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Oral immunotherapy in cow's milk allergic patients: course and long-term outcome according to asthma status

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ABSTRACT

Background: Patients with asthma and food allergy comprise a high-risk group for life-threatening reactions at accidental exposure.

Objective: To examine the course and long-term outcome of patients with asthma completing milk oral immunotherapy.

Methods: Children at least 6 years old with ($n = 101$) and without ($n = 93$) asthma and IgE-mediated cow's milk allergy, undergoing milk oral immunotherapy from April 2010 to December 2011, were compared. Milk dose escalations were performed until patients reached full (>7.2 g of milk protein) or partial desensitization. Skin prick tests in all patients and spirometry in those with asthma were performed. Patients who completed treatment were followed for longer than 6 months.

Results: Before immunotherapy, patients with asthma, regardless of severity, had more anaphylactic reactions (84.2% vs 64.5%, $P = .003$), emergency department visits (68.3% vs 51.6%, $P = .02$), and hospital admissions (32.7% vs 18.3%, $P = .03$) compared with patients without asthma. Patients with asthma, regardless of severity, had more reactions and injectable epinephrine use during induction ($P = .004$) and home treatments ($P = .007$) of immunotherapy. Moderate to severe asthma was associated with a lower likelihood of reaching full desensitization (51.5% vs 68.8%, $P = .019$), but most patients with asthma (87 of 101, 86.1%), regardless of severity, reached a dose likely to protect them against accidental exposure. Most patients with asthma continued to consume milk protein freely after completion of immunotherapy. Although adverse reactions were still observed, severe reactions appeared to subside with time.

Conclusion: Patients with asthma are at risk for more severe reactions and are less likely to reach full desensitization during food oral immunotherapy. However, most reach limited daily consumption and most who achieve full desensitization continue to consume milk protein freely after treatment.

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Introduction

Food allergy is a major health problem with an increasing prevalence (range 1–2% to $>10\%$), depending on the location and the diagnostic methods used.¹ Prevalence and major allergenic food products vary geographically. Peanuts and tree nuts are the major allergenic foods in children in the United States,² Australia,³ and Great Britain,⁴ whereas shellfish is more frequent in adults. Cow's milk has been most frequently incriminated as the offending food in children in Israel⁵ and as the most common cause of fatal food anaphylaxis in the United Kingdom.⁶ Although most patients

allergic to cow's milk outgrow their allergy during the first years of life, some remain allergic into adulthood.^{7–9}

The standard of care for patients with food allergy is strict avoidance of the offending food and the administration of injectable epinephrine in case of anaphylactic reaction.¹⁰ However, accidental exposures attributed to unintentional ingestion, label-reading errors, and cross-contact still occur, and severe and even fatal reactions can result from underuse of epinephrine owing to fear, lack of availability, or misperception of the reaction severity.¹¹ Patients with asthma form a unique subgroup among children and adults with food allergy, with increased risk for more severe reactions and even death. For example, in 1 study examining emergency department visits because of food-related allergic reactions, symptoms from the lower airways occurred more frequently in children with anaphylaxis who had asthma compared with children without underlying asthma.¹² Coexisting asthma was

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associated with increased severity of food-related reactions, including fatalities, compared with other types of allergic reactions in a study from the United Kingdom.¹³ In another study, children with asthma reported more severe reactions at accidental exposure to allergenic food than did those without asthma. Moreover, the level of asthma control did not seem to be associated with the severity of allergic reactions reported.¹⁴ Taken together, these studies suggest that a child with food allergy and asthma is at higher risk for severe food-related reactions.

In recent years, several reports have emerged on the use of milk oral immunotherapy (MOIT) demonstrating efficacy and safety in most, but not all, patients, even those with severe cow's milk protein (CMP)-induced reactions.^{15,16} MOIT also might reverse IgE-mediated cow's milk allergy associated decreased bone mineral density.^{17–20} However, data on the course and long-term outcome of patients with asthma during food oral immunotherapy are limited. In a recent study by Vázquez-Ortiz et al,²¹ patients with asthma had more frequent and persistent reactions during MOIT, but data on controller therapy and lung function were lacking. Unfortunately, in many cases, the small number of participants or the exclusion of high-risk patients, including those with severe asthma, does not enable the specific examination of the course and outcome of MOIT in patients with asthma.^{16,20,22–25} Given their increased risk for fatal reactions at accidental exposures, it is of paramount importance to examine the course of MOIT in patients with asthma to decide whether to exclude them from such programs. MOIT was initiated at Assaf Harofeh Medical Center (Zerifin, Israel) on April 2010.¹⁸ This report describes the results of MOIT in all patients older than 6 years with and without asthma who began treatment from April 2010 through December 2011.

