

Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the improving asthma control trial

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Summary

Background Inadequately controlled allergic rhinitis (AR) in asthmatic patients can contribute towards increased asthma exacerbations and poorer symptom control, which may increase medical resource use. We assessed asthma-related medical resource use and attacks in asthmatic patients who did and did not have concomitant AR and were adding montelukast or salmeterol to baseline treatment with inhaled fluticasone.

Methods A *post hoc* resource use analysis of a 52-week, double-blind multicentre clinical trial (IMPACT: IMProving Asthma Control Trial) including 1490 adults with chronic asthma, aged 15–72 years, with FEV₁ 50–90% of predicted and $\geq 12\%$ increase in FEV₁ after salbutamol administration, treated with either montelukast 10 mg daily or salmeterol 50 µg twice daily in addition to fluticasone 200 µg, was undertaken. Asthma-related medical resource use included medical visits (defined as either an unscheduled visit [to a general practitioner, a specialist or a non-medical provider] or a specialist visit), emergency room visits and hospitalizations during follow-up. Asthma attacks were defined as the worsening of asthma requiring unscheduled visit, emergency visit, hospitalization or oral/intravenous/intramuscular corticosteroids.

Results A self-reported history of concomitant AR was identified in 60% of the patients ($n = 893$). Univariate analysis suggests that significantly more patients with concomitant AR experienced emergency room visits (3.6% vs. 1.7%, $P = 0.029$) and asthma attacks (21.3% vs. 17.1%, $P = 0.046$). Multivariate analysis adjusting for treatment group, age and baseline asthma severity confirmed these results since the presence of concomitant AR in patients with asthma increases the likelihood of emergency room visit (odds ratio (OR) = 2.35, 95% confidence interval (CI) = 1.12–4.80) and asthma attack (OR = 1.35, 95% CI = 1.03–1.77). Patients with asthma alone compared with patients with both conditions did not differ in terms of unscheduled or specialist visits and hospitalizations.

Conclusions Presence of self-reported concomitant AR in patients with asthma resulted in a higher rate of asthma attacks and more emergency room visits compared with asthma patients without concomitant AR.

Keywords allergic rhinitis, asthma, attack, resource utilization

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Introduction

Asthma and allergic rhinitis (AR) are systemically linked by common and interrelated inflammatory processes of the upper and lower airways [1–3]. Furthermore, epidemiological studies have consistently demonstrated that asthma and rhinitis often co-exist in the same patient [3–10] (prevalence of AR among asthmatic patients is usually over 50%) and that their frequency is increasing worldwide [11, 12]. In addition to the symptomatic burden of AR in patients with asthma [13], AR can complicate asthma management and result in poorer asthma outcomes [14].

As a result and as preliminary evidence from observational studies suggest [4, 14–16], asthma-related medical resource use

may increase in patients with asthma and concomitant AR compared with those with asthma alone. Because of the lack of such evidence from controlled studies, the primary objective of this *post hoc* analysis was to estimate asthma-related medical resource use and asthma attacks according to the presence of concomitant AR in patients with asthma studied in a clinical trial. The secondary objective was to compare the effect of added second controller therapy (montelukast or salmeterol) to baseline treatment with inhaled fluticasone on the same endpoints in patients with asthma and concomitant AR.

Methods

Study design and data source

We performed a *post hoc* analysis of data from the IMProving Asthma Control Trial (IMPACT). As described previously in

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detail [17], this clinical trial was the first study designed to compare the efficacy of the addition of montelukast vs. salmeterol to inhaled fluticasone in mild-to-moderate asthmatic patients whose symptoms remain uncontrolled with inhaled fluticasone. Carried out from January 2000 to December 2001, this clinical trial was a 52-week randomized, double-blind, double dummy, parallel group, multicentre study. During the first 4-week run-in period, patients received opened inhaled fluticasone 100 µg twice daily. A single placebo of salmeterol or montelukast was added during the two last weeks of this period. Then, in addition to the fluticasone, patients received either montelukast 10 mg once daily or salmeterol 50 µg twice daily. The study included 1490 patients aged 15–72 years with chronic asthma for at least 1 year, a baseline forced expiratory volume in 1 s (FEV₁) of 50–90% predicted and an improvement of 12% or more in FEV₁ or in morning peak expiratory flow (PEF).

