

The effect of montelukast and different doses of budesonide on IgE serum levels and clinical parameters in children with newly diagnosed asthma

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Abstract

Background: Since IgE is considered to play a crucial role in allergic immune responses, the reduction of free IgE level has been an attractive target in the treatment of allergic diseases. The present study was conducted to determine the effects of a 6-month treatment with different doses of inhaled budesonide and montelukast sodium in children with newly diagnosed atopic asthma.

Methods: In this randomized, double-blind, double-dummy trial, 51 children with newly diagnosed asthma and sensitivity to house-dust mites were randomly allocated to receive budesonide (in two different doses 400 or 800 mcg) or montelukast for 6 months. The primary end point was the level of serum total and specific IgE before and after treatment. The secondary end points were clinical parameters and forced expiratory volume in 1 s (FEV1).

Results: After 6 months of treatment, a high dose of inhaled corticosteroid and montelukast, significantly decreased levels of total and specific IgE. Medium dose of inhaled corticosteroid had no effect on total and specific IgE serum level. Clinical score and FEV1 significantly improved after 6 months of treatment with medium ($P=0.002$) and high dose ($P=0.001$) of inhaled budesonide and montelukast ($P=0.002$). There were no differences between groups in changes of all clinical parameters after treatment.

Conclusion: Only high doses of inhaled corticosteroids and montelukast decreased the serum IgE levels. Perhaps long-term treatment with montelukast will be beneficial to asthma patients by decreasing IgE levels.

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1. Introduction

Asthma prevalence has been shown to be associated with increased levels of total IgE, even in subjects negative for specific IgE to common allergens [1,2]. In a survey of more than 800 patients, elevated serum IgE levels were associated with a threefold increase in bronchial hyper-responsiveness, independently of the presence of asthma symptoms or specific IgE [3]. An analysis of the demographics of 4756 patients with asthma involved in the TENOR study (a 3 year, multi-centre observational study) has shown elevated levels

of IgE, compared to non-asthmatic populations. The levels were higher in males and in current smokers, and a relationship was demonstrated between IgE and asthma severity among children [4]. Since allergic factors play a role in more than 90% of pediatric patients with asthma [5] there are advantages to treatments that may reduce IgE levels.

There is evidence that in asthmatic patients IgE levels might be affected by inhaled glucocorticosteroids [6] and a cys-LT1 receptor antagonists [7]. In previous studies we demonstrated that treatment with leukotriene antagonist, montelukast sodium significantly decreased serum level of interleukin 4 [8], essential for IgE synthesis, and that high doses of inhaled budesonide were able to reduce serum IgE in asthmatic children [9]. It encouraged us to conduct present study to determine the effects of 6 months of treatment with inhaled corticosteroid (GCS)—budesonide (in two different doses) and the leukotriene receptor

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antagonist—montelukast in children with newly diagnosed atopic asthma. We measured the level of serum IgE before and after treatment in three groups of subjects. The secondary end points were clinical parameters and forced expiratory volume in 1 s (FEV1).

2. Materials and methods

2.1. Patients

Fifty one children aged 6–18 ($SD=12.1 \pm 1.1$) with newly diagnosed asthma and sensitive to house-dust mites (*Dermatophagoides pteronyssinus* or/and *Dermatophagoides farinae*) participated in the 7-month study. We defined asthma in accordance with published criteria [10]. The diagnosis of asthma was established by typical symptoms and improvement in the prebronchodilator forced expiratory volume in 1 s (FEV1) of $\geq 15\%$ after salbutamol (200 μ g). Subjects had not received corticosteroids and anti-leukotriene therapy prior to the study. The study took place from April to October 2003, when the exposure to dust was at a constant level and all children remained in the same environment. Subjects were recruited from our Clinic Centre in Zgierz, Poland. Asthma symptoms were assessed using a questionnaire. Atopy was measured by skin prick tests and serum IgE.

2.2. Study design

A schema showing the flow of subjects through the trial is shown in Fig. 1.

This was a randomized, double-blind, double-dummy trial comparing the effect of monotherapy with budesonide

(Miflonide, Novartis, Switzerland), in different daily doses: one puff twice daily—400 or 800 μ g/day, delivered by dry powder capsules, and montelukast sodium (Singulair, MSD, Whitehouse Station, NJ, USA), 5 mg tablets in children aged 6–14 or 10 mg tablets in children over 14-years old, on serum levels of total and specific IgE and clinical parameters (score and FEV1) of asthma. A placebo only arm was not included because of ethical concerns. There were four study visits. At the first visit we enrolled subjects and put them on beta2-agonist (Ventolin, Glaxo Wellcome, London, UK) ‘as needed’ for symptomatic relief purposes. They were informed of the aim of the study and were told how to score asthma symptoms and to use the inhaler.

