergic rhinitis	410 (100.0)	6 (1.3)
Gender, male	171 (41.7)	184 (38.4)
Race		
White	319 (77.8)	365 (76.2)
Black	4 (1.0)	2 (0.4)
Asian	25 (6.1)	19 (4.0)
Other	62 (15.1)	93 (19.4)
History of atopic dermatitis	79 (19.3)	58 (12.1)
Family history of asthma	233 (57.3)	227 (47.8)
Family history of allergic rhinitis	135 (33.2)	91 (19.2)
FEV ₁ ≥ 60%	313 (76.3)	330 (68.9)
β-Agonist reversibility ≥12%	333 (81.2)	394 (82.3)
β-Agonist use < daily	151 (36.8)	183 (38.2)
Nocturnal awakening >1 night/week	307 (74.9)	353 (73.7)
Median (lower quartile, upper quartile)		
Age (years)	43.0 (30.0, 53.0)	45.0 (34.0, 56.0)
FEV ₁ (% predicted)	69.4 (60.9, 79.0)	66.8 (58.8, 76.3)
β-Agonist reversibility	18.2 (13.4, 24.8)	19.5 (14.0, 27.5)
β-Agonist use (puffs/day)	1.5 (1.0, 2.6)	1.6 (0.9, 2.6)
β-Agonist use (days/week)	7.0 (4.9, 7.0)	7.0 (4.2, 7.0)
Nocturnal awakenings (nights/week)	3.0 (2.0, 4.0)	3.0 (1.0, 4.0)

FEV₁, forced expiratory volume in 1 s.

Table 2. Demographics and baseline characteristics of patients with asthma and allergic rhinitis by treatment group

	Montelukast (10 mg) + budesonide (800 µg/day) (<i>n</i> = 221)	Budesonide (1600 µg/day) (<i>n</i> = 189)
Age in years (mean, SD)	42.3 (13.87)	41.4 (13.8)
Sex, male, <i>n</i> (%)	90 (40.7)	81 (42.9)
Race, <i>n</i> (%)		
White	171 (77.4)	148 (78.3)
Black	1 (0.5)	3 (1.6)
Asian	16 (7.2)	9 (4.8)
Other	33 (14.9)	29 (15.3)
Allergic rhinitis duration	Not collected	Not collected
Asthma duration (year)	17.9 (13.33)	18.5 (15.26)
FEV ₁ (l)	2.4 (0.75)	2.4 (0.71)
FEV ₁ (% predicted)	70.1 (13.59)	70.2 (13.09)
Daily β-agonist use (puffs/day)	2.1 (1.98)	2.1 (1.98)
Nocturnal awakenings (nights/week)	2.8 (1.30)	2.7 (1.34)

SD, standard deviation; FEV₁, forced expiratory volume in 1 s.

and 226 (55%) had rhinitis only during certain seasons. There were 33 patients in the MNT + BD group and 23 patients in the dBD group who were taking intranasal steroids, antihistamines, or other allergy medications to control symptoms of AR during the run-in period.

Efficacy

The AM PEF improved rapidly and consistently for both treatment groups with AR over the 12-week active treatment period (Fig. 1). After 12 weeks of treatment, there was a 9.2% increase in AM PEF for patients randomized to MNT + BD compared with a 6.0% increase in the dBD group. The AM PEF increase for

those who were taking allergy medications in the MNT + BD group was 21.1% compared with 1.9% in the dBD group (Table 3).

Patients in the MNT + BD group had significantly greater improvement in AM PEF than the dBD group ($P = 0.028$) (Fig. 2). The treatment difference [(MNT + BD) – dBD] was 14.2 l/min (95% CI: 1.58, 26.84) (Table 3). Patients in the MNT + BD group taking medications for their allergies also had significantly greater improvement in AM PEF than the dBD group ($P = 0.017$) (Fig. 3) with a treatment difference of 44.3 l/min (95% CI: 8.35, 80.25) (Table 3). The between-visit averages calculated for AM PEF for each treatment group were consistent within each of the visit periods (Figs 2 and 3). Patients in the MNT + BD group without AR showed improvement in AM PEF that was similar to that for patients in the dBD group; the treatment difference was –5.31 l/min (95% CI: –17.92, 7.31; $P = 0.409$).

