

PHARMACOTHERAPY

Effects of a Short Course of Pranlukast Combined with Systemic Corticosteroid on Acute Asthma Exacerbation Induced by Upper Respiratory Tract Infection

HIROTO MATSUSE, M.D., PH.D.,^{1,*} SUSUMU FUKAHORI, M.D., PH.D.,² TOMOKO TSUCHIDA, M.D., PH.D.,¹
TETSUYA KAWANO, M.D., PH.D.,¹ SHINYA TOMARI, M.D., PH.D.,³ NOBUKO MATSUO, M.D., PH.D.,⁴
TOMOYA NISHINO, M.D., PH.D.,¹ CHIZU FUKUSHIMA, M.D., PH.D.,¹ AND SHIGERU KOHNO, M.D., PH.D.¹

¹Second Department of Internal Medicine, University School of Medicine, Nagasaki, Japan.

²Department of Internal Medicine, City General Hospital, Sasebo, Japan.

³Department of Internal Medicine, Health Insurance General Hospital, Isahaya, Japan.

⁴Department of Internal Medicine, Municipal Medical Center, Nagasaki, Japan.

Background. Upper respiratory tract infections (URIs) represent the most frequent cause of acute asthma exacerbation. Systemic corticosteroid (CS) is presently recommended for URI-induced asthma exacerbation, although it might inhibit cellular immunity against respiratory virus infection. **Objectives.** To determine the effects of adding a short course (2 weeks) of a leukotriene receptor antagonist (LTRA) to systemic CS on URI-induced acute asthma exacerbation. **Methods.** Twenty-three adult asthmatics (mean age, 42.8 ± 9.8 y; Male:Female, 10:13) with URI-induced acute asthma exacerbation confirmed by a questionnaire and physical findings were randomly assigned to receive either oral prednisolone (PSL) alone or oral PSL plus the LTRA pranlukast (PRL) for 2 weeks (PSL + PRL). The cumulative doses of PSL and the amount of time required to clear asthma-related symptoms were determined. Levels of respiratory syncytial virus (RSV) RNA and influenza viral (IV) antigen in nasopharyngeal swabs were also determined. **Results.** Adding PRL significantly reduced the cumulative dose of PSL and tended to reduce the time required to clear asthma-related symptoms. Either RSV or IV was detected in about one-third of the patients. **Conclusion.** The combination of an LTRA and CS might be more useful than CS alone for treating URI-induced acute exacerbation of asthma and reducing the cumulative CS dose.

Keywords bronchial asthma, corticosteroid, leukotriene receptor antagonist, respiratory syncytial virus, upper respiratory tract infection

INTRODUCTION

Asthma is one of the most prevalent diseases in the world and it has a large socioeconomic impact. The primary objective of therapy for asthma includes not only preventing limitations to routine activities but also reducing the risk of death along with the economic impact from hospitalization and being absent from work. To date, inhaled corticosteroids (ICS) represent the most effective treatment for asthma and they can reduce mortality due to asthma by preventing acute exacerbation. Global asthma guidelines recommend systemic corticosteroid (CS) and short-acting β_2 agonists (SABAs) as soon as acute exacerbation occurs (1). Viral respiratory tract infections represent the most common trigger of acute exacerbation of asthma in both children and adults (2, 3), and systemic CS might worsen viral infections by suppressing cellular immunity. Furthermore, airway obstruction associated with virus-induced acute exacerbation of asthma is resistant to SABA (4). Thus, other medications should be added to systemic CS and SABA to treat virus-induced acute asthma exacerbation.

Although the precise underlying mechanism of virus-induced acute exacerbation of asthma remains unknown,

many molecular factors and cells are critically involved (5). Among involving factors, cysteinyl leukotrienes (cysLTs) have received considerable focus because levels increase in the airways of asthmatics during virus-induced acute exacerbation (6–8), and specific cysLT receptor antagonists (LTRAs) are routinely available in clinics. Moreover, systemic CS cannot inhibit cysLT production in asthmatics (9). Thus, as respiratory viral infections increase the amounts of cysLTs in the airways and CS does not reduce cysLT production, we postulated that LTRA combined with CS might be useful for treating virus-induced asthma exacerbation. This study compares the effects of short-term LTRA plus systemic CS on upper respiratory tract infection (URI)-induced asthma exacerbation with those of CS alone. We defined clinical URI based on symptoms and determined the presence of respiratory syncytial virus (RSV) and influenza virus (IV) in respiratory secretions.

