

Effects of Add-On Therapy with NDC-052, an Extract from *Magnoliae Flos*, in Adult Asthmatic Patients Receiving Inhaled Corticosteroids

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Background/Aims: There is a need for new anti-asthmatic medications with fewer side effects. NDC-052, an extract of the medicinal herb *Magnoliae flos*, which has a long history of clinical use, was recently found to have anti-inflammatory effects. Herein, we evaluated the effects of NDC-052 as an add-on therapy in patients with mild to moderate asthma using inhaled corticosteroids (ICS).

Methods: In a non-comparative, multi-center trial, 148 patients taking ICS received NDC-052 for eight weeks. We evaluated their forced expiratory volume in one second (FEV₁), morning and evening peak expiratory flow rate (AM and PM PEF_R), AM/PM asthma symptom scores, visual analogue symptom (VAS) scores, night-time waking, frequency of short-acting β_2 -agonist usage, and adverse events.

Results: After eight weeks, both AM and PM PEF_Rs were significantly improved. Asthma symptom scores, VAS scores, the frequency of nights without awakening, and the frequency of β_2 -agonist use were also reduced. Most of the adverse drug reactions were mild and resolved spontaneously.

Conclusions: The addition of NDC-052 to ICS had a beneficial effect on asthma control in patients with mild to moderate asthma, with good tolerability and fewer side effects. Further studies are necessary to evaluate the effects of NDC-052 in patients with severe and/or refractory asthma.

Keywords: Asthma; Drugs; Chinese herbal; Magnolin; *Magnoliae*

INTRODUCTION

Asthma is a common chronic inflammatory disease of the airways that is responsible for significant morbidity,

mortality, and healthcare costs [1,2]. Airway inflammation is a key pathophysiologic feature of asthma, leading to airway obstruction, airway hyperresponsiveness (AHR), and even remodeling of the airway. Recent guidelines for

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asthma management have therefore emphasized a need for the control of airway inflammation using inhaled corticosteroids (ICS) [3,4]. Chronic use of high-dose ICS, however, may result in serious side effects, including adrenal suppression and reduction in growth velocity, especially in children [5-7]. In addition, adequate ICS and other controller medications cannot achieve asthma control in some patients. Consequently, there is a pressing need for new alternative and/or complementary drugs with fewer side effects.

Recently, a number of clinical and laboratory studies have investigated the anti-asthmatic effects of Chinese herbal products. Some of these herbal remedies have been shown to be effective and safe alternatives or complements to standard therapy for asthma and other allergic diseases [8]. *Magnoliae flos* (Chinese name, 辛夷, Xin-yi) has a long history of clinical use in Asian countries, and is used to treat ulceration of the nasal mucosa, allergic rhinitis, sinusitis, bronchial asthma, and other conditions [9]. NDC-052 (Han Kook Sin Yak Pharmaceutical Co. Ltd., Nonsan, Korea) is a purified extract of *M. fargesii* and was developed to enhance and control bioactive lignan content, including magnolin and epimagnolin A [10]. These bioactive lignans have been shown to inhibit various inflammatory mediators, such as platelet-activating factor (PAF), cytosolic phospholipase A2, hexosaminidase, lipoxygenase, the complement system, and production of leukotriene C4 [11,12]. A recent study demonstrated that epimagnolin decreased nitric oxide (NO) levels by modulating inducible nitric oxide synthase (iNOS) in human respiratory epithelial cells [13]. In addition, oral administration of 50 mg/kg NDC-052 for eight weeks reduced airway resistance in a guinea pig chronic asthma model (unpublished data). Taken together, these reports suggest that concentrated NDC-052 extract might have anti-inflammatory, as well as anti-asthmatic effects.

Prior to the present study, the Korea Food & Drug Administration approved NDC-052 for clinical trials, and a phase II pilot study of NDC-052 in patients with persistent mild asthma found that a dose of 600 mg/day was effective and safe. We have evaluated the effects of NDC-052 as an add-on therapy to ICS in patients with persistent mild to moderate asthma symptoms.