Methods

This study is based on an open-label treatment program enrolling patients with persistent IgE-mediated cow's milk allergy. IgE-mediated allergy to CMP was diagnosed by a positive skin prick test reaction and/or specific serum IgE, together with a positive open oral food challenge, as recommended.²⁶ An oral food challenge was not performed when there was a clinical history of anaphylactic reaction after accidental ingestion in the past year. Skin prick tests to CMP (ALK-Abello, Port Washington, New York) were performed on the volar surface of the forearm and read after 20 minutes. Patients who did not tolerate 10 mg of CMP at the first induction or had a medical contraindication to receive epinephrine and patients unable to adhere to protocol were excluded. Informed parental (for patients <18 years old) or patient (for patients ≥18 years old) consent was obtained from all participants. In general, patients older than 4 years old were enrolled in the program. For this study, a retrospective chart review of all patients older than 6 years who enrolled in MOIT from April 2010 through December 31, 2011, with or without physician-diagnosed asthma, was performed. This age limit was chosen to allow a more accurate diagnosis of asthma and for the ability to perform pulmonary function tests. Patients who were at least 6 months old after completion of the program were contacted by email and/or phone and asked about their current daily consumption of CMP and adverse reactions.

The protocol was approved by the Israeli Ministry of Health, and Helsinki committee approval for the publication of patient data was obtained. No informed consent was required.

Milk OIT Protocol

Preparation of CMP doses and the individualized dose escalation protocol were performed as previously described.¹⁸ Briefly, a maximal individualized tolerated dose, defined as the amount of CMP safely consumed, was determined during an initial 4-day induction-and-desensitization phase. All CMP doses lower than

90 mg were prepared from a stock of powdered formulas of Materna Mehadrin Stage 3 (Maternal Industries, Maabaroth, Israel) reconstituted to 45 mg/mL of CMP with sterile water. For doses of at least 90 mg of CMP, 3% fat milk (30 mg/mL of CMP) was used.¹⁸ Then, the maximal individualized tolerated dose was consumed twice daily at home for 24 days. The 4-day cycle was repeated 2 more times with dose escalations up to 4-fold. Additional 1-day sessions, with dose increases of up to 50%, were performed monthly with the goal of reaching full (7,200 mg) milk protein consumption. For patients unable to reach full CMP consumption, the goal was to reach partial consumption (≥180–<7,200 mg of CMP), at a dose higher than the reported lowest threshold dose (180 mg) of CMP eliciting a reaction. Treatment was considered a failure when patients were unable to reach full or partial CMP consumption. Anticipatory home treatment guidance to patients and parents was given as previously described.¹⁸ No dose increases were allowed at home. Daily email reports were required from all participants to verify dosage compliance and to record adverse reactions or treatments required during the home therapy phase. Patients were instructed to use injectable epinephrine (Epi-Pen; Mylan, Canonsburg, Pennsylvania) in a liberal fashion in case of a reaction. A staff physician was on call at all times for consultation. Reactions, including skin rash or flushing, abdominal pain with or without vomiting, rhinoconjunctivitis, cough or wheeze, stridor, or hypotension, were monitored. Each patient received 2 up-to-date Epi-Pens, antihistamines, and a powered nebulizer for the administration of bronchodilators and/or nebulized epinephrine. Patients who completed the program were instructed to consume a daily dose of at least 4,500 mg of CMP under the same restrictions as during OIT. All patients were encouraged to consume additional CMP-containing products freely.