In the *post hoc* analysis, patients were stratified according to the presence of concomitant AR. Endpoints were asthma-related medical resource use and asthma attacks. The former was defined as medical visits (defined as either an unscheduled visit [to a general practitioner, a specialist or a non-medical provider] or a specialist visit), emergency room visits and hospitalizations during follow-up. Asthma attacks were defined as worsening of asthma requiring unscheduled physician visit, emergency visit, hospitalization or oral/intravenous/intramuscular corticosteroids. History of AR at baseline was self-reported by the patients. Use of allergy medications (antihistamines and/or nasal steroids) prior to randomization and during follow-up was also self-reported by the patients with both asthma and AR.

Statistical analysis

The difference between the two groups (asthma alone vs. asthma with AR) for baseline characteristics was assessed with a *t*-test for continuous variables and a χ^2 test for categorical variables. Differences in outcomes in patients with asthma alone vs. asthma with AR were estimated with an unadjusted analysis (χ^2 test) and with a multi-variable logistic regression after adjustment for treatment group and baseline variables that were significantly different including age and FEV₁% predicted. Differences in outcomes in asthmatic patients with concomitant AR by treatment group (fluticasone+montelukast vs. fluticasone+salmeterol) were analysed using a multi-variable logistic regression after adjustment for age, gender and race. Differences in proportion of patients with asthma and AR using concomitant allergy medications (antihistamines and/or nasal steroids) before and after second controller introduction (either salmeterol or montelukast) were evaluated using McNemar's test for difference. All analyses were performed using SAS v. 8.2.

Results

Out of 1490 asthmatic patients enrolled, 60% ($n = 893$) reported concomitant AR. Patients with both conditions were generally younger than those with asthma alone (39.2 vs. 44.0 years, $P < 0.0001$) and had less severe asthma (FEV₁% predicted 72.6 vs. 71.1, $P = 0.04$). Gender, race and baseline

Table 1. Baseline patient characteristics

	Asthma-with-allergic rhinitis	Asthma only
Patients [n , %]	893 (60%)	597 (40%)
Age [mean (SD)]*	39.2 (13.1)	43.9 (13.9)
Females [n , %]	497 (55.7%)	321 (53.8%)
White‡ [n , %]	680 (76.2%)	476 (79.7%)
FEV ₁ % predicted [mean, SD]†	72.6 (13.1)	71.1 (14.2)
Short-acting beta agonist use§ [mean puffs/day (SD)]	3.27 (2.37)	3.34 (2.39)

* $P < 0.01$; † $P = 0.04$; ‡Race classified as white and other; §During 3 month baseline period.

usage of short-acting beta agonists were not associated with concomitant AR (Table 1). Despite having milder asthma, significantly more asthmatic patients with concomitant AR experienced asthma attacks (21.3% vs. 17.1%, $P = 0.046$) and emergency room visits (3.6% vs. 1.7%, $P = 0.029$) in comparison with those with asthma alone (Fig. 1). After adjustment for differential asthma severity, treatment group and age, the presence of AR in patients with asthma remained associated with higher likelihood of asthma attack (OR = 1.35, 95% CI = 1.03–1.77) and emergency room visit (OR = 2.35, 95% CI = 1.12–4.80) (Table 2). Patients with asthma alone compared with patients with asthma and concomitant AR did not differ in terms of unscheduled visits (9.6% in asthma group vs. 11.8% in asthma-with-AR group) and specialist visits (4% vs. 5.5%) or hospitalizations (0.5% vs. 1.0%) (Fig. 1).

Results of the exploratory analysis among the 853 patients with concomitant AR are presented in Tables 3 and 4. Patients treated with montelukast in addition to fluticasone had a similar rate of asthma attacks and of asthma-related medical resource use compared with those receiving salmeterol in addition to fluticasone. The numerical trend suggests slightly better outcomes in patients on montelukast; however, the study was not powered to show these differences. Results also suggest that upon introduction of second controller therapy (either salmeterol or montelukast) the proportion of patients using allergy therapy declined in montelukast arm by 1.54% ($P = 0.55$) and increased in the salmeterol arm by 3.4% ($P = 0.18$) (Table 4).

Discussion

Asthma and AR share common and possibly linked pathophysiology with nasal and bronchial biopsies showing similar inflammatory processes [18] in lower and upper airways. Both conditions are characterized by inflammation of the respiratory mucosa and are associated with the same inflammatory cells and mediators [19, 20]. Nasal provocation as well as segmental bronchial provocation in non-asthmatic, seasonal AR patients induced inflammation in both bronchial and nasal mucosa, and produced pulmonary symptoms and decreased airway function [21]. It is therefore meaningful to study health outcomes in patients with both conditions.