METHODS

Study design

This prospective, multi-center, non-comparative study was conducted in six university hospitals in Korea. After screening (visit 1), patients who voluntarily agreed to participate underwent a two-week 'run-in' period, during which they discontinued all asthma medications except ICS, which they had taken for at least four weeks. At the end of the run-in period (visit 2), we selected suitable subjects based on pulmonary function tests, symptom diaries, and laboratory data. At this point, 'well-controlled' asthma patients were excluded. 'Well-controlled' asthma was defined as an average of < 2 points on the asthma symptom score test, calculated as the sum of the following items (one point per item): no night-time awakening caused by asthma, no exacerbation of asthma symptoms, no usage of rescue medications, less than 20% peak expiratory flow rate (PEFR) variation, and no change in medications for the control of asthma symptoms, except for medications prescribed for one week. Patients who met the inclusion criteria were given NDC-052 (600 mg/day) for eight weeks. At subsequent four-week intervals (visits 3 and 4), we evaluated their pulmonary function, clinical and laboratory parameters, and adverse reactions.

This study was conducted in accordance with the Declaration of Helsinki and in compliance with Korean Good Clinical Practice and International Conference on Harmonization (ICH) Good Clinical Practice Guidelines. Each patient provided written informed consent before initiation of any study procedures. The study protocol and a copy of the informed consent document were reviewed and approved by the Institutional Review Board of each study center.

Subjects

We included study subjects aged 18-70 years with an at least three month history of asthma symptoms. Inclusion criteria at visit 1 included: 1) FEV1 \geq 60% of the predicted value; 2) FEV1 increased \geq 15% after the administration of either short-acting β 2-agonist or oral corticosteroid (20-40 mg/day) for 2-3 weeks; 3) FEV1 decreased \geq 20% in response to the methacholine bronchial provocation test, with a PC20 value of less than 25 mg/mL; and 4) mild to moderate persistent asthma symptoms, based on the 2006 Global Initiative for Asthma (GINA) diagnostic criteria.

Patients were excluded if they had any other pulmonary diseases, any severe co-morbidity, or had smoked more than 10 packs/yr and stopped smoking four weeks before screening. We also excluded women who were pregnant or breast-feeding.

Pulmonary function tests and clinical evaluations

FEV₁ was measured at every visit and daily AM/PM PEF was measured with a mini peak flow meter. The PEF was measured in the standing position immediately after waking in the morning and before going to bed in the evening. Patients were asked to measure PEF before taking medications, if possible, and were not asked to discontinue medications, including controllers, during the monitoring period. On each occasion, the best of at least three attempts was recorded. PEF variability was defined by the following equation and was averaged over the period between each visit: $(\text{high PEF} - \text{low PEF}) / \text{mean PEF of the day} \times 100$. We asked patients to assess symptom severity for two weeks before each visit, using a 100 mm visual analogue scale (VAS), ranging from no symptoms (0 mm) to the worst ever symptom (100 mm). This scale was used as a responsive outcome measurement and had been validated in previous clinical studies of patients with bronchial asthma [14,15]. Daytime asthma symptoms were scored as none (0), once for a short period of time (1), twice or more for short periods of time (2), all day without any major impact on normal daily activities (3), all day with an impact on normal daily activities (4), and symptoms so severe that it was impossible to conduct normal daily activities or work (5). Nocturnal asthma symptoms were scored as none (0), one awakening due to symptoms (1), two or more awakenings due to symptoms (2), and could not sleep at all because of symptoms (3). The frequency of nocturnal awakenings was defined as the frequency of days without night awakening due to asthma symptoms. The frequency of use for rescue medications was measured as the number of days that patients used these medications.

Safety evaluation

Safety data were obtained over eight weeks of treatment in all subjects. Causality of the event was assessed by the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria [16]. We graded severity as mild, moderate, or severe. Laboratory test results at each

visit were compared with data obtained at the time of screening.

Statistical analysis

Results are shown as mean \pm SD. The mean daytime and nocturnal asthma symptom scores were analyzed for the entire period between visits. All data on '0 week' were obtained from a two-week 'run-in' period. Paired *t* tests were used to evaluate changes between baseline and after eight weeks of administration of the study drug. A *p* value < 0.05 was considered statistically significant. All statistical tests were performed using SAS version 8.0 (SAS Institute, Cary, NC, USA). For safety analysis, all abnormal events were placed into tables and their frequencies were calculated.

