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Recurrent Chronic Cough, Wheeze and their Control without Corticosteroids in 1 to 5 Year-old Children

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Abstract

Background: Recurrent persistent cough and wheezing often begin in early childhood; however, not all episodes of them are caused by asthma and/or an allergic reaction, they are exacerbated with several respiratory infections. Previous research suggests that the best treatment for toddlers and preschool-age children with persistent cough and/or wheeze is a difficult clinical challenge.

Methods: In this single-center prospective clinical trial, HIROSIMA study, we observed the clinical effect of oral leukotriene receptor antagonists (LTRAs: montelukast, pranlukast) with carbocystein and lysozyme chloride or ambroxol for over a year and assessed the relationship between infantile wheeze, chronic cough and rhinosinusitis. The patients were allocated to the intervention with their consent.

Results: Eighty patients, who were admitted to hospital for persistent cough and dyspnea episodes, completed the study for a year and showed significantly fewer asthma exacerbation episodes (clinical asthma scores/week; 16.1 ± 3.1 vs 7.9 ± 2.7) during the first eight weeks ($p < 0.01$), comparing to the use of LTRA alone (n = 40).; and the improvement of conditions persisted for over the twelve-month period. None of the subjects was admitted to the hospital for asthma exacerbation, and had any corticosteroid treatment during the study.

Conclusion: Our strategy for chronic cough including the management of allergic rhinitis and sinusitis significantly evaded persistent cough and wheeze of children age from 1 to 5 years, and reduced the frequency of recurrent otitis media.

Note: HIROSIMA study provides promising data for the control of persistent cough and wheeze of children age from 1 to 5 years without the use of corticosteroids for over a year with a good adherence to the treatment.

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Abbreviations

LT: Leukotriene, LTRA: Leukotriene Receptor Antagonist, ICS: Inhaled Corticosteroid, IL-8: Interleukin 8, C-ACT: Childhood Asthma Control Test

Introduction

The treatment and diagnosis of asthma in children <5 years old presents a particularly hard problem with important implications [1,2]. On the one hand, asthma at these ages is frequently overlooked and sometimes undertreated [2,3]. Wheezy patients often become in remission, however, the lung function in children with persistent wheeze becomes reduced by age 6 in several cases [1-3]. In a substantial minority of infants, wheezing episodes are related to a predisposition to asthma [1]. Therefore, trying to find the best treatment for a toddler or preschooler with chronic cough and/or wheeze is a troublesome clinical challenge [4,5].

The recent international guidelines recommend the use of low-dose inhaled corticosteroids (ICSs) as the preferred controller therapy, considering from the side of cost-effectiveness. Most epidemiologic studies have suggested that there are several different asthma phenotypes [6]. Three representative phenotypes are transient early wheezing (wheezing up to age 3 but not after), non-atopic wheezing of the toddler and early school years, and IgE-mediated wheezing/ a typical kind of pediatric asthma [6]. The treatment of children with intermittent, viral-induced wheezing or those with low/intermediate probability of asthma remains controversial [4,7,8]. Primary use of inhaled corticosteroids was not able to modify the subsequent development of asthma in all children [9]. Corticosteroid therapy cannot change the development of asthma symptoms or lung function during young childhood and it is also possible that some non-atopic wheezing can develop into asthma despite corticoid use [10]. Additionally, inhaled corticosteroid introduces growth disturbances in young children and that persist into adulthood [11]. So, effective and well-tolerated preventive therapy without corticosteroids appears to be the desirable for very young children.

Viral infections account for up to 70-80% of childhood asthma exacerbations [12,13]. Evidence suggests that leukotrienes play a key role in viral-induced respiratory illness [14,15]. The leukotriene C_4 concentrations in nasopharyngeal secretions of young children with viral-induced wheeze are elevated [14] and IL-8 has been reported following, and neutrophil infiltration has a direct correlation with severity of respiratory symptoms [16,17]. Allergic rhinitis also passively proceeds to a moderate/severe exacerbation of asthmatic bronchitis in children [18]. Susceptibility of bacterial and viral infections may be caused by a series of events beginning with mucosal edema in the nasal cavity and sinuses, leading to occlusion of the sinus ostia, oxygen reduction, impairment of ciliary function, and thus an accumulation of secretions. Direct allergen reaction in the sinuses, neurologic reflex, or systemic allergic reactions have been proposed

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for chronic and asthmatic cough/dyspnea even in children.