Table 1

Comparison of patients with and without asthma^a

Parameters	Asthma (n = 101)	No asthma (n = 93)	P value
Before OIT			
Age (mo)	129.3 ± 54.8	118.2 ± 42.9	.34
Boys	66 (65.3)	54 (58.1)	.31
Cow's milk wheal size (mm)	8.3 ± 2.9	7.1 ± 2.8	.002
Other food allergies	22 (21.8)	8 (8.6)	.016
Anaphylaxis	85 (84.2)	60 (64.5)	.003
Epinephrine	50 (49.5)	34 (36.6)	.09
Emergency department visit	69 (68.3)	48 (51.6)	.02
Hospital admission	33 (32.7)	17 (18.3)	.03
During MOIT			
MOIT—induction			
Starting dose (mg)	231 ± 547	665 ± 1,378	<.001
Doses ^b	44.6 ± 10.8	43.8 ± 11.9	.73
Reactions ^b	3.3 ± 1.8	2.6 ± 1.9	.004
Treatments ^b	2.7 ± 1.6	1.8 ± 1.4	<.0001
Epinephrine treatments ^b	1.1 ± 1.2	0.4 ± 0.7	<.0001
Epinephrine	62 (61.4)	32 (34.4)	<.0001
MOIT—home			
Doses ^b	282 ± 182	305 ± 302	.42
Reactions ^b	6.7 ± 9.8	3.4 ± 5.2	.007
Treatments ^b	4.6 ± 7.6	2.2 ± 4.2	.002
Epinephrine ^b	0.4 ± 0.8	0.1 ± 0.5	<.0001
Epinephrine	26 (25.7)	4 (4.3)	<.0001
MOIT—outcome			
Length of treatment (d)	231 ± 156	214 ± 199	.1
Current dose (mg)	3,952 ± 3,344	5,167 ± 3,072	.02
Reached partial desensitization^c			
Patients	87 (86.1)	82 (88.2)	.83
Dose (mg)	781 (180–2,400)	1,165 (210–5,400)	.26
Reached full desensitization	52 (51.5)	64 (68.8)	.019

Abbreviations: MOIT, milk oral immunotherapy; OIT, oral immunotherapy.

^aData are presented as number (percentage), mean ± SD, or median (range).

^bMean number of episodes per patient.

^cAchieved at least 180 to 7,200 mg of cow's milk protein.

Table 2Adverse reactions during long-term follow-up in patients with and without asthma^a

	Symptoms					Current disposition	
	Total ^b	Cutaneous	Respiratory	GI	Epi-Pen treated	Free consumption	Stopped OIT
Asthma (n = 49)	28 (57.1)	16 (32.6)	20 (40.8)	4 (8.2)	6 (12.2)	42 (85.7)	7 (14.2)
No asthma (n = 63)	33 (52.3)	22 (34.9)	18 (28.6)	4 (6.3)	3 (4.8)	57 (90.5)	6 (9.5)

Abbreviations: GI, gastrointestinal; OIT, oral immunotherapy.

^aData are presented as number (percentage).^bTotal number of patients who had reactions after OIT.

Asthma Classification

All patients with physician-diagnosed asthma were asked about symptom frequency and severity, including hospitalizations and treatments during the previous year. All patients underwent spirometry (Minispir, Rome, Italy; MIR) with or without a bronchodilator on their first day and subsequently as needed. Airway obstruction and bronchodilator responsiveness were defined according to American Thoracic Society criteria.²⁷ Patients' asthma was stabilized for 2 to 3 weeks before initiation of MOIT. Controller therapy was initiated at the beginning of the protocol or at any time during treatment at the discretion of a staff physician and based on National Heart, Lung, and Blood Institute guidelines.^{27,28}

Statistics

Statistical analyses were performed using SPSS 16 (SPSS, Inc, Chicago, Illinois). Comparisons were made between patients older than 6 years with and without physician-diagnosed asthma. Continuous variables were abnormally distributed and were analyzed using the Mann-Whitney test when 2 groups were compared and the Kruskal-Wallis test when more than 2 groups were compared. The Fisher exact test was used to analyze differences in categorical variables. All analyses were 2-tailed and a *P* value less than .05 was considered significant.