RESULTS

Subject characteristics

Of the 179 patients screened, 148 were enrolled and received NDC-052. These 148 patients included 56 (37.84%) males and 92 (62.16%) females. Based on the GINA guidelines for severity, 113 subjects had mild persistent and 35 had moderate persistent asthma. Of the enrolled subjects, 101 (68.24%) were non-smokers, 11 (7.43%) were current smokers, and 36 (24.32%) were ex-smokers (Table 1).

Effects of add-on NDC-052 on pulmonary function

Treatment with add-on NDC-052 for eight weeks resulted in increases in mean AM and PM PEF from baseline, and a decrease in mean daily PEF variation. However, NDC-052 treatment did not result in a statistically significant improvement in FEV₁ (Table 2).

Effects of add-on NDC-052 on clinical parameters

We found that eight weeks of add-on NDC-25 resulted in significant improvements in both daytime and nocturnal symptom scores. In addition, add-on treatment reduced 100 mm VAS scores, as well as reduced the frequency of nighttime awakening and use of rescue medication after eight weeks (Table 3).

Safety evaluation

A total of 103 adverse events were reported by 52

Table 1. Baseline demographic and clinical characteristics of patients

Characteristics	No. (%)
Male/Female	56 (37.84)/92 (62.16)
Age, yr	45.30 ± 13.93
History of atopic disease	
Yes	23 (15.54)
No	125 (84.46)
Asthma duration	60.85 ± 85.89
< 6 mon	21 (14.19)
6 mon-1 yr	26 (17.57)
1-2 yr	20 (13.51)
2-3 yr	12 (8.11)
3-5 yr	21 (14.19)
5-10 yr	23 (15.54)
> 10 yr	25 (16.89)
Smoking status	
Non-smoker	101 (68.24)
Ex-smoker	36 (24.32)
Current smoker	11 (7.43)
Pack year	6.25 ± 2.81
Severity ^a	
Mild persistent	113 (76.35)
Moderate persistent	35 (23.65)

^aAccording to Global Initiative for Asthma (GINA) 2006 guidelines.

patients. Analysis of the causality between adverse events and NDC-052 showed that only one event (0.97%) was 'probable,' 28 events (27.18%) were 'possible,' and 74 (71.84%) were 'unlikely.' The 29 adverse events classified as 'probably' and 'possibly' associated with NDC-052 are shown in Table 4. Although five events (4.85%) were classified as severe, none were correlated with NDC-052. Laboratory findings at screening and eight weeks showed no significantly abnormal findings.

DISCUSSION

We have shown here that the addition of NDC-052, an extract of an herbal remedy, to ICS may play a role in improving asthma control in patients with mild to moderate asthma. NDC-052 improved the results of pulmonary function tests, such as AM and PM PEFr and PEFr variation, as well as clinical parameters, including asthma symptom VAS, daytime and nocturnal asthma symptoms, the frequency of night-time awakening, and the frequency of β_2 -agonist use. In addition, NDC-052 was well tolerated and no severe adverse reactions were observed.

Traditional Chinese medicine (TCM) is one of the oldest types of medical practice in the world, and has played an

Table 2. Changes in pulmonary function during treatment

Variables	0 wk	4 wk	8 wk	Δ 8-0 wk	<i>p</i> value ^a
FEV1, mL	2,586.7 ± 845.5	2,594.7 ± 856.5	2,582.45 ± 855.1	-5.6 ± 268.9	0.8140
AM PEFr, mL	364.8 ± 106.6	377.0 ± 113.0	378.9 ± 114.1	11.4 ± 42.0	0.0026
PM PEFr, mL	373.3 ± 105.0	381.6 ± 110.2	385.2 ± 111.8	10.6 ± 35.4	0.0009
PEFr variation, %	7.7 ± 8.1	6.5 ± 5.6	5.9 ± 7.8	-1.3 ± 7.4	0.0427

Δ , difference between 0 and 8 wk; FEV1, forced expiratory volume in one second; PEFr, peak expiratory flow rate.

