Progress in the management of childhood asthma

Pakit Vichyanond[*], Rattana Pensrichon, and Suruthai Kurasirikul

Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

Asthma has become the most common chronic disease in childhood. Significant advances in epidemiological research as well as in therapy of pediatric asthma have been made over the past 2 decades. In this review, we look at certain aspects therapy of childhood asthma, both in the past and present. Literature review on allergen avoidance (including mites, cockroach and cat), intensive therapy with β_2-agonists in acute asthma (administering via continuous nebulization and intravenous routes), a revisit of theophylline use and its action, the use of inhaled corticosteroids in various phases of childhood asthma and sublingual immunotherapy in asthma are examined. Recent facts and dilemmas of these treatments are identified along with expression of our opinions, particularly on points of childhood asthma in the Asia-Pacific, are made in this review.

Key words: Asthma; Children; β_2-agonist; Theophylline; Inhaled corticosteroids; Sublingual immunotherapy

INTRODUCTION

International epidemiological studies on allergic diseases in children (the ISAAC-I and ISAAC-III) indicated that prevalence of childhood asthma is increasing worldwide, including among countries in Asia [1, 2]. Apparently, such increase could not be explained by changes that occurred in genetic alone, but rather by a combination of changing in environmental milieu, and changing in lifestyles which exerted effects on gene expression, resulting in increasing various phenotypes of asthma in children. Despite progress in molecular research such as the completion of the human genome project, the availability of technologies to perform genome-wide association studies and knowledge on epigenetics, clinical application of such knowledge on the treatment of asthma is still far from possible. Current treatment of childhood asthma is still mainly depending on pharmacological approach and on modification of immune response to allergens causing IgE sensitization.

The purpose of this article is to review some aspects of available treatment of childhood asthma with main emphasis on commonly used drug therapy for asthma (β_2-agonists, theophylline and corticosteroids) along with avoidance of common allergens causing sensitization among asthmatic children. Last but not least, sublingual immunotherapy, a growing area of immunomodulation, particularly suitable for young children, is also reviewed.

Correspondance: Pakit Vichyanond
Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand
Tel: +66-2-419-5940
Fax: +66-2-381-8940
E-mail: sipvy@mahidol.ac.th

Allergen avoidance

The latest US - National Asthma Education and Prevention Program asthma guidelines (NAEPP 2007) still recommends allergen avoidance as a basic part of management asthma [3]. In the PRACTALL 2008 document (a practical guidelines for diagnosis and treatment of asthma in childhood – published jointly by the American Academy of Allergy, Asthma and Immunology and the European Academy of Allergy and Immunology), allergen avoidance is recommended when there is sensitization and a clear association between allergen exposure and symptoms [4]. The Global Initiatives of Asthma (GINA) 2009, recommended allergen avoidance as a part of regimen for prevention asthma symptoms and exacerbations [5]. Morgan et al. [6] conducted a one-year controlled trial of environmental interventions for children with asthma. They found that the intervention group had fewer days with symptoms than the control group. The reduction of *Dermatophagoides pteronyssinus* (Der p 1), *Dermatophagoides farinae* (Der f 1) and cockroach allergens was significantly lower in the intervention group than in the control group. Despite such recommendation, a recent meta-analysis for house-dust mites (HDM) control in asthma, showed no statistically significant difference either in the numbers of patients who improved, asthma symptom scores and medication usage in the intervention group [7]. Such analysis concluded that HDM avoidance is ineffective in the treatment of asthma. However, trials included in the analysis were heterogeneous in methods of mite elimination, results of allergen reductions, patients' characteristics and outcome of management. Moreover, some large trials with positive results were excluded from the analysis. For such reasons, it is difficult to apply the results of such meta-analysis in a day-to-day management of allergic diseases [8] and most guidelines still endorse environmental control as a part of their recommendations.

HDM

In most humid areas around the world, house dust mites are the major sources of allergens found in house dust. The most common species of house dust mites are Der p and Der f.

To date, approximately 22 to 23 different HDM allergens have been identified, with Der p 1 and Der f 1 being the major allergens causing sensitization among mite-sensitive individuals. Mite fecal particles are the abundant sources of mite allergens [9]. Size of these particles can vary from large particles (over 100 μm) to those in respirable sizes (<10 μm). Mite allergens collect in bedding materials. The highest mite concentrations can be found in dusts from mattresses. It has been shown that dust mite exposure in early life is a major risk factor for future development of asthma [10]. Moreover, exposure to large amount of mite allergen leads to asthma exacerbations [11, 12].

Current recommendations for treatment of asthma (GINA) and allergic rhinitis (ARIA) includes measures for reduction of exposure to house dust mite allergens. These measures are:

1. Use of mite impermeable encasement for mattresses, pillows and other bedding material. Woven fabrics with pore size less than 10 μm are preferred [13]. Studies on effect of impermeable covers for mattresses on Der p 1 and Der f 1 concentrations showed mite-impermeable covers are effective in reducing levels of Der p 1 and Der f 1 after 12 months of study [14, 15]. The study by Halken et al. [15] found encasing of mattresses and pillows resulted in a significant long-term reduction in mite allergen concentrations in mattresses and in the need for inhaled steroids in asthmatic children with mite allergy.

2. Washing bed clothing in hot water (over 55ºC) can kill mites and reduce mite allergen concentrations by 90% [16]. Washing at room temperature has also been shown remove allergen from bed clothing. Freezing condition will also kill mites. Thus, stuffed animal may be placed in plastic bag in freezer before washing to remove left over allergen [17].

3. Carpets and upholstered furniture are major source of mite collections. Ideally, carpets should be replaced with polished wood or vinyl floor covering. Exposure of thin carpets to direct strong sunlight for at least 3 h has been found to eliminate mites [18]. However, this method is perhaps not applicable to thicker and wall-to-wall carpets.

Cockroach

Exposure to cockroaches has been found to be an important factor in the development of childhood asthma in inner-city environment of the United States [19]. The two major cockroach species are the American cockroach (*Periplanata Americana*) and the German cockroach (*Blattella germanica*). *Blatella germanica* is the major cockroach species found in the United States whereas *Periplanata Americana* are found in Thailand and throughout Asia [20].