MATERIALS AND METHODS

Subjects

This study received ethical approval from the special committee of Nagasaki University (project registration number 08090566) to proceed between September 2008 and March 2009, and each patient provided written informed consent to participate. Twenty-three (male:female, 10:13; mean age,

*Corresponding author: Hiroto Matsuse, M.D., PH.D., Second Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan; Tel: +81958197273; Fax: +81958497285; E-mail: hmatsuse@nagasaki-u.ac.jp

42.8 $\pm$ 9.8 y) patients with acute exacerbation of asthma participated in a 4-week, randomized, prospective, multicenter trial at outpatient clinics at four institutions in Nagasaki Prefecture, Japan. Eligible individuals were adults with asthma diagnosed according to the GINA guidelines (1) who had received a daily fixed dose of ICS for at least 1 year before the study. Atopy was defined by a positive skin prick test using 10 common aeroallergens and/or IgE radioallergosorbent test (RAST). We defined clinical URI-induced acute asthma exacerbation as described in (3). We defined URI based on having at least two of the following symptoms: runny nose, stuffy nose, sneezing, sore throat, hoarseness, red or watery eyes, face ache or earache, feeling unwell, muscle aches, chills, cough, painful swollen neck glands, or increased use of handkerchiefs. Asthma exacerbation was defined as an increase in one or more of wheeze, chest tightness, and breathlessness or wheeze during clinical examinations. URI-induced acute asthma exacerbation was defined as having symptoms of both URI and asthma exacerbation. All participants were considered to have URI-induced acute exacerbation of asthma if they attended a hospital within 48 hours of onset. Exclusion criteria comprised being regularly administered with oral CS, LTRA administration within 1 year before entry, pathogenic bacteria, fungi, or acid-fast bacilli in expectorated sputum, pulmonary infiltration suggesting pneumonia, or requiring hospitalization.

Study Design

After obtaining a clinical history regarding URI-induced acute asthma exacerbation, confirming wheezing by a physical examination, and completing a questionnaire, all patients were randomly assigned to receive either oral prednisolone (PSL) alone or oral PSL plus LTRA pranlukast (PRL; 225 mg b.i.d.; ONON®, ONO Pharmaceutical Co. Ltd., Osaka, Japan) for 2 weeks. During this period, patients recorded their symptoms and the number of puffs of SABA. All participants had to take a stable dose of ICS and patients who used long-acting β_2 agonists (LABA) before the study were required to use similar doses of these drugs throughout the study period. Other asthma medications such as xanthines and inhaled anticholinergics were prohibited during the study period. As a significant number of patients could not record peak expiratory flow (PEF) within a few days after the first visit due to instability, this study does not include PEF findings. All the patients received oral PSL (30 mg/day) during the first 4 days. Thereafter, each attending physician decided the PSL dose on days 4, 7, 14, 21, and 28 after the first visit based on the following criteria. The PSL dose was reduced by 10 mg when at least two among rescue SABA use and chest auscultation, and symptoms were improved compared with the previous assessment. The PSL dose was maintained when one or none rescue SABA use and chest auscultation, and symptoms were improved compared with the previous visit. The PSL was stopped when patients returned to baseline status before exacerbation. Peripheral blood and nasopharyngeal aspirates (NPAs) were collected at the first visit and on day 28. The primary

and secondary efficacy endpoints were the cumulative doses of PSL and elapsed time from the first visit to clear all asthma-related symptoms, respectively. Adverse effects associated with treatment were also monitored throughout the study period.

