

# LEUKOTRIENE RECEPTOR ANTAGONISTS IN PATIENTS WITH ASTHMA AND ALLERGIC RHINITIS

Robin J Green, PhD, Dip Allergy (SA)  
Department of Paediatrics, University of Pretoria

## ABSTRACT

Many asthmatics also have allergic rhinitis. The important link between upper and lower airway disease seems to be through a common pathology which affects similar epithelial structures, and the inflammatory process is the common factor where upper and lower airway diseases coexist. Inadequately controlled allergic rhinitis in asthmatic patients can contribute towards increased asthma exacerbations and poorer symptom control, which may increase medical resource use. Prompt and effective treatment of nasal disease with an anti-inflammatory therapy can have a marked beneficial effect. Recently there has been renewed interest in the value of the leukotriene receptor antagonists in the systemic management of these two closely linked diseases. Among children with asthma and concomitant allergic rhinitis, initiating montelukast compared with initiating inhaled steroids (for asthma) in usual practice resulted in lower costs of asthma 'rescue and acute' medications and lower costs of (anti)allergy medications. Appropriate therapy of one or both conditions may alter the natural course of the overall inflammatory airway disease, and would almost certainly impact on patients' quality of life as well as the treatment costs.

Both asthma and allergic rhinitis (AR) are defined as inflammatory conditions,<sup>1,2</sup> and share common trigger factors (including allergens). An estimated 58-78% of asthmatics also have AR.<sup>3,4</sup> Some authors have noted that the vast majority of asthmatics have upper airway disease.<sup>5,6</sup> AR occurs in between 4.5% and 38.3% of the general population.<sup>7,8</sup> Asthma occurs in up to 38% of individuals with AR.<sup>9</sup> A recent International Study of Asthma and Allergy in Children (ISAAC) investigated the complex of asthma, AR and eczema, and found that both asthma and AR are common in South Africa.<sup>10</sup> Many surveys have documented a rising prevalence of both these conditions.<sup>11-15</sup>

What then is the causal or mechanistic link between upper and lower airway diseases in these conditions? The important link seems to be through a common pathology which affects similar epithelial structures, and the inflammatory process is the common factor where upper and lower airway diseases coexist. The so-called sino- or nasal-bronchial reflex has been called into question by Bardin *et al.*<sup>16</sup> In an isotope scanning study, they failed to document any upper airway fluid passing down into the lower airway. It has also been postulated that rhinitis or nasal blockage and subsequent mouth breathing may contribute to greater inhalation of poorly humidified air as well as allergens and irritants.<sup>17</sup>

Evidence for this coexisting disease theory comes from pathological, clinical, pharmacological and challenge/provocative studies.<sup>18</sup> AR and asthma share a common immunopathology,<sup>19,20</sup> including similar cellular, cytokine, mediator and phasic responses. One of these mediator groups are the cysteinyl leukotrienes (CysLts). CysLts are lipid mediators synthesised from arachidonic acid, a normal constituent of the phospholipid bilayer present in many biological membranes, particularly the mast cell, eosinophils, basophils and macrophages. There are two distinct classes but the leukotrienes (LTs) LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub> are the most important in asthma. Activation of cytosolic phospholipase A2 liberates arachidonic acid from the membrane phospholipid. Arachidonic acid interacts with 5-lipoxygenase activating protein (FLAP) and the enzyme 5-lipoxygenase (5-LO) to form 5HETE and ultimately unstable LTA<sub>4</sub>. This is converted to LTB<sub>4</sub>, chemo-attractant for neutrophils, and via LTC<sub>4</sub> synthases to LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub>.

These LTs have numerous actions that contribute to allergy biology. They augment the pathophysiological effects on the allergic airway produced by polarisation of the immune response derived from the production of T-helper 2 (Th<sub>2</sub>) lymphocytes and subsequent activation of mast cells, eosinophils and macrophages to produce the interleukins (ILs), IL-3, IL-4, IL-5, IL-13 and pro-inflammatory cytokines, tumour necrosis factor alpha (TNF- $\alpha$ ), granulocyte macrophage colony-stimulating factor (GM-CSF), eotaxin, and endothelium-transforming growth factor beta (TGF- $\beta$ ). Thus on activation, epithelial cells, mast cells, eosinophils, neutrophils, macrophages and fibroblasts release a wide range of inflammatory mediators with further amplification of CysLt leading to exaggeration of inflammation and remodelling of lower airways.