Cockroach avoidance

Both physical and chemical measures have been used to control cockroach populations in the household. Patients and families should be instructed to properly discard left-over food and liquids

which can be source of nutrients for cockroaches. Chemicals used for cockroach extermination are abamectin, hydromethylnon and pyrethrin [21]. The most effective form appears to be gel, which is commonly placed in the cockroach bait station or even as a quick hardened gel in several sites in the household. Such treatment, together with family education, will be effective in reducing cockroach populations for 2-3 months [22]. Treatment by professional entomologists was found to be more effective in reducing cockroach allergen when compared to treatment by chemical companies [23]. Reduction in cockroach allergen can be achieved through combined intervention of occupant education, insecticide application and professional cleaning [6].

Pet allergen (cats and dogs)

The role of pet elimination in primary allergy prevention is still controversial. However, exposure to pets by sensitized individuals can aggravate allergic symptoms including asthma [24]. Because cat allergen exposure has also been shown to occur outside the home, particularly in schools, pet avoidance in the home alone may not be sufficient in reducing exposure to cat allergens. Cat allergens are found in 90% of all home and most public indoor areas even in homes of those without pets [25].

Pet avoidance

1. Removal of the animal from home. The best way to reduce exposure to cat or dog allergens is to remove the animals from home. It may take months (20-24weeks) after cat removal to achieve reduction of cat allergens to the normal level [26]. Cleansing of washable surfaces should be undertaken once pets are removed. For those who could not remove the animals, pets should be kept outdoor. Cat and dog washing can reduce allergen in the furs, but the effect is of short duration. Also, dog washing had to be done at least twice a week which is not physically possible to most families [27].

2. Control of airborne pet allergen levels in the home by air cleaners. Although high-efficiency particulate air filter was found to effectively reduce airborne cat allergen levels, there was insufficient evidence for the reduction of associated disease activities [28]. In a recent Cochrane analysis for determining the efficiency of air filtration unit in allergy to pets, only 2 smalls studies were found and no differences in clinical efficacy between intervention and control groups was demonstrated [29].

Short-acting β_2-agonists in acute asthma

Continuous β_2-agonists nebulizer for acute asthma

There is a general agreement that short-acting β_2-agonists such as albuterol (salbutamol) and terbutaline are the first-line agents for the treatment of acute asthma due to its rapid bronchodilating action. Since the late 1980s, uncontrolled studies in asthmatic children have demonstrated that β_2-agonists (terbutaline) could be safely and effectively administered by continuous nebulization. Moler et al. [30] studied 19 children and found that continuous nebulization of terbutaline (4 mg/h) was effective in improving clinical scores and in decreasing arterial carbon dioxide tension ($PaCO_2$). No significant toxicity was recorded during treatment lasting up to 37 h. Portnoy et al. [31] found that 12 patients treated with continuous nebulized terbutaline (1-12 mg/h for 1-24 h) had an improvement in gas exchange and respiratory rate within an average of 8 h. No significant toxicity was noted and all 12 patients were discharged from the intensive care unit within 24 h. In a study by the same authors, 26 children with severe exacerbations of asthma unresponsive to systemic theophylline, methylprednisolone and intermittent β_2-agonist inhalation, continuous nebulized terbutaline administered at doses of 1-12 mg/h, for a mean duration of 7-8 h (range 1-24 h) caused clinical scores to improve rapidly and all patients showed marked improvement in pH and $PaCO_2$ during the first 2 h [32]. A prospective randomized study by Papo et al. [33] treated 17 children with impending respiratory failure due to status asthmaticus with either continuous or intermittently nebulized salbutamol (0.3 mg/kg/h or 0.3 mg/kg over 20 min every h). As judged by the clinical score and blood gas values, the children in the continuous nebulization group improved faster and spent less time in hospital than those receiving intermittent treatment. No side effects were seen. It was quite apparent that continuous nebulization of either terbutaline or salbutamol was effective among hospitalized children with severe asthma. Surprisingly, when continuous nebulization was compared with intermittent nebulization among 2-18 years old patients presented with severe asthma in the emergency department (ED) setting, no difference in hospitalization rate was observed [34]. However, in this study, continuous therapy provided a significant time savings in the delivery of asthma therapy to patients in a busy ED.

For adult asthma, a systematic review of randomized controlled trials (6 studies) showed the equivalence of continuous and intermittent albuterol nebulization in term of pulmonary

function and hospital admission [35]. However, in an ED setting, a subgroup analysis among more severe patients with an initial peak expiratory flow rates (PEFRs) of 200 or less, continuous nebulization decreased admission rate and improved PEFRs when compared with intermittent therapy [36]. Camargo et al. [37] published a Cochrane systematic review of continuous vs. intermittent β2-agonists for acute asthma (8 trials and 1 in children) and concluded that differences were found between the two methods, with continuous nebulization producing a modest reduction in admissions compared to intermittent beta-agonist therapy. This finding was more pronounced in severe acute asthma. Continuous nebulizing therapy may be more effective than intermittent nebulization for delivering beta-agonist drugs to relieve airway spasm in selected asthma populations. Moreover, continuous treatment appears to be safe and well tolerated.

Intravenous (IV) β2-agonists for acute asthma

The general approach for treating patients with severe acute asthma is to use β2-agonist bronchodilators and corticosteroids. For rapid bronchodilation among these severe patients, penetration of inhaled drug to the affected small conducting airways may be impeded. In these circumstances, IV rather than inhaled administration of bronchodilators may provide an earlier clinical response. Stephanopoulos et al. [38] found that IV terbutaline was well tolerated in asthmatic children for up to 305 continuous h, at varying doses up to a maximum of 10 μg/kg/min without significant elevation of CPK-MB. Arrhythmia was rare and only two occasions of ST-depression was observed. In a randomized, double-blind, placebo-controlled trial of IV salbutamol (15 μg/kg as a single bolus over 10 min) vs. nebulized ipratropium bromide (250 μg), or IV salbutamol plus ipratropium bromide in an early management of severe acute asthma in children presenting to an emergency department, children who received IV salbutamol for severe acute asthma showed a more rapid recovery time, which resulted in earlier discharge from the hospital than those administered inhaled ipratropium bromide [39]. There was no additional benefit obtained by combining ipratropium bromide and IV salbutamol administration. For a safety concern, a retrospective study of admission records of 77 children admitted with acute severe asthma who needed IV terbutaline showed that there was a significant increase in heart rate and a significant fall in diastolic blood pressure among this cohort [40]. Four patients required inotropic support. None of the patients had cardiac arrhythmias. Potassium supplements were required in 10 patients

due to hypokalaemia. All patients improved and none required initiation of artificial ventilation after commencing terbutaline. There was no mortality in this cohort.