Diagnosis of RSV and IV Infections

We performed reverse transcription polymerase chain reaction (RT-PCR) to amplify RSV RNA and detected IV antigen from NPAs. In brief, total RNA was isolated from NPA using TRIzol® (Life Technologies Inc., Rockville, MD, USA) when the patients were first examined. Complementary DNA was synthesized using a SuperScript® One-Step RT-PCR system with Platinum®Taq DNA Polymerase (Invitrogen Life Technologies Inc., Carlsbad, CA, USA) and amplified using 200 ng of cDNA, with primers complementary to the sequence of RSV N protein mRNA (sense: 5-GCG ATG TCT AGG TTA GGA AGA A-3, antisense: 5-GCT ATG TCC TTG GGT AGT AAG CCT-3). The IV antigen was determined using an immunochromatographic assay (RapidTest® Flu II, Sekisui Medical Co. Ltd., Tokyo, Japan). To exclude infection with atypical pathogens, acute and convalescent serum samples were tested for antibodies to *Mycoplasma pneumoniae* and *Chlamydomphila pneumoniae* (SRL Co., Tokyo, Japan). A fourfold rise in antibody was taken as indicating infection.

Statistics

The intention-to-treat population was defined as randomized patients. The per-protocol population was defined as patients with confirmed assessments available by the end of therapy. Safety was analyzed in the intention-to-treat population. Results are expressed as means $\pm$ standard deviation (SD). Differences between groups were examined for statistical significance using Mann-Whitney *U* test and the χ^2 test. *P*-value < .05 denoted the presence of a statistically significant difference.

RESULTS

Enrollment and Characteristics of the Patients at Baseline

A total of 10 and 13 patients were assigned to the PSL and PSL + PRL groups, respectively, comprised the intention-to-treat population. One patient in the PSL group did not record symptoms by day 4, when symptoms and chest wheezes persisted. This patient did not attend the hospital again. One patient in the PSL group and two in the PSL + PRL group never returned to the hospital after initial randomization. Thus, these four patients were not evaluated at the primary and secondary end points, but were recruited for the safety analysis since we could contact them by telephone. Asthma-related symptoms disappeared and PSL was terminated by day 28 in the remaining 19 patients (PSL, *n* = 8; PSL + PRL, *n* = 11). These 19 patients comprised the per-protocol population. Table 1 summarizes the baseline characteristics of the patients in the intention-to-treat population. Baseline demographic

TABLE 1.—Characteristics of the intention-to-treat population.

Characteristics	PSL	PSL + PRL
N	10	13
Age* (y)	48.2 (12.9)	41.9 (11.7)
Gender, Male (Female)	5 (5)	5 (8)
Atopy (%)	40.0	38.5
Disease duration* (y)	23 (5.4)	28 (6.7)
Maintenance ICS FP equivalent* (µg/day)	375.0 (195.6)	368.8 (164.2)
LABA use (%)	20.0	30.8
Time from onset of symptoms to first assessment* (days)	4.1 (2.1)	3.7 (1.9)

Abbreviations: ICS, inhaled corticosteroids; FP, fluticasone propionate; LABA, long-acting β_2 agonists; PSL, prednisolone; PSL + PRL, PSL plus the pranlukast.

Note: *Values are shown as means (SD).

characteristics closely matched and no parameters significantly differed between the PSL and PSL + PRL groups. Demographic characteristics also did not notably differ between the intention-to-treat and per-protocol populations (data not shown).

Duration and Cumulative Doses of PSL Required to Eliminate Asthma-Related Symptoms

Figure 1 shows that the durations and cumulative doses of PSL were significantly more decreased in the PSL + PRL