Leukotriene receptor antagonists (LTRAs) are recognized as an alternative for the management of asthma in children under the age of five [4]. Montelukast significantly reduced symptoms and exacerbation in respiratory syncytial virus post-bronchiolitis [19]. Pranlukast is also known to be effective in the control of allergic rhinitis and is licensed by health insurance for the treatment of allergic rhinitis in Japan [20]. The PREVIA study [21] reported that a LTRA, montelukast, effectively reduces asthma exacerbation by 31.6% (1.19 corticosteroid courses with montelukast per year compared with 1.74 corticosteroid courses on placebo) in young children.

We tried to investigate the effect of lysozyme chloride or ambroxol hydrochloride, in addition to LTRA, these drugs are prescribed as mucolytic and for prevention of mucosal edema in the airway [22], on asthma exacerbations in young children under 5 years. L-Carbocystein was also used for proper mucociliary clearance to prevent infectious processes, sinusitis and/or bronchitis [3].

Methods

Drugs

This was a prospective, single-center investigation of the performance of LTRAs in the treatment of asthmatic young children; we observed the clinical effect of oral LTRAs (montelukast, pranlukast), together with carbocystein and lysozyme chloride / ambroxol for over a year. Lysozyme was used as a mucolytic except in patients with egg allergy, in which case ambroxol was used instead. During the study, intermittent oral theophylline (3–4 mg/kg per dose; once or twice daily in the morning and at bedtime) and/or a tulobuterol patch (a β2 agonist; 0.5 mg <3 years, 1 mg >3 years once-daily at bedtime), an appropriate inhaled beta-agonist were used for the relief of minimal respiratory symptoms. The nature of the study was explained to the children's parents/guardian, from whom informed consent was obtained. The study was registered by the ethical committee of Okayama University (# 080501) and Hiroshima City hospital, carried out in accordance with the principles of the Declaration of Helsinki, 1995, and revised in Seoul. Treatment protocol was discontinued in cases with worsening of asthma symptoms, and those in which inhaled corticosteroid was considered as necessary by physicians (nocturnal awakening, shortness of breath, cyanosis, persistent low oxygen saturation < 94%).

Patients

Patients (n =85; boy: girl, 47: 38; 37.2 ± 13.2 months old) recruited to the study since September 2012 to September 2014. They had been treated with LTRAs and with carbocystein and lysozyme chloride / ambroxol. Controls (n =40; boy: girl, 23: 17; 36.5 ± 11.7 months old) were treated with LTRA alone. All of them had a clinical history of asthma symptoms and admitted to our hospital resulting from respiratory infections, and presented with chronic cough and/or wheeze (Table 1). Their symptoms were intermittent and characterized by the absence of severe asthma symptoms and use of neither inhaled nor oral corticosteroids. The majority of patients had asthma symptoms no more than two times per week during the month before entry into the study, and 36 patients and 20 controls had experienced hospitalization and corticosteroid treatment for episodes of bronchiolitis and/or asthma attacks. Only five patients had used inhaled corticosteroids, but not during the two months before study entry. Serum IgE was checked before drugs were started in all patients. Possible severe atopic cases with high IgE (>250 IU) and/or hyper-eosinophilia (>750/μl) were excluded from the study.

Characteristic	Assess	Analysis	Controls
Total numbers	85	80	40
Male (n)	42	42	23
Female (n)	38	38	17
Age (median ± SD)	37.1 ± 13.3	37.2 ± 13.2	36.5 ± 11.7
(mo., range)	(12 – 60)	(12 - 60)	(11 – 60)
IgE (IU/mL)		52.5 ± 37.6	
(range)		(14 – 128)	
Frequency of Asthma symptoms		2.2 ± 4.5	2.1 ± 2.2
(times/mo.)		(1- 4)	(1 – 4)
Nocturnal coughs and awakenings		5.8 ± 4.5	4.6 ± 3.4
(times/mo.)		(1 – 25)	(2 - 25)

Table 1: Patient characteristics and history of asthma.