^aPaired *t* tests on the difference between 0 and 8 wk.

Table 3. Changes in clinical measurements

Variables	0 wk	4 wks	8 wk	Δ 8-0 wk	<i>p</i> value ^a
Daytime symptom score	1.5 ± 1.1	1.2 ± 1.1	1.0 ± 1.1	-0.5 ± 1.1	< 0.0001
Nocturnal symptom score	0.6 ± 0.6	0.4 ± 0.6	0.5 ± 0.7	-0.1 ± 0.6	0.0343
100 mm VAS, mm	42.4 ± 19.7	33.9 ± 19.3	31.6 ± 22.1	-10.6 ± 19.7	< 0.0001
Frequency of night-time awakening	3.8 ± 2.8	4.6 ± 2.9	4.5 ± 3.0	0.7 ± 2.9	0.0070
β_2 -agonist use	7.5 ± 12.1	5.3 ± 10.9	4.8 ± 11.7	-2.4 ± 10.4	0.0102

Δ , difference between 0 and 8 wk; VAS, visual analogue scale.

^aPaired *t* tests on the difference between 0 and 8 wk.

Table 4. Adverse events

Variables	No. (%)
Dyspnea	1 (0.97)
Epigastric soreness	4 (3.88)
Indigestion	7 (6.80)
Nausea	4 (3.88)
Constipation	2 (1.94)
Vomiting	1 (0.97)
Abdominal pain	1 (0.97)
Dysphagia	1 (0.97)
Paresthesia	1 (0.97)
Migraine	1 (0.97)
Facial swelling	1 (0.97)
Pruritus	1 (0.97)
Urticaria	1 (0.97)
Rash	1 (0.97)
Skin exfoliation	1 (0.97)
Myalgia	1 (0.97)
Total	29 (100)

important role for centuries in preventing and treating diseases in China and other Asian countries. Recently, TCM has been tested for the treatment of allergic diseases, including asthma, allergic rhinitis, and food allergy. The anti-asthma herbal medicines being evaluated include MSSM-002, modified Mai Men Dong Tang, Ding Chuan Tang, and STA-1, with clinical trials suggesting that these TCM remedies are efficacious and safe alternatives or complements to standard Western asthma therapy [8,17,18].

In this context, NDC-052 extracted from *M. flos* using ethanol, is a well-known natural herbal remedy in East Asian countries, including Korea, China, and Japan. *M. flos* refers to the flower buds of *M. denudata* and other plants belonging to the same genus, including *M. fargesii* (also known as *M. biondii*), *M. denudata*, *M. liliflora*, *M. salicifolia*, and *M. kobus*. Extraction yields many compounds, including oils, lignan compounds, and sesquiterpenes [10,19,20]. Some of the compounds extracted from both *M. fargesii* and *M. denudata* were shown to be calcium antagonists, inhibiting the activity of PAF and serum complement, and reducing tumor necrosis factor-alpha (TNF-alpha) production [11,12,20-23]. Using an anaphylaxis model in mice, *M. flos* was shown to inhibit immediate-type allergic reactions by inhibiting mast cell

degranulation, both *in vivo* and *in vitro* [24]. Moreover, epimagnolin, a major lignin of NDC-052, was shown to inhibit the expression of iNOS and the production of NO via extracellular signal-regulated kinase (ERK) pathway in cytokine-stimulated human respiratory epithelial cells [13]. Thus, NDC-052 may have both anti-inflammatory and antioxidant effects, and the pathway by which NDC-052 reduces inflammation may differ from that of steroids. Therefore, NDC-052 may provide additional benefits to asthma patients using ICS.