For treatment in the ED, guidelines in North America and Europe still recommend inhaled β2-agonist therapy for all cases of asthma presenting to emergency departments [3, 41, 42]. IV and subcutaneous β2-agonists are described as second line therapy for use in patients unresponsive to inhaled bronchodilator and systemic corticosteroid therapy, or if the inhaled route is not practical for such patients. Travers and Jones recently published a systematic review of IV β2-agonist for acute severe asthma in the ED and concluded that there is no evidence to support the advantage of the use of IV β2-agonists over inhaled β2-agonists limiting its use (IV route) in the ED situation [43].

Theophylline in the management of asthma in children, a revisit

Theophylline, a methylxanthine with a structure similar to xanthines found in coffee and tea, was isolated by the end of the 19th century. However, its use in asthma was not begun until after Hirsch described its bronchodilating effect [44]. Aminophylline, a soluble ethylenediamine salt of theophylline, was later developed for IV administration and was shown to be effective in acute severe asthma, particularly in patients who had not responded well to adrenaline [45]. Subsequently, its oral preparation, in fixed dose combination with ephedrine and phenobarbital, was later described [46] and was soon followed by the introduction of rapid release formulation [47]. Due to its low cost, oral theophylline became a very popular treatment for asthma, between the 1960's to 1980's, worldwide. However, because its short duration, slow-release theophylline formulations, that could be given once or twice daily, was later developed and became a standard of chronic therapy in the late 1970's for asthma due to their convenience and greater tolerability. Early dose–response studies demonstrated an increasing bronchodilator response above plasma concentrations of 10 μg/mL (55 μM) [48]. The upper recommended plasma concentration was 20 μg/mL due to unacceptable side effects above this level (headache, nausea, cardiac arrhythmia and convulsion). The therapeutic range for plasma concentrations was therefore established to be between 10 to 20 μg/mL. Doses should be adjusted individually due to interpersonal pharmacokinetic variations.

Since theophylline has a narrow therapeutic window, its use in acute asthma in children in the late 1980's was mainly

for those who did not respond adequately to inhaled β_2-agonists and particularly for those who required hospitalization. Some investigations conducted to determine the effect of IV theophylline in addition to inhaled β_2-agonists showed varying clinical results [49]. However, the results of a study of 163 children with acute severe asthma by Yung and South [50] showed that the aminophylline group had better spirometry results at 6 h with better oxygen saturation at 30 h compared to placebo. Moreover, 5 of the placebo group required endotracheal intubation compared to none in the aminophylline group. Of note in this study was all patients were given IV and oral corticosteroids. In 2005, recent Cochrane analysis by Mitra [51], analyzing 7 randomized controlled trial comparing aminophylline and placebo in 380 children with acute asthma who required hospitalization. The results indicated that those receiving aminophylline had no difference in length of hospital stay, symptoms, frequency of nebulizations, mechanical ventilation rates comparing to those receiving placebo. Together with the introduction of newer methods, devices for effective use of continuous nebulization of β-agonist in asthma [32], the use of IV aminophylline in acute asthma in children came to an almost complete halt with its use only limited chronic asthma.

Mechanism of action of theophylline in asthma

Although theophylline has been in clinical use for many years, its mechanism of action remains uncertain. Although it is generally considered to be a bronchodilator, evidence indicates that it may also have important immunologic and anti-inflammatory properties.

Bronchodilating action of theophylline

The molecular mechanism of bronchodilatation has been largely been ascribed to its ability to inhibition action of phosphodiesterase enzyme (PDE) which degrades cyclic AMP (cAMP) and cyclic GMP (cGMP). This results in an increase in cAMP and thereby leads to bronchodilation. Theophylline is a nonselective PDE inhibitor and the degree of PDE inhibition is small at concentrations of theophylline which are therapeutically relevant. In fact, total PDE activity in human lung extracts is inhibited by only 5-20% at therapeutic concentrations of theophylline [52]. Therefore, bronchodilation through PDE inhibition may not be the only mechanism and other mechanisms such as interference with K-maxi channel regulation was described [53]. Theophylline is also a potent inhibitor of adenosine receptors at therapeutic concentrations, with antagonistic action towards A1- and A2-receptors although it is less effective against A3-receptors [54]. Adenosine antagonism is likely to account for some of the serious side effects of theophylline, such as seizures and cardiac arrhythmias.

Theophylline has been shown to affect respiratory muscle. It increases diaphragmatic muscle contractility and strength [55]. This effect may be a mechanism for the small but significant decrease in the work of breathing demonstrated for theophylline [56].

Anti-inflammatory action

In allergen challenge studies in patients with asthma, IV theophylline inhibits late response to allergen, but had relatively little effect on the early response [57]. This has been interpreted as an effect on chronic inflammatory response, which is supported by a reduction of infiltration of eosinophils and CD4$^+$ lymphocytes into the airways after allergen challenge subsequent to low doses of theophylline [58]. In patients with nocturnal asthma, a low-dose theophylline inhibits the influx of neutrophils and, to lesser extent eosinophils in the early morning [59]. *In vitro*, theophylline was found to increase interleukin-10 release from peripheral blood mononuclear cells stimulated with mitogens [60].

These anti-inflammatory effects of theophylline in asthma and COPD are seen at concentrations that are usually less than 10 μg/mL, which is below the dose with associated with clinically useful bronchodilatation. Theophylline in low therapeutic concentrations has been shown to activate the nuclear enzyme histone deacetylase which switches off the transcription of activated inflammation genes. Such action is synergistic with corticosteroids [61] and thus, low concentration of theophylline could restore corticosteroid repression of pro-inflammatory mediator release and histone acetylation in oxidant exposed cells [62]. This interaction may open up possibilities for novel anti-inflammatory therapies in the future.