Endpoints

The primary endpoints included adverse drug reactions. Secondary endpoints included exacerbation of asthma symptoms, and clinical asthma symptoms were evaluated for severity by cough and sputum with Childhood Asthma Control Test (C-ACT), activities of daily living (minor attack, 3 points; moderate-severity attack, 6 points; severe attack, 9 points); the state of nocturnal sleeping and rhinorrhea were also evaluated in three stages (scores of 5, 3, or 0 points), respectively. Clinical symptoms were recorded in a diary as a fixed form. The patient who had earned over 13 points/day should be considered for the necessity of corticosteroids and/or hospitalization. Total points per week were evaluated.

Results

Overall, 85 patients were screened and considered eligible for the study and started the treatment. Five patients were withdrawn: two quit the medication without specific reason and three were moved due to changes in parents' employment. The remaining 80 patients (boys: girls, 42 : 38) and 40 controls participated in the study for a year and significantly reduced the number of episodes of asthma exacerbation (C-ACT scores/week; from 16.1 ± 3.1 to 8.9 ± 2.3) during the first eight weeks ($p < 0.01$); the reduction of C-ACT scores were also observed in controls (Figure 1). The clinical improvement was observed over the year (scores 3.7 ± 1.8 at 12 months, $p < 0.01$ compared to controls at 48 weeks; Figure 1). Consequently, the average percentage of patients who presented improved conditions were > 94 % (after 48 weeks, >good response, Figure 2b).

All patients could avoid hospital admission and corticosteroid courses for asthma exacerbation for over a year. None reported any hospitalization and use of oral or intravenous corticosteroid. All parents/guardians were satisfied with the results (in answer to questionnaire), and patients were highly compliant with the treatment (adherence: 94 %).

Additionally, the frequency of otitis media was remarkably reduced according to the treatment (Figure 3b). Fifteen of the 80 patients

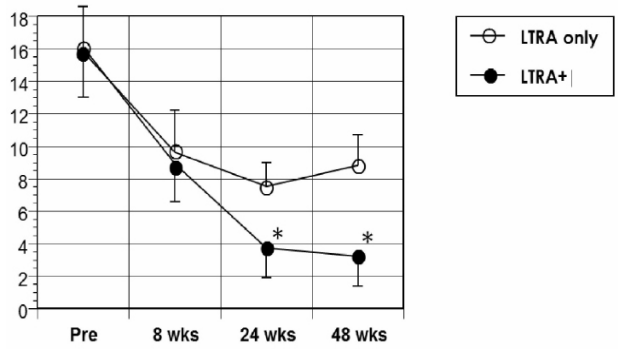

Figure 1: Changes in clinical asthma symptoms (data are expressed as means ± SD; scores per week). Clinical asthma symptoms were evaluated for the severity by cough and sputum, activities of daily living (minor attack, 3 points; moderately severe attack, 6 points; severe attack, 9 points). The state of nocturnal sleeping and rhinorrhea were also evaluated in three stages, respectively (points of 4, 2, and 0). *p<0.01 between data (LTRA only vs LTRA+; with carbocystein and lysozyme chloride / ambroxol).

had otitis media, a total of 36 episodes in the 6 months prior to the treatment was reduced to three episodes for the second 6 months during the treatment (p<0.01). A clinical diagnosis of otitis was made for otalgia, and patients were referred to a doctor of otolaryngology.

Safety

Adverse events were rare. Some patients were treated with theophylline and/or a tulobuterol patch, and no drug-related adverse effects occurred during the study.

Discussion

First, this study demonstrates beneficial control therapy in 1 to 5 year-old patients with recurrent infantile wheeze or mild intermittent asthma (persistent cough episodes) without corticosteroids over a year period. This age group often presents with intermittent symptoms (long asymptomatic periods interrupted by episodes of asthma generally in association with the common cold). Increased