Results

Characteristics of Patients before Initiation of MOIT

A total of 280 patients underwent MOIT during the study period. Of those, 194 patients were older than 6 years at initiation of the program and were included in the study. Asthma was diagnosed by a physician in 101 patients. Forty-five patients with asthma were treated only as needed before initiating MOIT, and 21 of them began daily controller therapy at the time of initiation or later during the course of MOIT owing to persistent asthma symptoms. An additional 56 patients were receiving various forms of asthma daily controller therapy (montelukast, inhaled corticosteroids, or combination therapy) before the initiation of MOIT. The remaining 93 patients who were older than 6 years when starting MOIT and who did not have physician-diagnosed asthma served as controls. Patients' characteristics are listed in Table 1. Patients with asthma were more atopic as evidenced by an increased rate of house dust mite sensitivity (*P* = .004), a slightly larger CMP wheal size at skin prick testing (*P* = .002), and a higher frequency of sensitization to other foods, especially nuts, eggs, and sesame (*P* = .016). Patients with asthma had more severe reactions (ie, anaphylactic reactions; *P* = .003), emergency department visits (*P* = .02), and hospital admissions (*P* = .03) induced by random exposure to CMP. Before the initiation of MOIT, lung functions were within normal range in most patients with asthma (Table 2). Airflow obstruction was found in 7 patients and 6 of them had significant bronchodilator responsiveness. One additional patient had normal baseline spirometric results with significant improvement after using a bronchodilator.

Frequency of Adverse Events and Efficacy of OIT in Patients with Asthma

Patients with asthma could not tolerate as high a starting dose during the first-week threshold-determining oral food challenge (*P* < .01). This was not related to asthma exacerbations (eTable 1). During OIT, patients with asthma had more reactions (unrelated to their asthma control) during induction (*P* = .004) and home treatments (*P* = .007) and required more injectable epinephrine (eTable 1) compared with those without asthma. Overall, 52 patients with asthma (51.5%) achieved full desensitization and an additional 35 achieved partial desensitization. Thus, 87 of 101 patients (86.1%) with asthma reached a dose considered protective against accidental exposure,²⁹ whereas treatment failed in 14 patients (they were unable to reach ≥180 mg of CMP consumption) and they discontinued OIT. Asthma was controlled in all patients with asthma during OIT and reasons for failed treatment included anaphylactic and non-anaphylactic (abdominal pain not related to a dose) reactions and psychological difficulties. Significantly fewer patients with asthma compared with those without asthma reached full desensitization (*P* = .019; eTable 1).

Severity of Asthma and Clinical Course during OIT

Patients with asthma were classified into 3 groups based on the use of controller therapy before and during OIT. In group 1, patients did not require controller therapy before and during MOIT (*n* = 24); in group 2, patients initiated controller therapy at the onset or during the course of MOIT (*n* = 21); and in group 3, patients required controller therapy before and during MOIT (*n* = 56; Table 2). Asthma controller therapy was augmented in 19 patients (34%) in group 3 during the course of MOIT. House dust mite allergy was more frequent in patients in group 3 compared with those in group 1 (*P* = .004). These patients also were more sensitized to other foods, although the difference was not statistically significant. There was no significant difference in the frequency of pre-MOIT severe reactions at random exposure to CMP among the 3 groups, as reflected in their

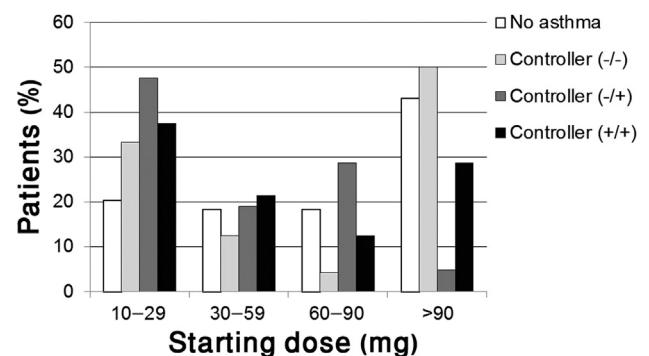


Figure 1. Amount of cow's milk protein safely consumed at the beginning of the program is shown for patients with various asthma severities (as detailed in Methods) and for patients without asthma.