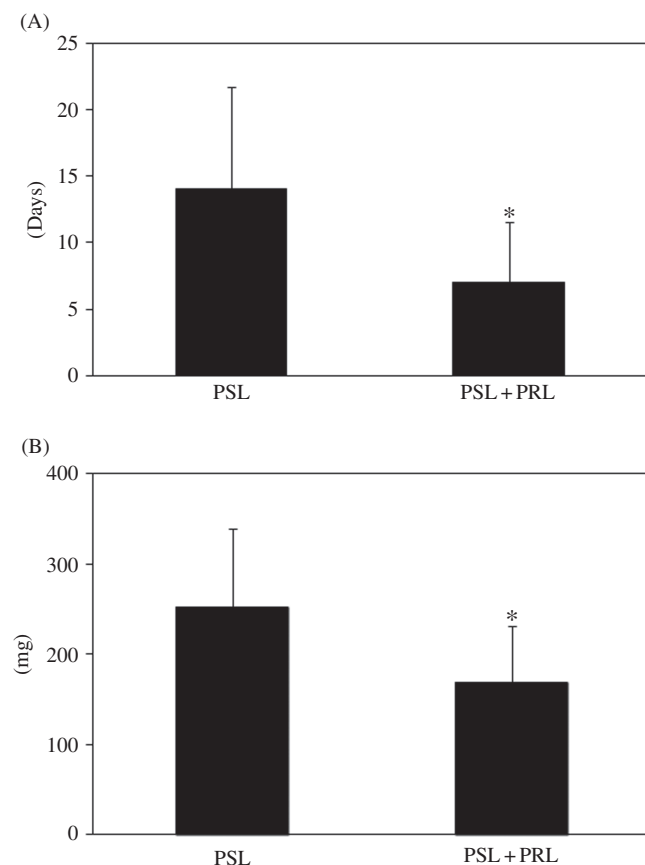


FIGURE 1.—Time using PSL (A) and cumulative doses of PSL (B) to eliminate asthma-related symptoms in the per-protocol population.

Bars represent means $\pm$ SD of PSL ($n = 8$) and PSL + PRL ($n = 11$) groups; * $p < .05$.

group than in the PSL group (Figure 1) (7.3 ± 4.5 vs. 14.0 ± 7.7 days, $p = .03$ and 169.1 ± 62.8 vs. 253.8 ± 86.0 mg, $p = .03$, respectively). In contrast, cumulative doses of SABA were similar between the PSL and PSL + PRL groups (14.0 ± 3.2 vs. 11.5 ± 3.4 puffs, $p > .1$).

Time Required to Eliminate Asthma-Related Symptoms

Adding PRL tended to shorten exacerbations compared with PSL alone, but the difference did not reach statistical significance (Figure 2) (PSL vs. PSL + PRL: 16.4 ± 6.7 vs. 10.7 ± 5.9 days, $p = .06$).

Virus Detection

Either RSV or IV was detected in six (31.6%) patients. Three patients (PSL, $n = 2$; PSL + PRL, $n = 1$) were positive for RSV according to RT-PCR. The IV antigen was detected in three patients (PSL, $n = 1$; PSL + PRL, $n = 2$). Asthma-related symptoms disappeared from the three patients infected with RSV at days 27, 21, and 10 and from the three infected with IV infected on days 14, 7, and 6. Significant differences in serum antibodies titers of *Mycoplasma pneumoniae* and *Chlamydomphila pneumoniae* were not identified between acute and convalescent phases, suggesting that atypical pathogens were absent.

Safety

Safety was evaluated in the intention-to-treat population. Among 23 patients, four patients (17.4%) experienced at least one adverse event during the study period. One patient in the PSL group developed headache, epigastralgia, and insomnia and another developed epigastralgia. One patient in the PSL + PRL group developed epigastralgia and another described having diarrhea. Severe infectious diseases did not occur. All adverse events were clinically mild and had subsided by the end of the study. Thus, the incidence of adverse events did not significantly differ between the two groups.

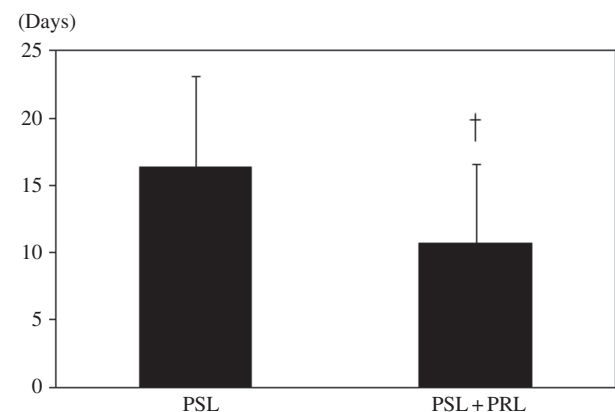


FIGURE 2.—Time required to clear asthma-related symptoms in the per-protocol population.

Bars represent means $\pm$ SD of PSL ($n = 8$) and PSL + PRL ($n = 11$) groups; † $p < .1$.

DISCUSSION

Although LTRAs reduce asthma symptoms or exacerbations in children with colds (10–12), few studies have evaluated their effects on asthma in adults. One study found that LTRAs do not improve symptoms of mild asthma caused by experimental rhinovirus infection in adults (13). Thus, the role of LTRA in acute asthma exacerbation in adults caused by naturally occurring viral respiratory infection remains unknown. This study showed that combining the LTRA PRL with systemic CS for 2 weeks slightly shortened the duration of asthma-related symptoms and significantly reduced cumulative CS doses in adult patients who developed acute asthma exacerbation after URI.