Results of this *post hoc* analysis of the IMPACT trial show that patients with asthma and concomitant AR are more than

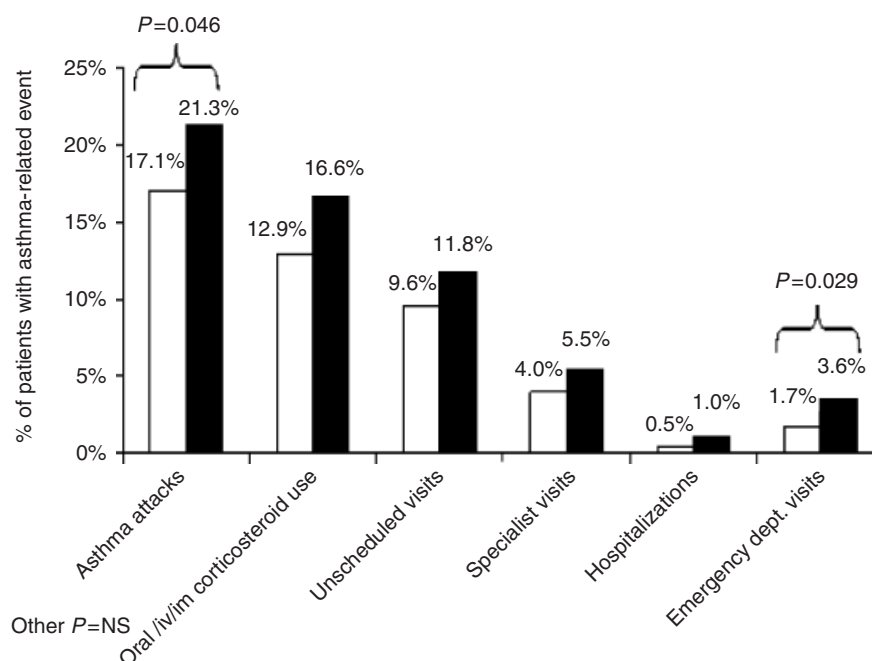


Fig. 1. Asthma-related resource use and asthma attacks according to the presence of concomitant allergic rhinitis (AR) (% patients). □, asthma; ■, asthma-with-AR.

Table 2. Likelihood of asthma-related resource use and asthma attacks according to presence of concomitant AR

	Odds ratio* [95% confidence interval]
N = 1490	Asthma-with-AR group vs. asthma group (ref. group)
Asthma attacks	1.35 [1.03–1.77]
Emergency dept. visits	2.32 [1.12–4.80]

*Adjusted for treatment group, baseline FEV₁ % predicted and age. AR, allergic rhinitis; FEV₁, forced expiratory volume in 1 s.

Table 3. Asthma-related resource use and asthma attacks among patients with asthma and concomitant allergic rhinitis by treatment group

	Odds ratio* [95% confidence interval]
N = 893	FLU+SAL vs. FLU+MON (ref. group)
Asthma attack	1.006 [0.73–1.39]
Emergency visit	1.04 [0.51–2.11]
Unscheduled visit	1.01 [0.67–1.52]
Specialist visit	1.40 [0.78–2.50]
Hospitalization	2.11 [0.52–8.5]

Study was not powered to show difference in individual endpoints, nor was it powered to show difference in 893 patients with asthma and allergic rhinitis.

*Adjusted for age, gender and race.

FLU, fluticasone; SAL, salmeterol; MON, montelukast.

twice as likely to require emergency visit for asthma and are also significantly more likely to experience asthma attacks compared with patients with asthma alone, despite having milder and slightly better controlled asthma at baseline. Among patients with both conditions inadequately controlled on fluticasone, adding montelukast results in similar asthma-related medical resource utilization and rate of asthma attacks as adding salmeterol. There is a numerical advantage

Table 4. Users of allergy medications* before and after introduction of second asthma controller therapy among patients with asthma and concomitant allergic rhinitis by treatment group

Asthma controller	Baseline period†	Follow-up period‡	% Difference	P-value§
ICS+salmeterol, % (n)	22.68% (100)	26.08% (115)	3.4% (15)	0.18
ICS+montelukast, % (n)	27.65% (125)	26.11% (118)	–1.54% (–7)	0.55

*Antihistamines and nasal steroids; †Baseline period was 3 months; ‡Follow-up period was 12 months; §McNemar's test for difference between pre and post periods.

for patients treated with montelukast. While the proportion of patients using concomitant allergy medications declined upon introduction of montelukast, it increased upon introduction of salmeterol in patients with asthma and AR.