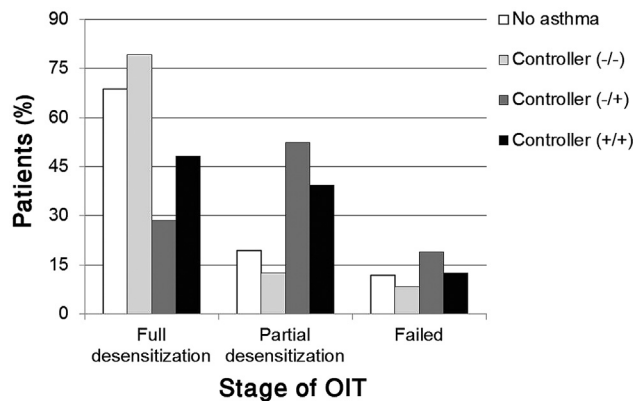


Figure 2. Percentage of patients with various asthma severities (as detailed in Methods) and patients without asthma who achieved partial (≥ 180 mg) or full (7,200 mg) cow's milk protein consumption during oral immunotherapy.

anaphylactic reactions, emergency department visits, and use of epinephrine, although patients in group 3 were admitted more frequently than those in group 1 ($P = .006$). Patients in whom controller therapy was initiated at the onset or during MOIT (group 2; Table 2) had a significantly lower ratio of forced expiration volume in 1 second to forced vital capacity before MOIT, reflective of airflow obstruction, particularly compared with those who received controller therapy before and during MOIT (group 3; $P = .003$).

The mean starting dose of group 2 (controller therapy initiated at onset or during MOIT) was lower compared with the other 2 groups but not statistically significantly different. Significantly fewer patients in group 2 compared with group 1 (controller not required before and during MOIT) were able to tolerate higher than 90 mg of CMP at the beginning of treatment ($P = .001$; Fig 1). There also were no significant differences among the 3 groups in the frequency of severe reactions requiring treatment or of the use of epinephrine during the course of the induction phase and home treatments of OIT (Table 2). Despite the similar course, the outcome of the 3 different asthma groups differed. The final dose of CMP reached by patients in groups 2 and 3 (controller therapy required before and during MOIT) were lower compared with group 1 ($P = .001$ and $.009$, respectively) and significantly fewer patients in groups 2 and 3 reached full desensitization ($P = .001$ and $.013$, respectively) by the end of the treatment (Fig 2). Nonetheless, more than 80% of patients in groups 2 and 3 reached a dose (180 mg) likely to protect against accidental exposure. Of those, 17 patients (10 with asthma and 7 without asthma) reached a dose higher than 1,000 mg of CMP. Combining all patients who required controller

therapy during OIT (groups 2 and 3) into 1 group and comparing them with patients not requiring controller therapy did not significantly change the results.

Long-term Follow-up of Patients with and without Asthma

Of the 116 patients in the study who reached full desensitization, 112 patients (49 of 51 with asthma and 63 of 65 without asthma) were followed for a median duration of 28.6 months (range 9–41 months). After completion of treatment, 23 of 49 patients with asthma (57.1%) and 33 of 63 patients without asthma (52.4%) had reactions to CMP, which were usually mild (Table 2). Thirteen patients (11.6%) discontinued OIT, some because of repeated reactions and some because of non-adherence. Overall, 42 patients (85.7%) with and 57 patients (90.5%) without asthma were consuming dairy products freely at time of follow-up. Epinephrine-treated reactions were observed in 6 patients (12.2%) with asthma and 3 patients (4.8%) without asthma. Two of these patients, 1 in each group, discontinued OIT owing to gradual re-sensitization and repeated reactions. Of the other 7 patients, only 1 required epinephrine again during the last year of long-term follow-up after completion of OIT. The description of patients requiring epinephrine after completion of OIT is presented in Table 3. The main presumed underlying reasons for reactions treated with epinephrine were exercise and viral infection. Interestingly, most of these patients did not require epinephrine during the course of OIT.