At the second visit the subjects were randomized according to a computer-generated allocation schedule for treatment with:

- budesonide 400 μ g/day, montelukast placebo (16 patients);
- budesonide 800 μ g/day, montelukast placebo (18 patients);
- montelukast, budesonide placebo (17 patients).

The third and fourth visits were after 3 and 6 months of treatment, respectively. Blood sampling for measurement of serum IgE and lung function testing in individual patients always took place on the same day of the week and on the same time at all visits. Salbutamol was withheld for at least 12 h before lung function testing. At each visit a short history was taken and the subject’s diary was evaluated.

2.3. Skin prick tests

Skin prick tests for common inhaled allergens (Allergopharma, Reinbek, Germany) were performed to

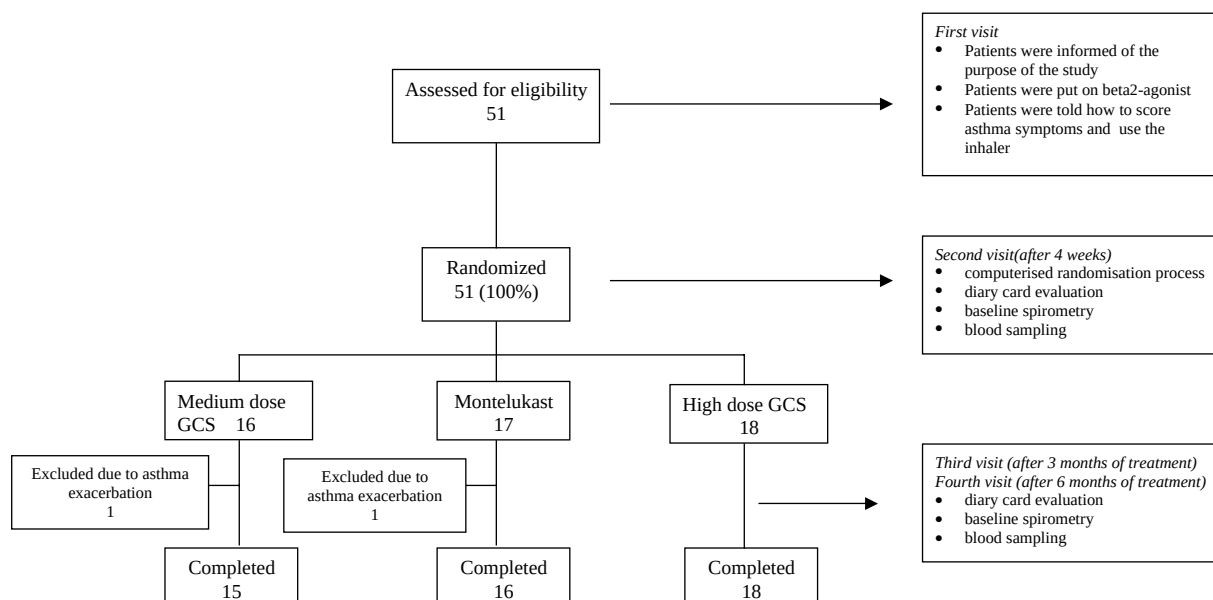


Fig. 1. Flow chart for the study.

identify the presence of atopy. A mean weal diameter ≥ 3 mm and $\geq$ the histamine control was defined as a positive response. Skin prick tests were positive against both *D. farinae* and *D. pteronyssinus* extract in all subjects. Out of the 51 subjects tested, 4 also showed positive skin prick tests to cat and two to dog. None of these 6 children had a cat or dog at home, nor did they have any clinical symptoms after contact with mentioned animals. And none of enrolled subjects was allergic to seasonal allergens: tree pollen, grass pollen, ragweed pollen, cereal pollen and molds.