Theophylline use in chronic asthma

GINA asthma guidelines recommend theophylline as add on therapy in patients who do not achieve control on inhaled corticosteroids alone [5]. As add-on therapy, theophylline is less effective than long-acting inhaled β_2-agonists [63, 64]. A Cochrane Database of Systematic Reviews in 2007 reviewed the comparative efficacy, safety and side-effects of long-acting β_2-agonists and theophylline in the maintenance treatment [64]. All included studies were RCTs involving adults and children with clinical

evidence of asthma. These studies compared oral sustained release and/or dose adjusted theophylline with an inhaled long-acting β_2-agonist in adults and adolescents with asthma. Thirteen studies with a total of 1,344 participants met the inclusion criteria of the review. Salmeterol was related with a greater improvement in lung function, and reduced the need for extra short-term inhalers in the day and the night. Salmeterol and formoterol were less likely to produce side-effects (such as headaches and nausea) when compared to theophylline [64].

Surprisingly, in a study by Evans et al. [65] low-dose inhaled budesonide with theophylline produced similar benefits on improvement lung function and reductions in β_2-agonists use when compared to high-dose inhaled budesonide, in adult patients with moderate asthma and persistent symptoms. In a recent meta-analysis in pediatric asthma population [66], xanthine was found to be more effective than placebo as first-line maintenance therapy. It was less efficient than inhaled steroids but was similar to short-acting β_2-agonists and sodium cromoglycate. The reviewers, however, did not find any evidence to support the synergy between xanthine and inhaled steroids.

Inhaled corticosteroids (ICS) in pediatric asthma

Effectiveness of inhaled steroids in chronic asthma

ICS became available for the treatment of asthma in the early 1960's. However, it use was not popular until the late 1970's due to limited understanding of pathophysiology of asthma and 'steroid phobia' among physicians, patients and parents alike. Together with availability of newer ICS's with increased potency, reduced systemic absorption and extensive hepatic first-pass degradation (such as budesonide and fluticasone) along with increasing understanding that inflammation of the lungs as the pathophysiologic basis of asthma, the use of ICS in asthma became rapidly accepted among pediatric allergists as well pediatricians. Administration of ICS to moderately severe asthmatic children led to a rapid decrease symptoms within 2 weeks [67]. In addition, ICS prevents asthma exacerbation in moderate to severe asthmatics both in adults [68] and children [69]. ICS is currently recommended as a first-line controller for 'persistent' asthma in most guidelines (NAEPP, PRACTALL, GINA). Beclomethasone dipropionate (BDP), despite being the first ICS with long standing clinical safety, has become less popular among pediatricians due to report of side effects on growth in children [70]. Currently, budesonide and fluticasone propionate are the two major recommend ICS for

pediatric use, although data for fluticasone [71] are relatively limited as compared to budesonide [72].

Use of inhaled steroids early in asthma and to prevent progressive loss of lung function

Since asthma is essentially an inflammatory disease of the lungs, progressive loss of the lungs has long been proposed. Indeed a long-term decline of lung function in chronic asthma in adults were reported by Lange et al. [73]. Agertoft and Pedersen reported a landmark findings of long-term use of budesonide (3 years) in a large number of asthmatic children, in which they reported that budesonide use was not only associated with lower rate of hospitalizations but also with a larger improvement of FEV_1 [74]. Remarkably, it was demonstrated that children who started ICS later in their course of disease (>5 years) attained lower lung growth than those used early (<2 years). After such observation, two large investigations were carried to verify such contention, i.e, the Childhood Asthma Management Program (CAMP in the USA) and the Inhaled Steroids As Regular Treatment in Early Asthma. A large numbers of publications have been generated from these two multicenter and premium studies. It was apparent that the use of ICS is constantly associated with lower degree of exacerbations of asthma but results on lung growth were not conclusive (not consistent in preventing decline in lung function as a whole but may/may not prevent the decline in severe patients) [75-78]. From the CAMP study, it was suggested that ICS were used too late in the course of disease (mean age of patients = 9 years old);instead of comma the same group of investigators (Childhood Asthma Research and Education Network USA – CARE network) further conducted a study using fluticasone propionate in wheezing toddlers with positive asthma predictive index [79]. The result of this 'PEAK' study again failed to show effect of ICS as a preventer (not preventing further development of asthma exacerbations after discontinuation of 2 years of use of ICS [80]). Thus, ICS is truly a 'controller' rather than a 'preventer' for asthma, as was previously conceived.

Use of inhaled steroids in acute asthma

Traditionally, ICS is used as a controller for chronic asthma. However, using high dose ICS in lieu of systemic steroids such as prednisolone was as attractive approach in order to avoid steroids side effect. Volovitz et al. [81] compared short-term use of high dose (1,600 μg) of budenoside with 2 mg/kg of prednisolone in a small group of children in the ED and found that there were

similar improvement in pulmonary index score and peak flow rate in both group. Levy and his group [82] compared short courses of prednisolone with inhaled fluticasone in a large group of adult asthmatics (double-blind, double dummy, parallel trial) with mild exacerbation of asthma and demonstrated that both treatment group had similar treatment failure (prednisolone = 23% and fluticasone = 27%). Rodrigo and Rodrigo [83] compared very high-dose of inhaled flunisolide given through volumatic spacer (6 mg per h for 3 h) vs. placebo in adult asthmatics with severe asthma ($FEV_1 < 50\%$) and found that patients in the flunisolide group improved significantly over placebo, from 90 to 180 min of therapy. It therefore appeared that ICS was effective in acute asthma in adult patients. In the year 2000, a pediatric study by Schuh et al. [84] comparing a single high-dose of inhaled fluticasone (2 mg) via MDI with spacer with 2 mg of prednisolone in severe asthmatics ($FEV_1 < 60\%$) was published. At 4 h of treatment, 31% of patients in the fluticasone group were hospitalized compared to 10% in the prednisolone group. The same group of investigators, later published a comparison (high-dose fluticasone vs. oral prednisolone) with longer therapy duration (5 days) in a less severe group of asthmatic children (FEV_1 50-79%) [85]. Again, oral prednisolone showed higher improvement of lung functions at 4 h (FEV_1) and with less relapse rate at 48 h (prednisolone 0% vs. fluticasone 12.5%). In the 2003 Cochrane analysis by Edmonds et al. [86] among 5 trials in adults and 5 in pediatric population, ICS use was found to reduce rate of hospitalization as compared to placebo. However, among the 7 trials comparing ICS with oral steroids, there were significant heterogeneity among trials to preclude meaningful pooling of the results [86].