Discussion

To the authors' knowledge, this is the first study to specifically examine the course and outcome of OIT to CMP in patients with asthma. Patients with asthma had more severe reactions during the course of treatment and were less likely to reach full desensitization. However, despite the more difficult course, most patients with asthma managed to reach a dose that would likely protect them from subsequent accidental exposures. Most patients with asthma who reached full desensitization were consuming dairy products freely several months after completion of treatment. Although severe reactions requiring epinephrine were still observed, in most cases they subsided with time. Baseline asthma severity does not seem to affect the risk of severe reactions at random exposure and during the course of MOIT, but patients with intermittent asthma have a more favorable outcome.

Several studies have reported that asthma is associated with greater sensitivity to CMP⁸ and is a risk factor for persistence of IgE-mediated milk allergy.^{9,30} More importantly, asthma has been found to be a risk factor for fatal food reactions, which might not be reversed even with a timely administration of injectable epinephrine, in patients with food allergies.^{12–14,31,32} In the present study, asthma also was associated with increased atopy, and patients with asthma had more severe reactions to accidental CMP exposure compared with those without asthma before MOIT. The high frequency of anaphylactic reactions ($>80\%$) in these patients emphasizes the limited efficacy of the elimination diet in patients with cow's milk allergy in general and specifically in those with asthma and the significant risk these patients are at.

The data on safety and efficacy of OIT in patients with asthma are limited. In 1 study, patients with food allergy and asthma were found to have a higher reaction rate during OIT to milk.²¹ However, asthma did not affect the resolution of reactions over time in that study.²¹ Suboptimally controlled asthma also was associated with home adverse reactions during peanut OIT in another study.³³ However, the relatively small number of patients enrolled in most studies, the lack of pulmonary function tests, and the lack of data regarding the use of controller therapy make it difficult to draw firm conclusions and make subgroup analysis impossible.^{16,17,21–23,34,35} In the present study, patients with asthma

Table 3
Patients receiving injectable epinephrine after completion of OIT

Patient	Starting Dose (mg)	Asthma	Epinephrine during OIT	Epinephrine after OIT			Current CMP consumption
				Time Induced by (mo)	During past 12 mo		
1	45	no	yes	5	menstrual period	NR	no
2	90	no	no	19	exercise	no	yes
3	45	no	no	26	exercise	no	yes
4	30	yes	no	?	?	no	yes
5	22.5	yes	yes	12	unknown	yes	yes
6	90	yes	no	17	unknown	NR	no
7	10	yes	yes	6	exercise/viral	no	yes
8	960	yes	no	12	viral infection	no	yes
9	45	yes	no	21	viral infection	no	yes

Abbreviations: CMP, cow's milk protein; NR, not relevant; OIT, oral immunotherapy.

tolerated a significantly lower dose of CMP at initiation of MOIT and had significantly more reactions and more severe reactions requiring epinephrine during induction and home treatment. The lower tolerated starting dose could have affected the course of MOIT in these patients, as the authors and other researchers have shown.^{18,21} The high rate of injectable epinephrine required by these patients could be accounted for by the fact that even patients with severe asthma were included and by the authors' instructions to these patients to liberally use injectable epinephrine in case of a reaction. Nonetheless, nearly all patients with asthma achieved a dose that would likely protect them against accidental exposure.²⁹

This large series of patients also enabled the authors to categorize patients into subgroups based on the need for controller therapy. Two main findings emerge from this analysis. The first is that the risk for adverse reactions at accidental exposure and during OIT is independent of asthma severity. This means that even patients considered to have mild asthma, who do not require daily controller therapy, are at a significant risk for severe reactions at accidental exposure. Patients and physicians should be aware of this higher risk. In addition, OIT programs should take into account that patients with even mild asthma are at increased risk for severe reactions during OIT. The second finding is that asthma severity affects the outcome of OIT. Significantly more patients with intermittent asthma achieved full desensitization at the end of OIT and maintained a state of desensitization months later while consuming CMP daily.

The authors were able to examine the long-term effect of OIT in these patients. They found that most patients who had successfully completed OIT continued to consume dairy products. Although many patients continued to have reactions, those were usually infrequent and mild. Nine patients (8%) were treated with epinephrine but that was used in some cases for relatively mild, non-life-threatening reactions, with no need for emergency department visits. Further, epinephrine use did not lead to cessation of treatment and was not required subsequently in most patients, suggesting that severe reactions become less frequent with time.