We found that treatment with add-on NDC-052 did not noticeably increase FEV₁. Most of our subjects, however, had mild persistent asthma, with FEV₁ > 80% of the predicted value. Nevertheless, NDC-052 improved AM and PM PEF_R and other clinical indicators of asthma control, such as the need for β -agonist relief therapy and both day and night asthma symptom scores. In recent guidelines, these clinical outcomes were regarded as important characteristics for evaluating asthma control. Therefore, our data indicate that patients with close-to-normal FEV₁ levels may be symptomatic and require additional control of asthma symptoms. In addition, our results were similar to those of previous studies showing that addition of ICS to leukotriene receptor antagonists, currently used as alternatives to ICS in patients with mild persistent asthma, improved various measurements of asthma control, despite failing to cause a significant improvement in FEV₁ [25,26]. Pharmacologically, NDC-052 has anti-inflammatory, rather than bronchodilating, effects. Therefore, NDC-052 may not directly affect FEV₁ level. We did not measure inflammatory markers in these patients, suggesting the need for additional clinical studies involving measurements of inflammatory markers, such as induced sputum analysis or exhaled NO, to determine the mechanisms by which NDC-052 affects airway inflammation. Further clinical trials are necessary to determine if the addition of NDC-052 to ICS is effective in patients with more severe or refractory asthma, or if it can decrease the frequency of asthma exacerbation.

ICS has been shown to improve both asthma-related symptoms and pulmonary function in many patients, although a subset of patients required additional medications to achieve asthma control. Updated GINA guidelines suggest that symptoms can be improved by: 1) increasing the dose of ICS, 2) adding inhaled long-acting β_2 -agonists (LABA), or 3) adding other controller

medications, such as leukotriene modifiers and sustained-release theophylline. Since ICS has a plateau effect, such that increased doses are not matched by further increases in efficacy [27,28], the updated GINA recommends the addition of a controller, preferably LABA, rather than increasing the dose of ICS. LABA, however, does not have anti-inflammatory effects, raising concerns that it may enhance airway remodeling [29]. In addition, inhaled agents may fail to reach the small airways, i.e., the site of inflammation in asthma. Theophylline, a currently available oral controller, has a narrow therapeutic window and many side effects, limiting its utility as an add-on therapy in asthmatics suboptimally controlled with ICS. These findings indicate the need for novel alternative agents that can improve airway inflammation and asthma symptoms in patients who cannot be controlled by ICS alone.

However, the design of this study imposes some limitations on the interpretation of the results. First, the absence of a placebo group precluded assessment of any placebo effect on asthma symptoms; thus, improvements in outcome measures may have been influenced by the expectation of a benefit from treatment. Secondly, the increased compliance to ICS may have affected the results. However, we strongly suggested that participants use their ICS regularly during the whole study period, including run-in periods, and enrolled symptomatic patients despite regular ICS usage. Finally, eight weeks was a relatively short period to evaluate the long-term effects of therapeutic drugs on asthma control. Further clinical trials are necessary to address these issues.

In conclusion, we have shown that add-on NDC-052 was well tolerated and shows potential for improving asthma control in patients with persistent symptoms treated with ICS. Further clinical trials are needed to test the efficacy and safety of NDC-052 in patients with severe and/or refractory asthma.

Conflict of interest

This study was financially supported by Han Kook Sin Yak Pharmaceutical Co. Ltd., Nonsan, Korea.