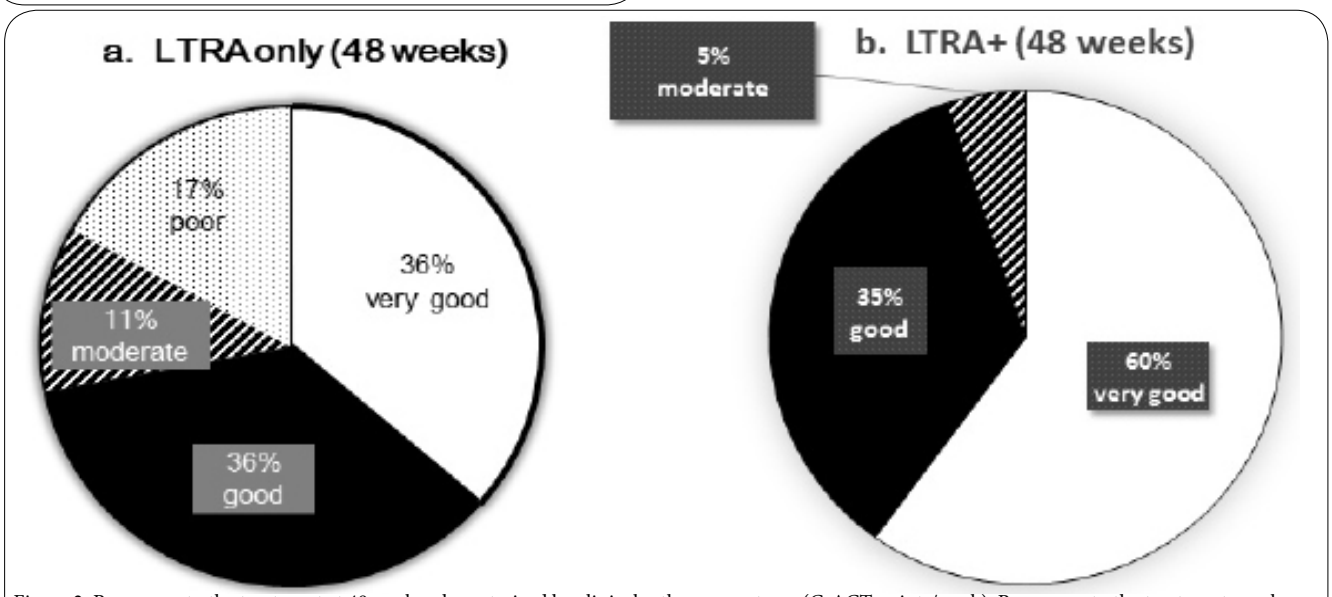

Figure 2: Responses to the treatment at 48 weeks, characterized by clinical asthma symptoms (C-ACT points/week). Responses to the treatment are shown as follows: very good (>75% reduction), good (50 to 75% reduction), moderate (25 to 50% reduction) and poor (<25% reduction) [LTRA only (a) vs LTRA+ (b); with carbocystein and lysozyme chloride / ambroxol).

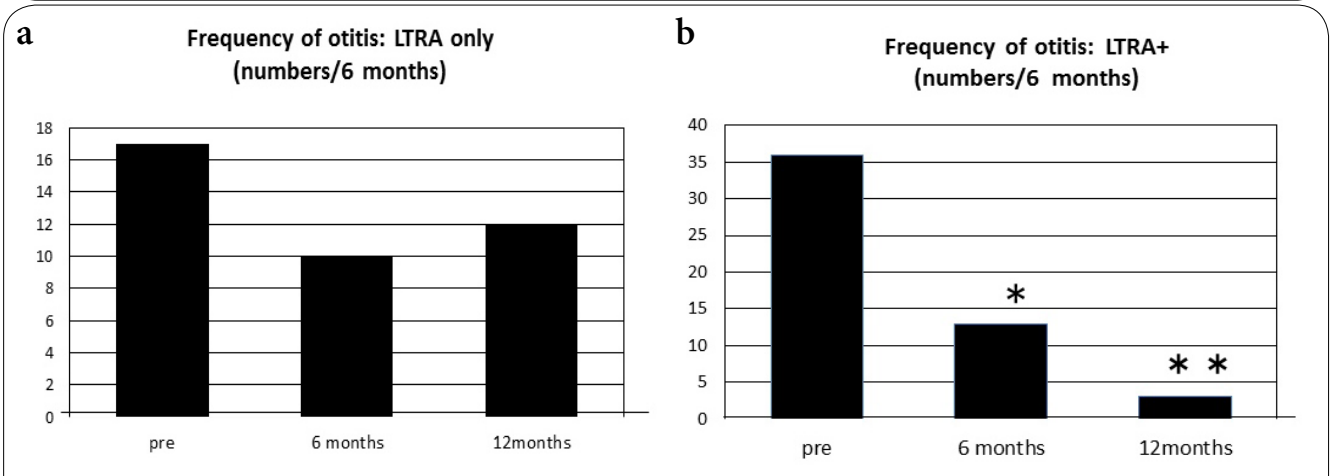

Figure 3: Frequency of otitis media (total episodes) in children (n = 80) with treatment for the first six months (months 1-6) and the second six months (months 7-12). P* < 0.01, was obtained from Pearson (χ^2) analysis. LTRA only (a) vs LTRA+ (b); with carbocystein and lysozyme chloride / ambroxol.