For patients with AR, β-agonist use fell by 27.8% in the MNT + BD group compared with a 21.0% decrease in the dBD group; the least square (LS) mean difference was –5.87 (95% CI: –6.59, 19.33; $P = 0.279$). For patients without AR, β-agonist use was decreased by 26.3% in the MNT + BD group compared with a 30.4% decrease in the dBD group; the LS mean difference was –4.08 (95% CI: –16.27, 8.10; $P = 0.510$). The median number of asthma-free days for patients with AR was 87.3% in the MNT + BD group and 79.8% in the dBD group ($P = 0.14$). For patients without AR, the median number of asthma-free days for MNT + BD was 85.2% and 83.7% in the dBD group ($P = 0.63$). The mean number of nocturnal awakenings for patients with AR was 2.3% in the MNT + BD group and 5.5% in the dBD group ($P = 0.171$) compared with 2.3% in the MNT + BD group and 2.5% in the dBD group ($P = 0.778$) for patients without AR.

At 12 weeks of therapy, 11.1% of patients with AR and 11.5% without AR in the MNT + BD group as well as 5.3% with AR and 8.9% without AR in the dBD group achieved control of their asthma as defined by reaching an AM PEF $\geq 80\%$, daily asthma symptoms score > 1 on no more than 2 days, and no more than 2 days of β-agonist use per week (Table 4). The percentage of patients with AR achieving asthma control was significantly greater for MNT + BD than for dBD ($P = 0.04$) (Table 4).

Discussion

In this analysis, asthmatic patients with AR were identified among patients who participated in a large clinical trial that demonstrated that either doubling the dose of budesonide or adding montelukast was effective in improving several measures of asthma control, with this effect increasing over time (22). When patients with

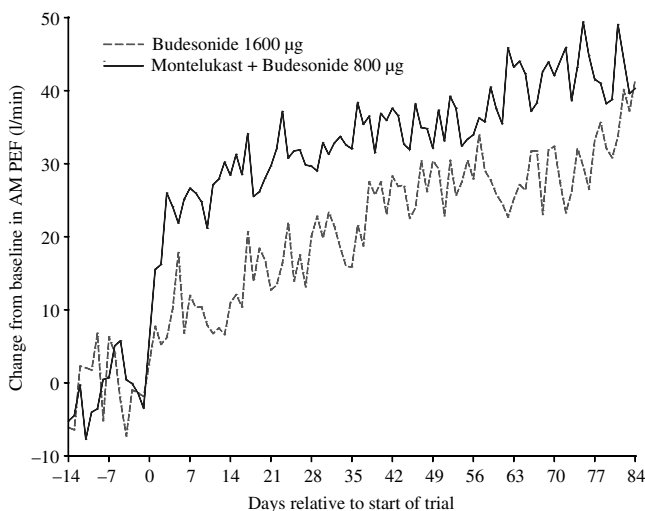


Figure 1. Mean change from baseline in morning peak expiratory flow (AM PEF) for all patients with asthma and allergic rhinitis throughout the treatment period.

Table 3. Change in morning peak expiratory flow (AM PEF) from baseline for patients with asthma and allergic rhinitis over 12 weeks of treatment

Patient group	n	Montelukast (10 mg) + budesonide (800 µg/day)		n	Budesonide (1600 µg/day)			P-value
		Baseline AM PEF (l/min)	Increase from baseline (%)		Baseline AM PEF (l/min)	Increase from baseline (%)	LS mean difference* (95% CI)	
Asthma/AR+	216	391.0	33.5 (9.2)	184	403.4	24.1 (6.0)	14.2 (1.58, 26.84)	0.028
Asthma/AR+ using allergy medications	33	431.1	52.1 (21.1)	23	411.9	7.8 (1.9)	44.3 (8.35, 80.25)	0.017

AR, allergic rhinitis; CI, confidence interval; LS, least squares.
*Difference = (montelukast + budesonide) – double-dose budesonide.