In addition it has been shown that nasal mucosal inflammation exists in asthma regardless of the presence of AR in many subjects.<sup>21</sup> Bronchial allergen challenge has also been shown to increase eosinophil presence in nasal tissue.<sup>22</sup> Lastly, the association between upper and lower airway disease can be found in the response to therapy. Welsh *et al.*<sup>23</sup> documented improvement in asthma symptoms in patients with both AR and asthma treated only with topical nasal steroids during the ragweed pollen season. Topical nasal therapy does not enter the lung, and direct therapeutic effect is limited to the upper airway; consequently this pulmonary effect must either be through a neural mechanism or, more likely, by modification of the generalised inflammatory cytokine response. Similar studies have shown improvements in lung function parameters from nasal therapy.<sup>24,25</sup>

## AR and asthma

Inadequately controlled AR in asthmatic patients can contribute towards increased asthma exacerbations and poorer symptom control, which may increase medical resource use. 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

Correspondence: Prof. R Green, PO Box 67, Pretoria 0001.  
E-mail robingreen@up.ac.za

inhaled fluticasone, were assessed.<sup>26</sup> A post hoc resource use analysis of a 52-week, double-blind multicentre clinical trial (IMPACT: IMProving Asthma Control Trial) including 1 490 adults with chronic asthma, aged 15-72 years, with FEV<sub>1</sub> 50-90% of predicted and 12% increase in FEV<sub>1</sub> after salbutamol administration, treated with either montelukast 10 mg daily or salmeterol 50 mg twice daily in addition to fluticasone 200 mg, was undertaken. Asthma-related medical resource use included medical visits (defined as either an unscheduled visit (to a general practitioner, a specialist or a nonmedical provider) or a specialist visit), emergency room visits and hospitalisations during follow-up. Asthma attacks were defined as the worsening of asthma requiring unscheduled visit, emergency visit, hospitalisation or oral/intravenous/intramuscular corticosteroids. A self-reported history of concomitant AR was identified in 60% of the patients (N = 5 893). Univariate analysis suggests that significantly more patients with concomitant AR experienced emergency room visits (3.6% vs 1.7%, P50.029) and asthma attacks (21.3% vs 17.1%, P50.046). 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) 52.35, 95% confidence interval (CI) 51.12-4.80) and asthma attack (OR 51.35, 95% CI 51.03-1.77). Patients with asthma alone compared with patients with both conditions did not differ in terms of unscheduled or specialist visits and hospitalisations. 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.

The studies listed confirm suspicions held by doctors for many years, that upper and lower airway diseases are linked by inflammation, and this link between chronic rhinitis and asthma should be sought in patients presenting with one disease and certainly in patients with difficult asthma. Uncontrolled AR can lead to worsening of coexisting asthma. Prompt and effective treatment of nasal disease with an anti-inflammatory therapy can have a marked beneficial effect. Appropriate therapy of one or both conditions may alter the natural course of the overall inflammatory airway disease, and would almost certainly impact on patients' quality of life as well as the treatment costs.

### Leukotriene receptor antagonist (LTRA) therapy

Recently there has been renewed interest in the value of the LTRAs in the systemic management of these two closely linked diseases. In a study of patients with seasonal AR in addition to asthma, there was statistically significant improvement in both asthma and AR symptom scores after 2 weeks of montelukast use (10 mg daily).<sup>27</sup> This was a randomised, multicentre study of patients (N = 831) with seasonal allergen sensitivity, active symptoms of seasonal AR, and active asthma. After a 3-5-day single-blind placebo run-in period, patients received either montelukast 10 mg or placebo during a 2-week double-blind treatment period. The primary endpoint was the daily rhinitis symptoms score, defined as the average of the daytime nasal symptoms and the night-time symptoms scores, as self-rated by patients in daily diaries. Montelukast significantly reduced

the daily rhinitis symptoms score, compared with placebo: the difference in mean change from baseline between montelukast and placebo [with 95% CI; *p* value] was -0.12 [-0.18, -0.06; *p* ≤ 0.001]. Similar improvements were seen in the main components of the primary endpoint, the daytime nasal symptoms score (-0.14 [-0.21, -0.07; *p* ≤ 0.001]) and the night-time symptoms score (-0.10 [-0.16, -0.04; *p* ≤ 0.001]). Significant improvements were also seen in the Global Evaluations of Allergic Rhinitis by Patient (*p* ≤ 0.001) and by Physician (*p* ≤ 0.001), and rhinitis quality of life questionnaire (RQLQ) overall score (*p* = 0.002).