Use of inhaled steroids intermittently in mild persistent asthma

GINA and NAEPP recommend that patients with asthma should attain the 'controlled' condition prior to decrease controllers [3, 5]. The major question is when to discontinue controller, particularly ICS, in patients with less degree of severity. In the GINA recommendation, discontinuation of ICS is recommended when a patient does not have an exacerbation for 1 year. The recommendation for NAEPP is less stringent (2 episodes per year). Such recommendations pose a significant burden to patients, family and caretakers alike, particularly those with less frequent attacks. In the authors 'experience, several patients opted to discontinue ICS on their own and used ICS on an intermittent basis. Recently, Boushey et al. [87] evaluated 225 adults with mild persistent asthma treated with daily ICS vs. daily zafirlukast vs. intermittent ICS or oral steroids. Frequency of exacerbations and peak flow rates were surprisingly similar among the three groups suggesting that in mild intermittent asthma, patients could be weaned to intermittent use of ICS. Recently, two major studies in pediatric populations were published to confirm the results in adults. In the Treating Asthma to Prevent Exacerbation study by Martinez et al. [88], 843 adolescent and children with mild intermittent asthma were studied. The group randomized to receive BDP with albuterol as rescue treatment did better than albuterol alone group with respect to exacerbations and treatment failure [88]. The daily ICS group provided the best results followed by the combined (daily ICS + rescue ICS with albuterol). The author suggested that pediatric patients with mild intermittent asthma may be considered weaned to rescue ICS + albuterol when considered appropriate. Most recently, the Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers therapy published by Zeiger et al. [89] indicated that intermittent use of nebulized budesonide (1 mg twice daily) was as effective as daily budesonide (0.5 mg nightly) with respect to frequency of exacerbations and asthma severity.

Allergen immunotherapy in asthma

Specific allergen immunotherapy (SIT) has been one of the most debated aspects in the field of asthma treatment for several decades. Various reviews reported contradictory results of SIT in asthma, not only for adults, but also for children. Despite the presence of limitations and confounding factors, there were some evidences available to suggest that both subcutaneous (SCIT) and sublingual (SLIT) immunotherapy may be a viable treatment for asthma. We review recent advances of SLIT in pediatric asthma.

SLIT and asthma

There are more than 60 randomized control trials of SLIT. Few trials have been specifically designed for asthma. A large number of studies were performed in children, particularly with house dust mites [90-92]. Most studies reported that SLIT can reduce asthma symptom scores and medication use [93, 94]. SLIT has been evaluated among Asian children who were sensitized to mites in at least 3 studies [92, 94, 95]. Most of these studies showed satisfactory results. In both trials from Taiwan, improvement in spirometry parameters was also observed [94, 95].

Calamita et al. [96] were the first to perform a meta-analysis on SLIT in asthma (including adults and children) asthma. They reported a significant difference between SLIT and placebo for

categorical outcomes (better/unchanged/worsened), but not in the difference using the symptoms or medication scores of asthma. Nevertheless, there was high degree heterogeneity among studies (dose, duration, and outcome measures) thus limited some extent the positive conclusion. In 2008, a meta-analysis of effective of SLIT in pediatric asthma patients 3 to 18 years of age was reported by Penagos et al. [97]. The analysis included 441 patients from 9 studies (5 mites 2 pollen, and 1 with mixed allergens). Overall results found a significant reduction in both symptoms (SMD −1.14; 95% CI −2.10 to −0.18, p = 0.02) and medication use (SMD −1.63; 95% CI −2.83 to −0.44, p = 0.007). However, again, there was a high degree of heterogeneity between studies. Problems of meta-analysis are high heterogeneity across studies, variation in studies, pool allergen use and dosages. In contrast, there were 3 studies randomized controlled trial reported no effect on asthma symptom scores [98-100]. Two studies showed almost no symptom of asthma at baseline and during trials (due to concomitant pharmacotherapy and environmental control to mites) and thus leaving for no room for improvement of the intervention examined.

Safety of SLIT

SLIT was found generally found to be safer than SCIT. No fatality has been reported with SLIT. Only 6 clinical cases of anaphylaxis to SLIT have been published. In a post marketing surveillance study of SLIT among pediatric patients (96,000 SLIT doses of extract administered), local side effects were mild, i.e., throat irritation and oral itching [101]. Only 3% of patients or 0.083 per 1,000 doses were associated with side effects. Seven systemic side effects, including abdominal pain, conjunctival itching, and rhinitis were noted. Most of these reactions were mild and required no treatment. No life-threatening events occurred. Neither fatal reaction nor need for hospitalization was observed [97]. Most of SLIT studies utilized continuous regimen with maintenance vaccine giving all year round. However, co-seasonal ultra-rush administration of SLIT to birch pollen has recently been reported to be efficacious and safe [102]. SLIT appeared to be a well tolerated and safe treatment for pediatric asthma.