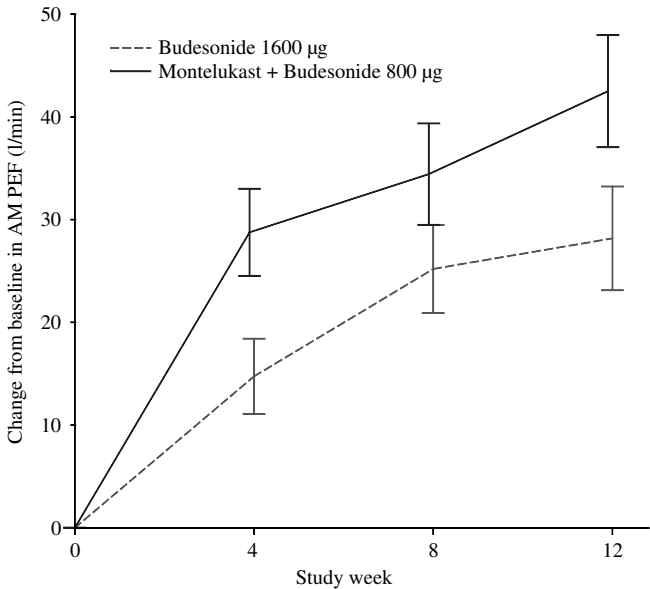


Figure 2. Mean change from baseline in morning peak expiratory flow (AM PEF) (l/min) by week for patients with asthma and allergic rhinitis.

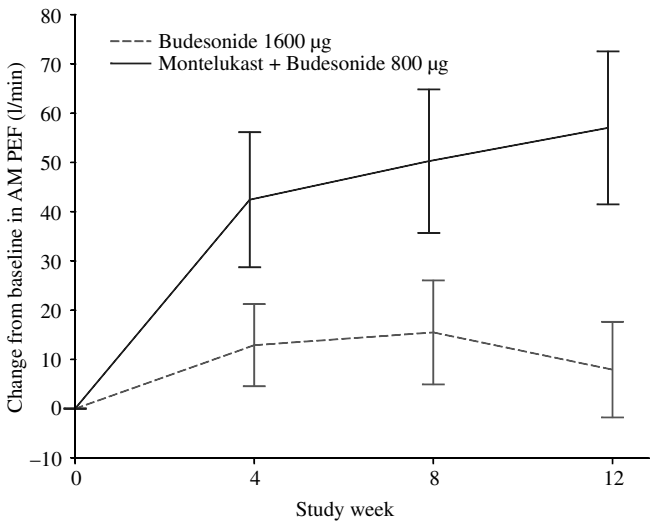


Figure 3. Mean change from baseline in morning peak expiratory flow (AM PEF) in patients with asthma and allergic rhinitis taking medications for their allergies.

Table 4. Number of patients who had an AM PEF $\geq$ 80%, daily asthma symptoms score >1 on no more than 2 days, and no more that 2 days of β -agonist use per week during the treatment period

	Montelukast (10 mg) + budesonide (800 µg/day) (n = 221)	Budesonide (1600 µg/day) (n = 189)	P-value
4 weeks			
Asthma/AR+	9 (4.2)	6 (3.3)	0.63
Asthma/AR–	18 (8.4)	9 (3.8)	0.04
8 weeks			
Asthma/AR+	14 (6.6)	8 (4.4)	0.35
Asthma/AR–	14 (6.5)	13 (5.6)	0.69
12 weeks			
Asthma/AR+	22 (11.1)	9 (5.3)	0.04
Asthma/AR–	24 (11.5)	20 (8.9)	0.37

Values in parentheses are percentages.
AM PEF, morning peak expiratory flow; AR, allergic rhinitis.

comorbid AR were evaluated in the current study, the addition of montelukast was significantly better at improving AM PEF than was doubling the dose of budesonide. This effect was consistent over the 12-week observation period.