2.4. Diary card

The daily diary card included daytime symptoms (completed at bedtime) and incidents of nocturnal awakening (recorded in the morning upon awakening). The scales were previously shown to have acceptable evaluative measurement properties. Additionally, the amount of as-needed beta2-agonist was recorded daily as the number of puffs. Daytime asthma symptom score and nocturnal awakenings were scored subjectively, as follows: 0, no symptoms during the day/night; 1, symptoms, but they do not affect any activities during the day/night sleep; 2, symptoms affect at least one daily activity/disturb night sleep; 3, symptoms affect two or more daily activities/disturb sleep all night or most of the night.

Use of beta2-agonists was scored: 0=none, 1=once a day, 2=two to three times a day, 3=more than three times a day. Minimum score for each day was 0 (no symptoms daytime, no symptoms at night and no use of beta2-agonists). Maximum score was 9 (severe symptoms daytime and night and more than three uses of beta2-agonists). Mean values were taken after visits two, three and four. The asthma questionnaire was based on the Pediatric Asthma Quality of Life Questionnaire and scales previously shown to have acceptable evaluative measurement properties [11,12].

2.5. Laboratory tests

Two millilitres of blood were taken from each subject at visit two, three and four. In each sample serum levels of total and specific IgE to *D. farinae* (*D. far.*) and *D. pteronyssinus* (*D. pter.*) were measured using a commercially available immunoassay technique (Pharmacia CAP; Pharmacia Biotech, Uppsala, Sweden) according to the instructions of the manufacturer.

2.6. Lung function measurements

FEV₁ was measured by a spirometer (Lungtest 1000, MES, Krakow, Poland), taking the highest of

three successive measurements. Reference values were computed according to the recommendations of American Thoracic Society standards of acceptability and reproducibility [13].

2.7. Statistical methods

The results were analysed according to well-known statistical methods by using StatSoft Statistica for Windows, release 6.0 (StatSoft, Inc., Tulsa, USA). Before analysis total and specific IgE level were transformed to the normal distribution. All parameters were analysed using a repeated measures analysis of variance (ANOVA). To determine the difference within groups Student's *t*-test was used. *P*-values > 0.05 were considered to be significant.

2.8. Ethics

The study was approved by the Medical Ethics Committee of the Medical University. All parents or guardians gave their written consent for participation in this study.

3. Results

Forty-nine subjects, 15 from the budesonide 400 mcg, 18 from the budesonide 800 mcg and 16 from the montelukast group, completed the study. Two subjects were withdrawn from the study because of asthma exacerbation (need to inhale more than six puffs of beta2-agonists per day). Characteristics of the subjects who completed the study are given in Table 1. Primary and secondary outcomes measurements before and after treatment are presented in Table 2.

At the beginning of the study, serum levels of total and specific IgE did not differ among all three groups. After 6 months of treatment, the high dose of inhaled corticosteroid and montelukast significantly decreased the levels of total and specific IgE (Figs. 2 and 3 and Table 2). The effect of treatment with the high dose of inhaled corticosteroid on total and specific IgE (*D. farinae*) was greater than effect of

Table 1
Patients baseline characteristics. Data are presented as mean and standard error mean

	Medium dose GCS N=15	High-dose GCS N=18	Montelukast N=16	P (between group)
Male (%)	60	55.6	56.3	NS
Age (years)	11.6 $\pm$ 1.4	11.6 $\pm$ 1.8	12.1 $\pm$ 1.6	NS
FEV1 (% pred.)	84.3 $\pm$ 0.5	83.4 $\pm$ 0.3	83.4 $\pm$ 0.4	NS
Total IgE (IU/ml)	344.7 $\pm$ 51.2	342.9 $\pm$ 46.0	269.6 $\pm$ 54.3	NS

Table 2

Effect of treatment with medium dose of inhaled corticosteroid (GCS) or high-dose GCS or montelukast sodium on asthma symptoms score, FEV1, total IgE level and specific *Dermatophagoides pteronyssinus* (*D. pter.*)/*Dermatophagoides farinae* (*D. far.*) IgE level