Viral respiratory tract infections often exacerbate asthma, which can be significantly reduced by the regular administration of inhaled CS (14). In contrast, systemic CS significantly increased viral loads in healthy individuals after experimental RV infection (15) and reactivated chronic metapneumoviral infection in a murine model (16). As systemic CSs are recommended for acute exacerbation of asthma even by respiratory viral infection (1), the notion that they might suppress immunity against respiratory virus should be a concern. Thus, an additive therapy that would increase the beneficial effects and decrease the toxicity of systemic CS would be useful. From this viewpoint, *cysLTs* are appealing because their concentrations increase during respiratory virus-induced asthma (6–8) and CSs cannot inhibit their production (9). In fact, the LTRA montelukast prevents respiratory virus-induced acute asthma in children (10–12). We also reported that PRL inhibits RSV-induced allergic airway inflammation in a murine model of allergic asthma (17). Currently, LTRAs are used as controlling, anti-inflammatory medication. Notably, LTRAs have bronchodilator as well as anti-inflammatory effects and a rapid onset of action. Thus, LTRAs are potentially useful to relieve acute asthma (18, 19).

RSV is a representative lower respiratory tract pathogen in children that has recently become recognized as an adult pathogen (20–22). One study *in vitro* has demonstrated that RSV enhances 5-lipoxygenase expression in the human airway epithelium and thus increases LT production (23), which potentially exacerbates allergic airway inflammation. Furthermore, RSV among respiratory viruses causes acute asthma exacerbation more frequently than IV (24). Although we identified a few causative viruses, this study found that RSV actually causes acute asthma exacerbation in adults. Although the study cohort was too small to be statistically meaningful, the results suggested that acutely exacerbated asthma takes longer to improve when caused by RSV rather than by IV.

Besides LTRA, LABA also has antiviral as well as bronchodilator effects (25). Probably due to the small number of patients ($n = 6$), the use of LABA before entry did not significantly affect the present results (data not shown). A future study should also examine the effects of adding LABA in URI-induced acute exacerbation of asthma.

This study has several critical limitations. First, we defined URI based on clinical symptoms, and only RSV

and IV were detected. Although bacterial and other infections were excluded by physical and laboratory examinations, nonviral infections might have been included. Second, asthma-related symptoms were also evaluated based on clinical symptoms and objective measures of pulmonary functions such as PEF or FEV1.0 were missing because the patients had unstable asthma. Finally, this was not a placebo-controlled study and the cohort was small.

CONCLUSIONS

The present findings suggest a new therapeutic modality for LTRAs as a means of controlling chronic asthma. As in intermittent childhood asthma (14), LTRAs could be combined with CS only to relieve acute asthma induced by URI. Placebo-controlled, large-scale studies including many types of representative respiratory viruses are warranted.

DECLARATION OF INTEREST

None of the authors have conflicts of interest to claim other than a grant from ONO Pharmaceutical Co. Ltd. to conduct the study.

REFERENCES

- GINA Report, Global Strategy for Asthma Management and Prevention. National Institutes of Health, National Heart, Lung, and Blood Institute; Updated 2011.
- Lemanske Jr RF. Viruses and asthma: inception, exacerbation, and possible prevention. *J Pediatr* 2003; 142:S3–S7.
- Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *Br Med J* 1993; 307:982–986.
- Moore PE, Cunningham G, Calder MM, DeMatteo AD, Jr., Peebles ME, Summar ML, Peebles RS Jr. Respiratory syncytial virus infection reduces beta2-adrenergic responses in human airway smooth muscle. *Am J Respir Cell Mol Biol* 2006; 35:559–564.
- Tauro S, Su YC, Thomas S, Schwarze J, Matthaei KI, Townsend D, Simson L, Tripp RA, Mahalingam S. Molecular and cellular mechanisms in the viral exacerbation of asthma. *Microbes Infect* 2008; 10:1014–1023.
- Dimova-Yaneva D, Russell D, Main M, Brooker RJ, Helms PJ. Eosinophil activation and cysteinyl leukotriene production in infants with respiratory syncytial virus bronchiolitis. *Clin Exp Allergy* 2004; 34:555–558.
- Gentile DA, Fireman P, Skoner DP. Elevations of local leukotriene C4 levels during viral upper respiratory tract infections. *Ann Allergy Asthma Immunol* 2003; 91:270–274.
- Matsuse H, Kondo Y, Saeki S, Nakata H, Fukushima C, Mizuta Y, Kohno S. Naturally occurring parainfluenza virus 3 infection in adults induces mild exacerbation of asthma associated with increased sputum concentrations of cysteinyl leukotrienes. *Int Arch Allergy Immunol* 2005; 138:267–272.
- Dworski R, Fitzgerald GA, Oates JA, Sheller JR. Effect of oral prednisone on airway inflammatory mediators in atopic asthma. *Am J Respir Crit Care Med* 1994; 149:953–959.
- Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, Tozzi CA, Polos P. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005; 171:315–322.
- Johnston NW, Mandhane PJ, Dai J, Duncan JM, Greene JM, Lambert K, Sears MR. Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics* 2007; 120:e702–e712.