It could be argued that in some patients the milk allergy would have spontaneously resolved even without treatment. However, given that more than 98% of these patients had a positive challenge result to milk immediately before or during the first 2 days of treatment and that all patients were older than 4 years at time of initiation of OIT, an age when spontaneous recovery is less likely,^{7,8} the authors believe it is safe to say that the vast majority of them would have remained allergic without OIT.

In summary, despite the higher reaction rate these patients showed during therapy, it is encouraging that half the patients with asthma achieved full desensitization, and most achieved a dose that would likely protect them against unintentional exposures. Given the higher risk of anaphylactic reactions in patients with asthma at random unintentional exposures, these patients should not be excluded from consideration for MOIT.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.12.006>.

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eTable 1Comparison of parameters in patients with asthma and with and without controller therapy^a

Parameters	Group 1 (n = 24)	Group 2 (n = 21)	Group 3 (n = 56)	P value		
				1 vs 2	1 vs 3	2 vs 3
Controller therapy before MOIT	–	–	+			
Controller therapy during MOIT	–	+	+			
Before MOIT						
Age (mo)	130.7 ± 48	127.4 ± 51.4	129.4 ± 59.4	NS	NS	NS
Boys	75	61.9	62.5	NS	NS	NS
CMP wheal size (mm)	7.4 ± 2.6	9.3 ± 3	8.4 ± 2.9	NS	NS	NS
Other food allergies	16.7	4.8	30.4	NS	NS	NS
Pre-BD FEV ₁ (predicted)	97.5 ± 10	96.2 ± 11.2	96.5 ± 11.7	NS	NS	NS
Pre-BD FVC (predicted)	102.5 ± 14.1	106.3 ± 13.8	98.9 ± 12.8	NS	NS	NS
Pre-BD FEV ₁ /FVC (%)	83.7 ± 8.5	79.2 ± 7.1	86.1 ± 7.8	NS	NS	.003
Anaphylaxis	79.2	90.5	83.9	NS	NS	NS
Epinephrine	43.5	52.4	51.8	NS	NS	NS
ED visits	58.3	81	67.9	NS	NS	NS
Hospital admissions	12.5	23.8	44.6	NS	.006	NS
During MOIT						
MOIT—induction						
Starting dose (mg)	344 ± 496	86 ± 202	238 ± 644	NS	NS	NS
Doses ^b	45 ± 14	45 ± 11	44 ± 9	NS	NS	NS
Reactions ^b	2.8 ± 1.7	4 ± 1.8	3.2 ± 1.7	.013	NS	NS
Treatments ^b	2.2 ± 1.6	3.2 ± 1.5	2.6 ± 1.6	NS	NS	NS
Epinephrine ^b	0.8 ± 0.7	1.3 ± 1.2	1.1 ± 1.3	NS	NS	NS
Epinephrine	62.5	66.7	58.9	NS	NS	NS
MOIT—home						
Doses ^b	253 ± 192	307 ± 191	284 ± 177	NS	NS	NS
Reactions ^b	4.7 ± 7	8.2 ± 11.1	7 ± 10.3	NS	NS	NS
Treatments ^b	2.3 ± 3.5	7.2 ± 10.7	4.7 ± 7.4	NS	NS	NS
Epinephrine ^b	0.2 ± 0.5	0.4 ± 0.9	0.4 ± 0.8	NS	NS	NS
Epinephrine	16.7	28.6	28.6	NS	NS	NS
MOIT—outcome						
Treatment length (d)	237 ± 177	219 ± 118	232 ± 161	NS	NS	NS
Current dose (mg)	5,842 ± 2,718	2,467 ± 3,113	3,699 ± 3,354	.001	.009	NS
Reached full desensitization	79.2	28.6	48.2	.001	.013	NS
Reached ≥180 mg CMP	95.87	81.9	83.9	NS	NS	NS

Abbreviations: CMP, cow's milk protein; ED, emergency department; FEV₁, forced expiration volume in 1 second; FVC, forced vital capacity; MOIT, milk oral immunotherapy; NS, not significant; Pre-BD, before use of bronchodilator.

^aData are presented as percentage or mean ± SD. *P* < .016 after Bonferroni correction was considered significant for categorical variables.

^bMean number of episodes per patient.