Group	Parameter	0 months		3 months		6 months		P-level (ANOVA)	
		Mean	SEM	Mean	SEM	Mean	SEM	Versus Monte-lukast	Versus high-dose GCS
Medium dose GCS	Score ^a (points)	7.0	0.3	3.4	0.2	1.9	0.2	0.12	0.09
	FEV1 (%pred.)	84.3	0.5	92.5	0.8	93.4	0.9	0.061	0.704
	Total IgE (IU/ml)	344.7	51.2	307.9	48.3	269.5	43.1	0.198	<0.001
	<i>D. pter.</i> (IU/ml)	50.8	8.1	63.5	8.4	42.8	8.0	<0.001	<0.001
	<i>D. far.</i> (IU/ml)	35.2	8.3	47.0	9.1	34.7	8.7	0.008	<0.001
High-dose GCS	Score ^a (points)	7.2	0.2	3.2	0.1	2.2	0.1	0.798	–
	FEV1 (%pred.)	83.4	0.3	91.6	0.6	93.0	0.6	0.072	–
	Total IgE (IU/ml)	342.9	46.0	188.2	27.8	127.4	18.3	0.04	–
	<i>D. pter.</i> (IU/ml)	43.0	7.0	25.9	5.1	16.8	4.5	0.481	–
	<i>D. far.</i> (IU/ml)	43.0	6.8	26.9	4.4	13.6	2.9	0.008	–
Montelukast	Score ^a (points)	7.1	0.2	3.0	0.1	1.9	0.2	–	–
	FEV1 (%pred.)	83.4	0.4	90.7	0.6	90.9	0.5	–	–
	Total IgE (IU/ml)	269.6	54.3	195.3	39.7	145.2	26.3	–	–
	<i>D. pter.</i> (IU/ml)	50.8	9.1	37.4	8.1	31.1	7.2	–	–
	<i>D. far.</i> (IU/ml)	37.3	6.8	29.5	5.9	22.6	4.5	–	–

Values are expressed as means with standard error mean (SEM).

^a Daytime, nocturnal asthma symptoms and use of β -agonists were scored as 0 (best) to 3 (worst) each.

treatment with montelukast (Table 2). The medium dose of inhaled corticosteroid had no effect on total and specific IgE level in serum after 6 months of treatment, however, we observed slight increase of specific IgE in the third month (Figs. 2 and 3).

Clinical score, significantly improved after 6 months of treatment with medium and high dose of inhaled budesonide and montelukast ($P=0.002$, $P=0.001$, $P=0.002$, respectively) followed by significant lung function improvement

after treatment in all groups ($P=0.002$, $P=0.001$, $P=0.002$, respectively). There were no differences between groups in changes of all clinical parameters after treatment (Table 2).

4. Discussion

Since IgE is considered to play a crucial role in the allergic immune responses the reduction of free IgE levels is

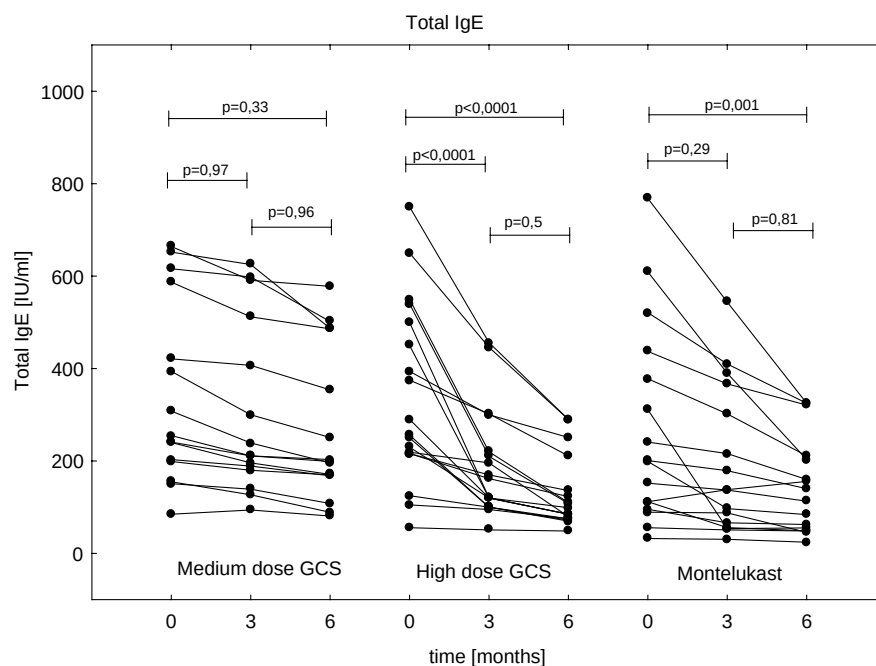


Fig. 2. Total serum IgE level (IU/ml) before (0 months) and after 3 and 6 months of treatment with medium dose of inhaled corticosteroid (GCS)—left panel, high-dose GCS—middle panel or montelukast sodium—right panel.