To our knowledge, this is one of the first studies to evaluate the impact of concomitant AR on asthma-related medical resource use among asthmatic patients in a clinical trial setting. In a similarly designed study [22], a *post hoc* analysis (data on file) found that patients with a self-reported history of AR experienced a numerically higher, although not statistically different, rate of asthma attacks compared with patients without a history of AR. Other studies include retrospective observational designs [4, 15, 16, 22], using general practice databases, medical records or survey questionnaire methodologies. Price et al. [14] carried out a retrospective cohort study based on a general practice database in 27 303 adults with asthma. They found that those with concomitant AR ($n=4611$) experienced more asthma-related hospitalizations (0.76% vs. 0.45%) and general practitioner visits (5.2 vs. 4.2) than those with asthma alone ($n=22 692$). They also incurred higher asthma drug costs (average drug cost = GBP 70.2 vs. 65.0). Similarly, in a cross-sectional analysis of medical claims data from a US

health insurance plan [15], Halpern et al. reported that patients with both conditions ($n = 9226$) experienced a threefold higher rate of outpatient episodes linked to asthma or related conditions than those with asthma alone ($n = 18172$). They also presented greater rates of prescription for asthma medication (inhaled β -agonists: 54% vs. 48%; inhaled steroids: 33% vs. 22%). In a US study using medical charts from 1245 patients with asthma [4], Yawn et al. observed that yearly medical charges (excluding medication charges) were on average 46% higher for those with asthma and concomitant AR ($n = 653$) than for those with asthma alone ($n = 592$). However, these charges were not asthma specific and were inconsistent across age categories. Larger differences in utilization between asthma with concomitant AR group and asthma alone group were found in younger patients. A retrospective cross-sectional German study by Schramm et al. [16], based on survey questionnaire and records from 224 adults with asthma and/or AR, found no consistent relationship between concomitant AR and medical resource utilization.

Based on this evidence, two observational studies [4, 16] suggest a weak or inconclusive impact of concomitant AR on asthma-related medical resource use and two studies [14, 15] suggest that concomitant AR increases asthma-related medical resource use. The former two [4, 16] include smaller sample sizes, one of them [4] relies on total medical medication utilization (rather than asthma specific) and one of them [16] may be subject to recall bias because of survey design. The latter two [14, 15] include large patient populations and use computerized records. Our study, prospective, used a different design and adds to the evidence of increased medical resource use with concomitant AR in asthmatic adults.

Moreover, three studies have demonstrated that among patients with asthma and concomitant AR, those receiving treatment for AR have a significantly lower risk of subsequent asthma-related events (emergency care visits/hospitalizations) than those not receiving treatment for AR [23–25]. The design of these studies was as follows: Corren et al. [23] carried out a case-control study (cases = 361 and controls = 1444) while Chang et al. [24], as well as Crystal-Peters et al. [25] conducted a retrospective study based on a MarketScan claims database (including, respectively, 55 600 and 4944 patients). Similarly, Adams et al. [26] performed a retrospective cohort study in patients with asthma ($n = 13844$) and concomitant upper airway disease. They found that treatment of nasal conditions confers significant protection against exacerbations of asthma leading to an emergency visit for asthma.

A further step in this direction is outlined in the ARIA guidelines [12]. Optimal management of rhinitis may improve coexisting asthma and, thus, a combined treatment strategy should ideally be used to treat these two conditions. Preliminary evidence suggests that among patients with both asthma and AR enrolled in a large clinical trial, adding montelukast to budesonide provided greater benefit in reducing airflow obstruction, compared with doubling the dose of budesonide [27]. Further studies will be needed to determine what treatment options offer benefits in patients with both conditions; novel measurements to evaluate outcomes in those have already been proposed [28].

Some limitations of this study need to be mentioned. The IMPACT study was not specifically designed to compare the outcomes in asthmatic patients with concomitant AR to those in patients with asthma alone. Consequently, this *post hoc* analysis may lack the power to draw strong conclusions. In addition, AR was self-reported by the patients and, therefore, may have been misestimated. Also, some of the patients labelled as asthmatics may have had COPD with a reversible airflow obstruction. Future studies should further evaluate whether concomitant AR diagnosed by physicians increases asthma complications and medical resource use related to asthma.

Conclusion

This study suggests that the presence of concomitant AR in asthmatic patients results in a higher rate of asthma attacks and more emergency room visits compared with asthmatic patients without concomitant AR. As recommended by guidelines, strategies to treat both diseases simultaneously and with limited burden on patients should be considered.

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