REFERENCES

1. Barnes PJ, Jonsson B, Klim JB. The costs of asthma. *Eur Respir*

- J 1996;9:636-642.
2. Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59:469-478.
 3. National Institutes of Health, National Heart, Lung, and Blood Institute. National asthma education and prevention program: global strategy for asthma management and prevention. Global Initiative for Asthma report [Internet]. National Institutes of Health, National Heart, Lung, and Blood Institute, 2009 [cited 2011 Dec 20]. Available from <http://www.ginasthma.org>.
 4. Jang AS. Inhaled steroids in asthma therapy: an update. *Korean J Med* 2011;80:129-134.
 5. Visser MJ, van der Veer E, Postma DS, et al. Side-effects of fluticasone in asthmatic children: no effects after dose reduction. *Eur Respir J* 2004;24:420-425.
 6. Eid N, Morton R, Olds B, Clark P, Sheikh S, Looney S. Decreased morning serum cortisol levels in children with asthma treated with inhaled fluticasone propionate. *Pediatrics* 2002;109:217-221.
 7. Casale TB, Nelson HS, Stricker WE, Raff H, Newman KB. Suppression of hypothalamic-pituitary-adrenal axis activity with inhaled flunisolide and fluticasone propionate in adult asthma patients. *Ann Allergy Asthma Immunol* 2001;87:379-385.
 8. Li XM. Traditional Chinese herbal remedies for asthma and food allergy. *J Allergy Clin Immunol* 2007;120:25-31.
 9. Shen Y, Li CG, Zhou SF, Pang EC, Story DF, Xue CC. Chemistry and bioactivity of Flos Magnoliae, a Chinese herb for rhinitis and sinusitis. *Curr Med Chem* 2008;15:1616-1627.
 10. Chen CC, Huang YL, Chen HT, Chen YP, Hsu HY. On the Ca⁺⁺-antagonistic principles of the flower buds of *Magnolia fargesii*. *Planta Med* 1988;54:438-440.
 11. Jung KY, Kim DS, Oh SR, et al. Magnone A and B, novel anti-PAF tetrahydrofuran lignans from the flower buds of *Magnolia fargesii*. *J Nat Prod* 1998;61:808-811.
 12. Ahn KS, Jung KY, Kim JH, Oh SR, Lee HK. Inhibitory activity of lignin components from the flower buds of *Magnolia fargesii* on the expression of cell adhesion molecules. *Biol Pharm Bull* 2001;24:1085-1087.
 13. Baek JA, Lee YD, Lee CB, et al. Extracts of *Magnolia flos* inhibit inducible nitric oxide synthase via ERK in human respiratory epithelial cells. *Nitric Oxide* 2009;20:122-128.
 14. Brightling CE, Monterio W, Green RH, et al. Induced sputum and other outcome measures in chronic obstructive pulmonary disease: safety and repeatability. *Respir Med* 2001;95:999-1002.
 15. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. *Lancet* 1999;353:2213-2214.
 16. The Uppsala Monitoring Centre. The use of the WHO-UMC

- system for standardized case causality assessment [Internet]. Uppsala: The Uppsala Monitoring Centre, 2010 [cited 2011 Dec 20]. Available from: <http://who-umc.org/Graphics/24734.pdf>.
17. Bielory L, Lupoli K. Herbal interventions in asthma and allergy. *J Asthma* 1999;36:1-65.
 18. Li XM, Zhang TF, Sampson H, et al. The potential use of Chinese herbal medicines in treating allergic asthma. *Ann Allergy Asthma Immunol* 2004;93(2 Suppl 1):S35-S44.
 19. Iida T, Nakano M, Ito K. Hydroperoxysesquiterpene and lignan constituents of *Magnolia kobus*. *Phytochemistry* 1982;21:673-675.
 20. Pan JX, Hensens OD, Zink DL, Chang MN, Hwang SB. Lignans with platelet activating factor antagonist activity from *Magnolia biondii*. *Phytochemistry* 1987;26:1377-1379.
 21. Chae SH, Kim PS, Cho JY, et al. Isolation and identification of inhibitory compounds on TNF-alpha production from *Magnolia fargesii*. *Arch Pharm Res* 1998;21:67-69.
 22. Huang YL, Chen CC, Chen YP, Hsu HY, Kuo YH. (-)-Fargesol, a new lignan from the flowers buds of *Magnolia fargesii*. *Planta Med* 1990;56:237-238.
 23. Jung KY, Oh SR, Park SH, et al. Anti-complement activity of tiliroside from the flower buds of *Magnolia fargesii*. *Biol Pharm Bull* 1998;21:1077-1078.
 24. Kim HM, Yi JM, Lim KS. *Magnoliae flos* inhibits mast cell-dependent immediate-type allergic reactions. *Pharmacol Res* 1999;39:107-111.
 25. Price DB, Hernandez D, Magyar P, et al. Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;58:211-216.
 26. Vaquerizo MJ, Casan P, Castillo J, et al. Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax* 2003;58:204-210.
 27. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids: new developments. *Am J Respir Crit Care Med* 1998;157(3 Pt 2):S1-S53.
 28. Holt S, Suder A, Weatherall M, Cheng S, Shirtcliffe P, Beasley R. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001;323:253-256.
 29. Vanacker NJ, Palmans E, Pauwels RA, Kips JC. Effect of combining salmeterol and fluticasone on the progression of airway remodeling. *Am J Respir Crit Care Med* 2002;166:1128-1134.