In the present study, patients with rhinitis were identified based on their self-report also confirmed by their physician. There were few patients (105) who had either patient-reported rhinitis or physician-confirmed rhinitis but not both. The original study was an asthma trial, so patients who had severe AR were excluded. What may have made the current population unique was that rhinitis was also recognized by their physician. This implies that symptoms, when they occurred, were bothersome enough to consult a physician. Additionally, patients in the Price et al. (22) study probably had a greater degree of inflammation as evidenced by the higher dose of budesonide (800 µg/day) at baseline and because their asthma was not well controlled by ICS. All of these factors define a population with more severe asthma confounded by rhinitis. Adding montelukast was significantly better in improving lung function than increasing ICS dose. However, a comparison of the changes in AM PEF in the montelukast group in the present study (33.5 l/min) was virtually identical to the changes in the montelukast group in the original study (33.5 l/min). The

small group with active rhinitis, as defined by current treatment in the beginning of the study, did show added benefit (52.1 l/min) with montelukast. Doubling the dose of budesonide in the current analysis resulted in a change in AM PEF (24.1 l/min) that was less than the changes in the original study (30.1 l/min) (22). Patients with active AR had even less improvement in AM PEF (7.8 l/min) on budesonide, although the numbers in this population were too small to make inferences. One conclusion that could be drawn is that in this population, ICS was less effective in patients with concomitant rhinitis. The results with montelukast in this study are supportive of the Allergic Rhinitis and its Impact on Asthma initiative developed with the World Health Organization that recommends a unified approach to treating asthma and AR (12).

Although all patients in this study were on ICS and could take nasal steroids and antihistamines for their allergies, it appears that inflammation was not well controlled until montelukast was added to the regimen. This suggests that increasing doses of ICS in similar patients will not be a successful strategy for asthma in patients with comorbid disease. This is supported by studies showing that asthma is more likely to be uncontrolled in patients with physician-diagnosed rhinitis despite greater asthma therapy (10).

Patients were evaluated to determine who achieved a target level of control of their asthma using some of the criteria of the GOAL study (24). Information on asthma exacerbations, and emergency department visits were part of the GOAL criteria but were not captured in the present study. The level of ICS usage in the Price et al. (22) study would make the population similar to the most severe patients (Stratum 3) in the GOAL study (24). The proportion of patients who reached control of their asthma in the MNT + BD group increased from 4.2% at 4 weeks to 11.1% at 12 weeks. The proportion of patients achieving control in the dBD group also increased slightly over time as it did for patients without AR in both groups. In the GOAL study, the proportion of patient in any treatment group that achieved well-controlled asthma ranged from 33% to 51% in the more severe patients (24). This supports the lung function findings in this population of patients with asthma and rhinitis.

In the current study, montelukast probably was more effective because it improved inflammation associated

with nasal symptoms and this impacted on the lung inflammation associated with asthma. Treating AR in asthmatic patients has been shown to significantly lower the risk of asthma-related emergency department or hospitalizations (25). Large prospective trials that focus on both asthma and AR endpoints will be needed to better elucidate the therapeutic connections and efficacy of treatments in patients with comorbid disease. To date, montelukast has been shown to be protective against both lower and upper airway responses during exposure to high level of antigen challenge (20) and to provide significant relief of symptoms of AR while reducing β -agonist use in patients with allergies and asthma (21).

A limitation of this analysis is that data were taken from a study that focused on asthma endpoints, with no daily information on rhinitis symptoms recorded. Except for the fact that patients sought a physician for their allergies, the severity of rhinitis is unknown. Additionally, it is not known whether they had active allergic symptoms during the trial and how long they remained symptomatic. Only the small group of patients who were taking allergy medications during the run-in period had evidence of active rhinitis, and even this group had no information on the duration. Presumably, rhinitis symptoms were dependent on exposure and season over the 12 weeks, so the results from our retrospective analysis would be modified by the variability of symptoms.

The results of *post hoc* analyses should be considered exploratory in nature and cannot be given the same level of legitimacy that prespecified analyses can be given. Although this was a retrospective analysis, an additional look at patients with comorbid AR was intended in the original study and a subgroup analysis by patient reported AR was prespecified in the data analysis plan. Because subgroup analyses always include fewer patients than the overall analysis, they carry a greater risk of type II error (i.e. falsely concluding that there is no difference when in fact one does exist). Although the size of the subgroup is not adequate to demonstrate statistical significance for all the efficacy endpoints, a net benefit was demonstrated for MNT + BD over dBD in a variety of efficacy measures of asthma control.

In conclusion, montelukast significantly improved lung function in asthmatics with concomitant AR compared with ICS. The effect was consistent over 12 weeks of active treatment.

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