In order to determine the effectiveness of montelukast treatment in improving the control of asthma symptoms during the allergy season in patients with active asthma and seasonal aero-allergen sensitivity, adults with a history of chronic asthma who are also symptomatic during the allergy season and with skin test sensitivity to seasonal aero-allergens were enrolled in a randomised, parallel-group, multicentre study with a 1-week, single-blind, placebo run-in period followed by 3 weeks of double-blind treatment during the spring of 2004.<sup>28</sup> After the run-in period, eligible patients were randomly assigned to receive either oral montelukast (10 mg) or placebo. Daytime and night-time asthma symptom scores, beta<sub>2</sub>-agonist use, and morning and evening peak expiratory flow rates were recorded daily using an electronic diary. The primary endpoint was mean change from baseline to week 3 in the daytime asthma symptom score (0.54 vs 0.34; *p* = 0.002) and in beta<sub>2</sub>-agonist use, night-time symptoms, and peak expiratory flow rates. Few patients in the montelukast and placebo groups discontinued study participation because of asthma (1.3% and 3.0%, respectively). In patients with chronic asthma and seasonal aero-allergen sensitivity, montelukast treatment provided significant asthma control during the allergy season compared with placebo.

In a further study to evaluate the effect of asthma-controller initiation, either montelukast or inhaled corticosteroids (ICS), on asthma rescue/acute and anti-allergy medication costs among children with asthma and concomitant AR treated in usual practice, a retrospective cohort study (1 236 of the 3 217 children were matched to ICS and montelukast groups) was conducted.<sup>29</sup> Results are shown in Table I.

**Table I. Medco Study: Post-pre cost differences (US\$ per child/per month) of all studied medications (unadjusted)**

	Montelukast (N = 618)	ICS* (N = 618)	<i>p</i> value
Combined cost (\$)	5.55	12.08	0.0003
Rescue/acute medications:	0.94	3.82	0.0026
Short-acting β-agonists	1.79	3.34	0.008
Antibiotics	-0.65	-0.51	0.096
Oral corticosteroids	-0.20	-0.04	0.068
(Anti)allergy medications:	5.29	10.06	<0.001
Antihistamines	4.44	7.43	0.0037
Nasal steroids	0.85	2.63	<0.0001
Other respiratory medications <sup>†</sup>	0.68	-1.79	0.0458

\*Inhaled corticosteroids

<sup>†</sup>Xanthines, mast cell stabilisers, anti-leukotrienes other than montelukast

Among children with asthma and concomitant AR, initiating montelukast compared with initiating ICS in usual practice resulted in the following:

1. Lower costs of asthma 'rescue and acute' medications:
  - Significantly smaller increase in costs of SABA:
    - SABA costs greater by 87% in ICS group
  - Decrease in costs of antibiotics
  - Decrease in costs of oral corticosteroids
2. Lower costs of (anti)allergy medications:
  - Significantly smaller increase in costs of:
    - Prescription antihistamines: Costs greater by 67% in ICS group.
    - Nasal steroids: Costs greater by 209% in ICS group.
3. Cost of other respiratory medications decreased in both groups.

## Conclusion

Asthma and AR are common diseases and where they occur together there is now evidence that the use of montelukast will alleviate symptoms of both diseases. In addition this is a cost-saving exercise which makes this form of therapy truly cost-effective.

## Declaration of conflict of interest

Robin Green has received fees for lecturing on behalf of MSD. He received a travel bursary to attend the ATS Conference 2006 from MSD. He is a member of the MSD Advisory Board.