12. Robertson CF, Price D, Henry R, Mellis C, Glasgow N, Fitzgerald D, Lee AJ, Turner J, Sant M. Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med* 2007; 175:323–329.
13. Kloepper KM, DeMore JP, Vrtis RF, Swenson CA, Gaworski KL, Bork JA, Evans MD, Gern JE. Effects of montelukast in subjects with asthma after experimental inoculation with Rhinovirus-16. *Ann Allergy Asthma Immunol* 2011; 106:252–257.
14. Venarske DL, Busse WW, Griffin MR, Gebretsadik T, Shintani AK, Minton PA, Peebles RS, Hamilton R, Weisshaar E, Vrtis R, Higgins SB, Hartert TV. The relationship of rhinovirus-associated asthma hospitalizations with inhaled corticosteroids and smoking. *J Infect Dis* 2006; 193:1536–1543.
15. Gustafson LM, Proud D, Hendley JO, Hayden FG, Gwaltney Jr JM. Oral prednisone therapy in experimental rhinovirus infections. *J Allergy Clin Immunol* 1996; 97:1009–1014.
16. Liu Y, Haas DL, Poore S, Isakovic S, Gahan M, Mahalingam S, Fu ZF, Tripp RA. Human metapneumovirus establishes persistent infection in the lungs of mice and is reactivated by glucocorticoid treatment. *J Virol* 2009; 83:6837–6848.
17. Matsuse H, Kondo Y, Machida I, Kawano T, Saeki S, Tomari S, Obase Y, Fukushima C, Mizuta Y, Kohno S. Effects of anti-inflammatory therapies for recurrent and low-grade respiratory syncytial virus infections in a murine model of asthma. *Ann Allergy Asthma Immunol* 2006; 97:55–60.
18. Ramsay CF, Pearson D, Mildenhall S, Wilson AM. Oral montelukast in acute asthma exacerbations: a randomised, double-blind, placebo-controlled trial. *Thorax* 2011; 66:7–11.
19. Silverman RA, Nowak RM, Korenblat PE, Skobeloff E, Chen Y, Bonuccelli CM, Miller CJ, Simonson SG. Zafirlukast treatment for acute asthma: evaluation in a randomized, double-blind, multicenter trial. *Chest* 2004; 126:1480–1489.
20. Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. *Clin Microbiol Rev* 2000; 13:371–384.
21. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh E. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med* 2005; 352:1749–1759.
22. Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med* 2001; 344:1917–1928.
23. Behera AK, Kumar M, Matsuse H, Lockey RF, Mohapatra SS. Respiratory syncytial virus induces the expression of 5-lipoxygenase and endothelin-1 in bronchial epithelial cells. *Biochem Biophys Res Commun* 1998; 251:704–709.
24. Fleming DM, Pannell RS, Elliot AJ, Cross KW. Respiratory illness associated with influenza and respiratory syncytial virus infection. *Arch Dis Child* 2005; 90:741–746.
25. Singam R, Jena PK, Behera S, Hellermann GR, Lockey RF, Ledford D, Mohapatra SS. Combined fluticasone propionate and salmeterol reduces RSV infection more effectively than either of them alone in allergen-sensitized mice. *Virol J* 2006; 3:32.

Copyright of Journal of Asthma is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.