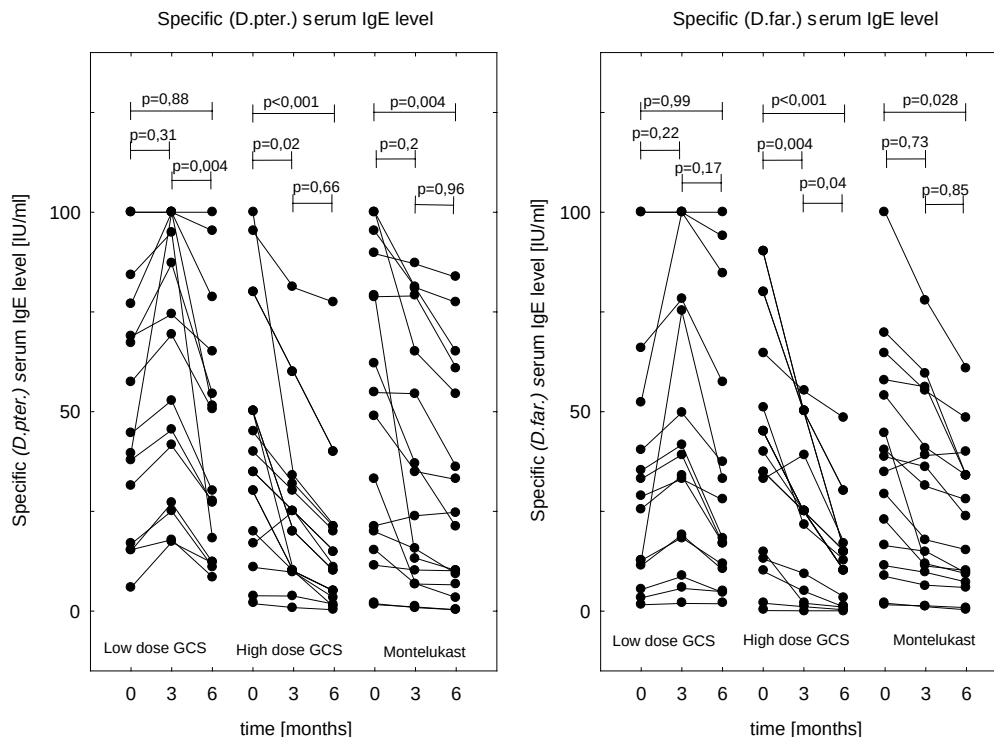


Fig. 3. Specific *Dermatophagoides pteronyssinus* (*D. pter.*) (left figure) and specific *Dermatophagoides farinae* (*D. far.*) (right figure) serum IgE level (IU/ml) before (0 months) and after 3 and 6 months of treatment with medium dose of inhaled corticosteroid (GCS)—left panel or high-dose GCS—middle panel or montelukast sodium—right panel.

a rational target in the treatment of allergic diseases [14]. In our study a significant decrease of serum levels of IgE was observed after treatment with montelukast and the high daily dose of budesonide, while the medium dose of budesonide had no influence on IgE. Since there is no placebo arm we cannot be sure to what extent the declines in IgE could relate to environmental effects and be unrelated to the treatment, but the behaviour of the medium dose GCS and the fact that all children were not allergic to seasonal allergens suggest that the changes in IgE are most likely treatment related. Our results compare favourably with those revealed by Ohru et al., where 3 months treatment with inhaled beclomethasone dipropionate (800 mcg/day) in adult asthmatics significantly decreased total serum IgE levels and specific IgE antibodies to house-dust mite and cedar; decreases in total serum IgE significantly correlated with an improvement in asthma symptom scores [6]. Nong et al., examined 77 children suffering from moderate to severe asthma who were treated with 100 mcg per day of fluticasone propionate or 200 mcg per day of beclomethasone dipropionate and noted no influence on serum IgE levels [15]. Those results are in accordance with our observations that the relatively low dose of inhaled corticosteroids causes no change in serum IgE.