## REFERENCES

1. National Institutes of Health. *Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention. A Pocket Guide for Physicians and Nurses*. Publication No. 95-3659B. Bethesda, MD: National Institutes of Health, 1998.
2. Bousquet J, the ARIA Workshop Group. Allergic rhinitis and its impact on asthma: the ARIA Workshop report. *J Allergy Clin Immunol* 2001; **108**: suppl, S147-S334.
3. Pedersen PA, Weeke ER. Asthma and allergic rhinitis in the same patients. *Allergy* 1983; **38**: 25-29.
4. Spector SL. Overview of comorbid associations of allergic rhinitis. *J Allergy Clin Immunol* 1997; **99**: S773-S780.
5. Meltzer EO. Treating allergic rhinitis: Overview and update. *Am J Asthma Allergy Pediatr* 1992; **6**: 13-17.
6. Evans RM, Mullally DI, Wilson RW, et al. National trends in the morbidity and mortality of asthma in the US: prevalence, hospitalization and death from asthma over two decades, 1965 - 1984. *Chest* 1987; **91**: 65S-74S.
7. Luyt DK, Green RJ, Davis G, et al. Allergic rhinitis in South Africa – diagnosis and management. *S Afr Med J* 1996; **86** (part 2): 1313-1328.
8. Vondra V, Reisova M, Petrik P, Skulova Z, Maly M. Prevalence of bronchial asthma, chronic bronchitis and allergic rhinitis in a South Moravian district. *Vnitr Lek* 1994; **40**: 21-25.
9. Settipane GA. Allergic rhinitis – update. *Otolaryngol Head Neck Surg* 1986; **94**: 470.
10. ISAAC Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema. ISAAC. *Lancet* 1998; **351**: 1225-1232.
11. Burney PG, Chinn S, Rona RJ. Has the prevalence of asthma increased in 1986? *BMJ* 1990; **300**: 1306-1310.
12. Burr ML, Butland B, King S, Vaughan-Williams E. Changes in asthma prevalence: two surveys 15 years apart. *Arch Dis Child* 1989; **64**: 1452-1456.
13. Ninan TK, Russell G. Respiratory symptoms and atopy in Aberdeen school children: evidence from two surveys 25 years apart. *BMJ* 1992; **304**: 873-875.
14. Robertson CF, Heycock E, Bishop J, Nolan T, Olinsky A, Phelan PD. Prevalence of asthma in Melbourne school children: changes over 26 years. *BMJ* 1991; **302**: 1116-1118.
15. Shaw RA, Crane J, O'Donnell TV, Porteous LE, Cleman ED. Increasing asthma in a rural New Zealand adolescent population: 1975-1989. *Arch Dis Child* 1990; **65**: 1319-1323.
16. Bardin PG, Van Heerden BB, Joubert JR. Absence of pulmonary aspiration of sinus contents in patients with asthma and sinusitis. *J Allergy Clin Immunol* 1990; **86**: 82-88.
17. Griffin MP, McFadden ER, Ingram RH. Airway cooling in asthmatic and non-asthmatic subjects during nasal and oral breathing. *J Allergy Clin Immunol* 1982; **69**: 354-359.
18. Corren J. Allergic rhinitis and asthma: How important is the link? *J Allergy Clin Immunol* 1997; **99**: S781-S786.
19. Yssel H, Abbal C, Pene J, et al. The role of IgE in asthma. *Clin Exp Allergy* 1998; **5**: 104-109.
20. Kay AB. Allergy and allergic diseases. First of two parts. *N Engl J Med* 2001; **344**: 33-37.
21. Gaga M, Lambrou P, Papageorgiou N, et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. *Clin Exp Allergy* 2000; **20**: 663-669.
22. Braunstahl G-J, Kleinjan A, Overbeek SE, et al. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000; **61**: 2051-2057.
23. Welsh PW, Stricker WE, Chu C-P, et al. Efficacy of beclomethasone nasal solution, flunisolide and cromolyn in relieving symptoms of ragweed allergy. *Mayo Clin Proc* 1987; **62**: 125-134.
24. Henriksen JW, Wenzel A. Effect of an intra-nasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing and asthma. *Am Rev Respir Dis* 1984; **130**: 1014-1018.
25. Watson WTA, Becker AB, Simon FER. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993; **91**: 97-101.
26. Bousquet J, Gaugrisw S, Sazonov Kocevarz V, et al. Increased risk of asthma attacks and emergency visits among asthma patients with allergic rhinitis: a subgroup analysis of the improving asthma control trial. *Clin Exp Allergy* 2005; **35**: 723-727.
27. Philip G, Nayak AS, Berger WE, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin* 2004; **20**: 1549-1558.
28. Busse WW, Casale TB, Dykewicz MS, et al. Efficacy of montelukast during the allergy season in patients with chronic asthma and seasonal aeroallergen sensitivity. *Ann Allergy Asthma Immunol* 2006; **96**: 60-68.
29. Luskin A, Bukstein D, Sazonov Kocevar V, Harris H, Yin DD. Cost of asthma rescue and anti-allergy medications among asthmatic children with prior anti-allergy prescriptions initiating asthma controller therapy. *J Allergy Clin Immunol* 2004; **113** (Suppl 2): S338.