REFERENCES

1. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998;351:1225-32.
2. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733-43.
3. National Heart, Lung, and Blood Institute. Expert panel report 3: guidelines for the diagnosis and management of asthma—full report 2007. August 28, 2007. Available from: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.
4. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Götz M, Helms PJ, Hunt J, Liu A, Papadopoulos N, Platts-Mills T, Pohunek P, Simons FE, Valovirta E, Wahn U, Wildhaber J. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy 2008;63:5-34.
5. Kroegel C. Global Initiative for Asthma (GINA) guidelines: 15 years of application. Expert Rev Clin Immunol 2009;5:239-49.
6. Morgan WJ, Crain EF, Gruchalla RS, O'Connor GT, Kattan M, Evans R 3rd, Stout J, Malindzak G, Smartt E, Plaut M, Walter M, Vaughn B, Mitchell H. Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 2004;351:1068-80.
7. Gøtzsche PC, Johansen HK. House dust mite control measures for asthma: systematic review. Allergy 2008;63:646-59.
8. Platts-Mills TA. Allergen avoidance in the treatment of asthma: problems with the meta-analyses. J Allergy Clin Immunol 2008;122:694-6.
9. Platts-Mills TA, Vervloet D, Thomas WR, Aalberse RC, Chapman MD. Indoor allergens and asthma: report of the Third International Workshop. J Allergy Clin Immunol 1997;100:S2-24.
10. Squillace SP, Sporik RB, Rakes G, Couture N, Lawrence A, Merriam S, Zhang J, Platts-Mills AE. Sensitization to dust mites as a dominant risk factor for asthma among adolescents living in central Virginia. Multiple regression analysis of a population-based study. Am J Respir Crit Care Med 1997;156:1760-4.
11. Sterk PJ, Buist SA, Woolcock AJ, Marks GB, Platts-Mills TA, von Mutius E, Bousquet J, Frew AJ, Pauwels RA, Aït-Khaled N, Hill SL, Partridge MR. The message from the World Asthma Meeting. The Working Groups of the World Asthma Meeting, held in Barcelona, Spain, December 9-13, 1998. Eur Respir J 1999;14:1435-53.
12. Peat JK, Li J. Reversing the trend: reducing the prevalence of asthma. J Allergy Clin Immunol 1999;103:1-10.
13. Vaughan JW, McLaughlin TE, Perzanowski MS, Platts-Mills TA. Evaluation of materials used for bedding encasement: effect of pore size in blocking cat and dust mite allergen. J Allergy Clin Immunol 1999;103:227-31.
14. Frederick JM, Warner JO, Jessop WJ, Enander I, Warner JA. Effect of a bed covering system in children with asthma and house dust mite hypersensitivity. Eur Respir J 1997;10:361-6.
15. Halken S, Høst A, Niklassen U, Hansen LG, Nielsen F, Pedersen S, Osterballe O, Veggerby C, Poulsen LK. Effect of mattress and pillow encasings on children with asthma and house dust mite allergy. J Allergy Clin Immunol 2003;111:169-76.

16. McDonald LG, Tovey E. The role of water temperature and laundry procedures in reducing house dust mite populations and allergen content of bedding. J Allergy Clin Immunol 1992;90:599-608.

17. Bush RK. Does allergen avoidance work? Immunol Allergy Clin North Am 2011;31:493-507.

18. Tovey ER, Woolcock AJ. Direct exposure of carpets to sunlight can kill all mites. J Allergy Clin Immunol 1994;93:1072-4.

19. Rosenstreich DL, Eggleston P, Kattan M, Baker D, Slavin RG, Gergen P, Mitchell H, McNiff-Mortimer K, Lynn H, Ownby D, Malveaux F. The role of cockroach allergy and exposure to cockroach allergen in causing morbidity among inner-city children with asthma. N Engl J Med 1997;336:1356-63.

20. Tungtrongchitr A, Sookrung N, Munkong N, Mahakittikun V, Chinabut P, Chaicumpa W, Bunnag C, Vichyanond P. The levels of cockroach allergen in relation to cockroach species and allergic diseases in Thai patients. Asian Pac J Allergy Immunol 2004;22:115-21.

21. Eggleston PA. Cockroach allergen abatement in inner-city homes. Ann Allergy Asthma Immunol 2003;91:512-4.

22. Arbes SJ Jr, Sever M, Mehta J, Gore JC, Schal C, Vaughn B, Mitchell H, Zeldin DC. Abatement of cockroach allergens (Bla g 1 and Bla g 2) in low-income, urban housing: month 12 continuation results. J Allergy Clin Immunol 2004;113:109-14.

23. Sever ML, Arbes SJ Jr, Gore JC, Santangelo RG, Vaughn B, Mitchell H, Schal C, Zeldin DC. Cockroach allergen reduction by cockroach control alone in low-income urban homes: a randomized control trial. J Allergy Clin Immunol 2007;120:849-55.

24. Gent JF, Belanger K, Triche EW, Bracken MB, Beckett WS, Leaderer BP. Association of pediatric asthma severity with exposure to common household dust allergens. Environ Res 2009;109:768-74.

25. Wallace DV. Pet dander and perennial allergic rhinitis: therapeutic options. Allergy Asthma Proc 2009;30:573-83.

26. Wood RA, Chapman MD, Adkinson NF Jr, Eggleston PA. The effect of cat removal on allergen content in household-dust samples. J Allergy Clin Immunol 1989;83:730-4.

27. Hodson T, Custovic A, Simpson A, Chapman M, Woodcock A, Green R. Washing the dog reduces dog allergen levels, but the dog needs to be washed twice a week. J Allergy Clin Immunol 1999;103:581-5.

28. Wood RA, Johnson EF, Van Natta ML, Chen PH, Eggleston PA. A placebo-controlled trial of a HEPA air cleaner in the treatment of cat allergy. Am J Respir Crit Care Med 1998;158:115-20.

29. Kilburn S, Lasserson TJ, McKean M. Pet allergen control measures for allergic asthma in children and adults. Cochrane Database Syst Rev 2003;CD002989.

30. Moler FW, Hurwitz ME, Custer JR. Improvement in clinical asthma score and PaCO2 in children with severe asthma treated with continuously nebulized terbutaline. J Allergy Clin Immunol 1988;81:1101-9.

31. Portnoy J, Aggarwal J. Continuous terbutaline nebulization for the treatment of severe exacerbations of asthma in children. Ann Allergy 1988;60:368-71.

32. Portnoy J, Nadel G, Amado M, Willsie-Ediger S. Continuous nebulization for status asthmaticus. Ann Allergy 1992;69:71-9.

33. Papo MC, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. Crit Care Med 1993;21:1479-86.

34. Khine H, Fuchs SM, Saville AL. Continuous vs intermittent nebulized albuterol for emergency management of asthma. Acad Emerg Med 1996;3:1019-24.

35. Rodrigo GJ, Rodrigo C. Continuous vs intermittent beta-agonists in the treatment of acute adult asthma: a systematic review with meta-analysis. Chest 2002;122:160-5.

36. Rudnitsky GS, Eberlein RS, Schoffstall JM, Mazur JE, Spivey WH. Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. Ann Emerg Med 1993;22:1842-6.

37. Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. Cochrane Database Syst Rev 2003;CD001115.

38. Stephanopoulos DE, Monge R, Schell KH, Wyckoff P, Peterson BM. Continuous intravenous terbutaline for pediatric status asthmaticus. Crit Care Med 1998;26:1744-8.