susceptibility to viral respiratory infections, and/or decreased effectiveness of control treatment are well documented in younger-aged children [1,4]. Although daily persistent symptoms are rare, asthmatic exacerbations with viral respiratory infections are more common in toddlers and preschoolers than in school children [12]. Strikingly, the patients had very few asthma symptoms or none at all during the treatment. This study reduced to zero the overall rate of corticosteroid use (both inhaled and oral) and hospitalization. The medications administered in the study were well tolerated and the patients were compliant with them (high adherence; 94%).

Our experimental treatment combined carbocystein and lysozyme chloride or ambroxol with leukotriene receptor antagonists (LTRAs). LTRAs suppress eosinophil activation, and may lead to reduction of serum eosinophilic cationic protein, and they inhibit cellular infiltration of inflammatory cells into the bronchial mucosa [24, 25]. Together, the medications focus on eosinophilic inflammation, anti-allergic effects, mucolysis and rinsing of a mucous membrane to prevent airway inflammation and ultimately, modulating asthmatic reaction. Rhinosinusitis often coexists with, and is well related to allergic rhinitis, which precedes asthma exacerbation [16,17]. Purulent rhinorrhea, sneezing, and postnasal drip secondary to sinusitis also lead to chronic cough [26]. Impairment of ciliary function is known to be related to this event in children. Nasal obstructions caused by rhinitis and/or sinusitis bring about mouth breathing, which more easily allows direct viral invasion. As mentioned above, allergic rhinitis and asthma often coexist, suggesting the concept of "one airway, one disease" [27]. To treat them, we should understand the inflammatory reactions involved in asthmatic disease. Recurrent infectious diseases well explain the clinical behavior of asthma exacerbation. We emphasize that the management of recurrent upper viral respiratory infections involving rhinosinusitis also should be targeted at decreasing the total inflammatory responses in the airway in toddlers and preschoolers.

Over the course of one year, no patients were hospitalized for asthma or even made an unscheduled visit to a physician for asthma exacerbation. Our treatment focused on the management of chronic rhinosinusitis and allergic rhinitis for the control of asthma. With regard to the relationship between allergy and infectious diseases, it has been reported that basophils are activated in the presence of suboptimal doses of allergens and virus/bacteria and may explain the clinical behavior of asthma exacerbation [26]. Therefore, the management of rhinosinusitis may decrease the inflammatory airway response. Additionally, the treatment of rhinosinusitis significantly reduced the occurrence of otitis media.

In this study, we were unable to clarify the patient's socioeconomic background, and racial differences should be considered for a global strategy. A prospective large-scale double blind clinical trial considering these limitations is essential in the near future.

Conclusion

Wheezing and persistent cough in children ages 1–5 are of major public concern; however, until now, no preventive strategy has improved these patients' prognosis except for PREVIA (LTRA) study. As the patients get older, growing up could be an alternative explanation. However, comparing to PREVIA study (LTRA alone), our new strategy significantly reduced the rate of corticosteroid use to zero with the management of rhinosinusitis ($p < 0.01$). Our HIROSIMA study (Hiroshima City-Hospital initiated rhinitis, otitis, sinusitis and intermittent asthma) provides hopeful data for the control of infantile wheeze and persistent cough without corticosteroids; in addition, the treatment provides a higher probability of making the intervention cost-effective.

Statistical Analysis

Between the two comparing groups, the differences in the parameters were evaluated using the paired t-test and Pearson (χ^2) analysis as appropriate. Rates of exacerbation episodes were analyzed by applying a Poisson regression model. For all analyses, values of $p < 0.05$ were considered statistically significant. All statistical analyses were performed using Statmate mini (Atms Co., Tokyo, Japan).

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

Dr Yasui conceptualized and designed the study, and drafted the initial manuscript, and approved the final manuscript as submitted.

Dr Nagaoka also designed the study, and carried out the initial analysis, and approved the final manuscript as submitted.

Dr Ogawa and Dr Itamura coordinated and supervised the data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr Yashiro prepared the application form to Okayama University's ethical committee and designed the study, and approved the final manuscript as submitted.

Dr Ochi supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

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