There are some inconsistent data published in the 1970s and 1980s regarding the effect of systemic administration of corticosteroids on IgE. Johansson suggested that systemic corticosteroids had no effect on the serum level of IgE [16]

whereas other authors reported that systemic administration of corticosteroids decreased serum IgE in atopic children [17]. In the 1990s Jabara et al., contrary to expectations, revealed that hydrocortisone might enhance IgE production by inducing IgE isotype switching in human B cells [18]. Recent evidence in a mouse model has shown that treatment with weekly budesonide encapsulated in stealth liposomes and treatment with daily budesonide significantly lowered the total serum IgE level and was effective in decreasing lung inflammation, lowering eosinophil peroxidase activity and peripheral blood eosinophils in experimental asthma [19]. These results suggest that the route of administration, doses of corticosteroids and period of treatment may alter the effects of corticosteroids on serum levels of immunoglobulin E. We cannot be sure if the decrease of IgE in our study is a systemic steroid effect or a local effect on mucosal IgE production. We feel that this is systemic effect and it should be similar to other steroids although it should be checked in similar studies.

After 3 months of treatment with medium dose of budesonide we observed a slight increase of specific IgE. The reason for the transient increase of the level of specific IgE in this group remains uncertain. That phenomenon is similar to observations of Settupane et al., who showed that systemic administration of corticosteroids initially increased serum IgE levels during the first 2 weeks of treatment followed by the subsequent inhibition of serum IgE [20].

Unfortunately, there have been only few data on the effect of antileukotriene agents on inflammatory mediators. Tohda et al., showed in an in vitro study that pranlukast acts directly on peripheral blood mononuclear cells and can dose-dependently suppress the production of IL-4, IL-5 and GM-CSF in patients with bronchial asthma [21]. The findings of our previous trial in asthmatic children revealed that montelukast significantly reduced the serum concentration of ECP and the blood eosinophil count followed by a significant decrease in the serum levels of IL-4 and ICAM-1 [8]. So far, there is only sparse information available on the effects of anti-leukotriene agents on serum levels of immunoglobulin E. Wu et al., determined the effect of a 3-day course of high-dose montelukast (25 mg/kg) on mediators of airway inflammation induced by a single allergen challenge in ovalbumin-sensitized mice [22]. IL-4 levels in the lung and BAL, and IL-13 levels in the lung significantly decreased after treatment with montelukast. Serum IgE level and lung VCAM-1 expression were significantly lower in treated animals as well as significant reduction was found in IL-5 in the BAL, lung and the serum, and IL-5 mRNA expression in the lung. They suggest that montelukast inhibited the serum total IgE as a result of the reduction in IL-4. The investigators hypothesized a novel mechanism of montelukast's action on anti-inflammatory response in children with allergic asthma. Gagro et al., in a 6-week study with asthmatic children receiving an oral leukotriene receptor antagonist suggested that a decreased percentage of CD11b CD4+ T cells might lead to down-regulation of IgE synthesis in their interaction with CD23-expressing B cells [7]. We can only speculate that the decrease of IgE may have resulted from IL-4 modulation by this leukotriene receptor antagonist.

Our study has shown significant improvement in clinical parameters—clinical score and FEV₁—after treatment with budesonide (both doses) as well as with montelukast in children with asthma. Surprisingly, no significant difference was found between treatment groups. The mean baseline FEV₁ was relatively high which indicates that our patients have not yet experienced significant pulmonary deterioration connected with asthma duration. Malmstrom et al., remarked that some patients experience large increases in FEV₁ in response to treatment with beclomethasone or montelukast, whereas other patients experience small improvements [23].

It is well known that corticosteroids are effective in increasing lung function, reducing bronchial hyper-responsiveness, preventing exacerbations and hospitalization in asthmatic children [24,25] and in reducing airway inflammation [26,27]. Montelukast is a leukotriene receptor antagonist that improves asthmatic inflammation and prevents bronchoconstriction [28,29]. Also we have expected that allocated treatment will provide clinical control for our asthmatic patients.

Pivotal to the pathophysiology of allergic diseases is allergen binding to IgE on the surface of effector cells,

which causes the release of proinflammatory mediators [30]. IgE inhibition represents a therapy which seems to improve IgE-mediated allergic reactions and reduce the severity of asthma [31]. Topical glucocorticosteroids have beneficial effect on local IgE production [32–34]. This action may help us to understand the comparable clinical efficacy of all three treatments. Unfortunately we did not examine mucosal IgE production because our patients are children. However, we speculate that there may be advantages to treatments that reduce IgE levels, either through effects on mucosal or systemic synthesis, since allergic factors play a role in more than 90% of cases of childhood asthma.

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