39. Browne GJ, Trieu L, Van Asperen P. Randomized, double-blind, placebo-controlled trial of intravenous salbutamol and nebulized ipratropium bromide in early management of severe acute asthma in children presenting to an emergency department. Crit Care Med 2002;30:448-53.

40. Kambalapalli M, Nichani S, Upadhyayula S. Safety of intravenous terbutaline in acute severe asthma: a retrospective study. Acta Paediatr 2005;94:1214-7.

41. Beveridge RC, Grunfeld AF, Hodder RV, Verbeek PR. Guidelines for the emergency management of asthma in adults. CAEP/CTS Asthma Advisory Committee. Canadian Association of Emergency Physicians and the Canadian Thoracic Society. CMAJ 1996;155:25-37.

42. Lipworth BJ. Treatment of acute asthma. Lancet 1997;350 Suppl 2:SII18-23.

43. Travers AH, Rowe BH, Barker S, Jones A, Camargo CA Jr. The effectiveness of IV beta-agonists in treating patients with acute asthma in the emergency department: a meta-analysis. Chest 2002;122:1200-7.

44. Hirsch S. Klinischer und experimenteller beitrag zur Krampflösenden wirkung der purinderivate. Klin Wochenschr 1922;1:615-8.

45. Herrmann G, Aynesworth MB. Successful treatment of persistent extreme dyspnea "status asthmaticus". Use of theophylline ethylene diamine (aminophylline, U. S. P.) intravenously. 1938. J Lab Clin Med 1990;115:512-25.

46. Brown EA. A new type of medication to be used in bronchial asthma and other allergic conditions — preliminary note. N Engl J Med 1940;223:843-46.

47. Weinberger M, Hendeles L, Bighley L. The relation of product formulation to absorption of oral theophylline. N Engl J Med 1978;299:852-7.

48. Katz RM, Rachelefsky GS, Siegel SC, Mickey R. Theophylline administration in children with asthma: optimal pulmonary function and possible tolerance to chronic administration. Ann Allergy

1983;50:23-6.

49. Siegel D, Sheppard D, Gelb A, Weinberg PF. Aminophylline increases the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. Am Rev Respir Dis 1985;132:283-6.

50. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. Arch Dis Child 1998;79:405-10.

51. Mitra A, Bassler D, Goodman K, Lasserson TJ, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Cochrane Database Syst Rev 2005;CD001276.

52. Bergstrand H. Phosphodiesterase inhibition and theophylline. Eur J Respir Dis Suppl 1980;109:37-44.

53. Miura M, Belvisi MG, Stretton CD, Yacoub MH, Barnes PJ. Role of potassium channels in bronchodilator responses in human airways. Am Rev Respir Dis 1992;146:132-6.

54. Pauwels RA, Joos GF. Characterization of the adenosine receptors in the airways. Arch Int Pharmacodyn Ther 1995;329:151-60.

55. Murciano D, Aubier M, Lecocguic Y, Pariente R. Effects of theophylline on diaphragmatic strength and fatigue in patients with chronic obstructive pulmonary disease. N Engl J Med 1984;311:349-53.

56. Jenne JW, Siever JR, Druz WS, Solano JV, Cohen SM, Sharp JT. The effect of maintenance theophylline therapy on lung work in severe chronic obstructive pulmonary disease while standing and walking. Am Rev Respir Dis 1984;130:600-5.

57. Pauwels R, Van Renterghem D, Van der Straeten M, Johannesson N, Persson CG. The effect of theophylline and enprofylline on allergen-induced bronchoconstriction. J Allergy Clin Immunol 1985;76:583-90.

58. Sullivan P, Bekir S, Jaffar Z, Page C, Jeffery P, Costello J. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. Lancet 1994;343:1006-8.

59. Kraft M, Torvik JA, Trudeau JB, Wenzel SE, Martin RJ. Theophylline: potential antiinflammatory effects in nocturnal asthma. J Allergy Clin Immunol 1996;97:1242-6.

60. Mascali JJ, Cvietusa P, Negri J, Borish L. Anti-inflammatory effects of theophylline: modulation of cytokine production. Ann Allergy Asthma Immunol 1996;77:34-8.

61. Ito K, Lim S, Caramori G, Cosio B, Chung KF, Adcock IM, Barnes PJ. A molecular mechanism of action of theophylline: Induction of histone deacetylase activity to decrease inflammatory gene expression. Proc Natl Acad Sci U S A 2002;99:8921-6.

62. Marwick JA, Wallis G, Meja K, Kuster B, Bouwmeester T, Chakravarty P, Fletcher D, Whittaker PA, Barnes PJ, Ito K, Adcock IM, Kirkham PA. Oxidative stress modulates theophylline effects on steroid responsiveness. Biochem Biophys Res Commun 2008;377:797-802.

63. Davies B, Brooks G, Devoy M. The efficacy and safety of salmeterol compared to theophylline: meta-analysis of nine controlled studies. Respir Med 1998;92:256-63.

64. Tee AK, Koh MS, Gibson PG, Lasserson TJ, Wilson AJ, Irving LB. Long-acting beta2-agonists versus theophylline for maintenance treatment of asthma. Cochrane Database Syst Rev 2007;CD001281.

65. Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. N Engl J Med 1997;337:1412-8.

66. Seddon P, Bara A, Ducharme FM, Lasserson TJ. Oral xanthines as maintenance treatment for asthma in children. Cochrane Database Syst Rev 2006;CD002885.

67. Volovitz B, Amir J, Malik H, Kauschansky A, Varsano I. Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. N Engl J Med 1993;329:1703-8.

68. Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, Nikander K, Persson T, Reinikainen K, Selroos O, Sovijärvi A, Stenius-Aarniala B, Svahn T,Tammivaara R, Laitinen LA. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med 1991;325:388-92.

69. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. The Dutch Chronic Non-specific Lung Disease Study Group. Am Rev Respir Dis 1992;146:547-54.

70. Skoner DP, Rachelefsky GS, Meltzer EO, Chervinsky P, Morris RM, Seltzer JM, Storms WW, Wood RA. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. Pediatrics 2000;105:E23.

71. Guilbert TW, Mauger DT, Allen DB, Zeiger RS, Lemanske RF Jr, Szefler SJ, Strunk RC, Bacharier LB, Covar R, Sorkness CA, Taussig LM, Martinez FD. Growth of preschool children at high risk for asthma 2 years after discontinuation of fluticasone. J Allergy Clin Immunol 2011;128:956-63.e1-7.

72. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med 2000;343:1064-9.

73. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998;339:1194-200.

74. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. Respir Med 1994;88:373-81.

75. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, Lamm CJ, O'Byrne PM. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003;361:1071-6.

76. Chen YZ, Busse WW, Pedersen S, Tan W, Lamm CJ, O'Byrne PM. Early intervention of recent onset mild persistent asthma in children aged under 11 yrs: the Steroid Treatment As Regular Therapy in early asthma (START) trial. Pediatr Allergy Immunol 2006;17 Suppl 17:7-13.

77. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. N Engl J Med 2000;343:1054-63.

78. Covar RA, Spahn JD, Murphy JR, Szefler SJ. Progression of asthma measured by lung function in the childhood asthma management

program. Am J Respir Crit Care Med 2004;170:234-41.

79. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000;162:1403-6.

80. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, Bacharier LB, Lemanske RF Jr, Strunk RC, Allen DB, Bloomberg GR, Heldt G, Krawiec M, Larsen G, Liu AH, Chinchilli VM, Sorkness CA, Taussig LM, Martinez FD. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med 2006;354:1985-97.

81. Volovitz B, Bentur L, Finkelstein Y, Mansour Y, Shalitin S, Nussinovitch M, Varsano I. Effectiveness and safety of inhaled corticosteroids in controlling acute asthma attacks in children who were treated in the emergency department: a controlled comparative study with oral prednisolone. J Allergy Clin Immunol 1998;102:605-9.

82. Levy ML, Stevenson C, Maslen T. Comparison of short courses of oral prednisolone and fluticasone propionate in the treatment of adults with acute exacerbations of asthma in primary care. Thorax 1996;51:1087-92.

83. Rodrigo G, Rodrigo C. Inhaled flunisolide for acute severe asthma. Am J Respir Crit Care Med 1998;157:698-703.

84. Schuh S, Reisman J, Alshehri M, Dupuis A, Corey M, Arseneault R, Alothman G, Tennis O, Canny G. A comparison of inhaled fluticasone and oral prednisone for children with severe acute asthma. N Engl J Med 2000;343:689-94.

85. Schuh S, Dick PT, Stephens D, Hartley M, Khaikin S, Rodrigues L, Coates AL. High-dose inhaled fluticasone does not replace oral prednisolone in children with mild to moderate acute asthma. Pediatrics 2006;118:644-50.

86. Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database Syst Rev 2003;CD002308.

87. Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, Chinchilli VM, Craig TJ, Dimango EA, Deykin A, Fagan JK, Fish JE, Ford JG, Kraft M, Lemanske RF Jr, Leone FT, Martin RJ, Mauger EA, Pesola GR, Peters SP, Rollings NJ, Szefler SJ, Wechsler ME, Israel E. Daily versus as-needed corticosteroids for mild persistent asthma. N Engl J Med 2005;352:1519-28.

88. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF Jr, Mauger DT, Strunk RC, Szefler SJ, Zeiger RS, Bacharier LB, Bade E, Covar RA, Friedman NJ, Guilbert TW, Heidarian-Raissy H, Kelly HW, Malka-Rais J, Mellon MH, Sorkness CA, Taussig L. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. Lancet 2011;377:650-7.

89. Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, Lemanske RF Jr, Strunk RC, Covar R, Szefler SJ, Boehmer S, Jackson DJ, Sorkness CA, Gern JE, Kelly HW, Friedman NJ, Mellon MH, Schatz M, Morgan WJ, Chinchilli VM, Raissy HH, Bade E, Malka-Rais J, Beigelman A, Taussig LM. Daily or intermittent budesonide in preschool children with recurrent wheezing. N Engl J Med 2011;365:1990-2001.

90. Eifan AO, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN, Barlan IB. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. Clin Exp Allergy 2010;40:922-32.

91. Ferrés J, Justicia JL, García MP, Muñoz-Tudurí M, Alvà V. Efficacy of high-dose sublingual immunotherapy in children allergic to house dust mites in real-life clinical practice. Allergol Immunopathol (Madr) 2011;39:122-7.

92. Ma XP, Muzhapaer D. Efficacy of sublingual immunotherapy in children with dust mite allergic asthma. Zhongguo Dang Dai Er Ke Za Zhi 2010;12:344-7.

93. Ippoliti F, De Santis W, Volterrani A, Lenti L, Canitano N, Lucarelli S, Frediani T. Immunomodulation during sublingual therapy in allergic children. Pediatr Allergy Immunol 2003;14:216-21.

94. Niu CK, Chen WY, Huang JL, Lue KH, Wang JY. Efficacy of sublingual immunotherapy with high-dose mite extracts in asthma: a multi-center, double-blind, randomized, and placebo-controlled study in Taiwan. Respir Med 2006;100:1374-83.

95. Lue KH, Lin YH, Sun HL, Lu KH, Hsieh JC, Chou MC. Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. Pediatr Allergy Immunol 2006;17:408-15.

96. Calamita Z, Saconato H, Pelá AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 2006;61:1162-72.

97. Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza A, Canonica GW. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. Chest 2008;133:599-609.

98. Dahl R, Stender A, Rak S. Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis. Allergy 2006;61:185-90.

99. Pham-Thi N, Scheinmann P, Fadel R, Combebias A, Andre C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. Pediatr Allergy Immunol 2007;18:47-57.

100. Hirsch T, Sähn M, Leupold W. Double-blind placebo-controlled study of sublingual immunotherapy with house dust mite extract (D.pt.) in children. Pediatr Allergy Immunol 1997;8:21-7.

101. Rienzo VD, Minelli M, Musarra A, Sambugaro R, Pecora S, Canonica WG, Passalacqua G. Post-marketing survey on the safety of sublingual immunotherapy in children below the age of 5 years. Clin Exp Allergy 2005;35:560-4.

102. Pajno GB, Caminiti L, Crisafulli G, Vita D, Valenzise M, De Luca R, Passalacqua G. Direct comparison between continuous and coseasonal regimen for sublingual immunotherapy in children with grass allergy: a randomized controlled study. Pediatr Allergy Immunol 2011;22:803-7.