Original Article

Risk Factors and Treatment Outcomes for Oral Immunotherapy–Induced Gastrointestinal Symptoms and Eosinophilic Responses (OITIGER)

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What is already known about this topic? Recurrent non–IgE-mediated gastrointestinal symptoms occur during the course of oral immunotherapy.

What does this article add to our knowledge? These non–IgE-mediated gastrointestinal symptoms may be reversible or transient in most patients with dose modification. Their occurrence is related to oral immunotherapy starting dose, its rate of increase, and baseline absolute eosinophil count.

How does this study impact current management guidelines? Risk stratification based on baseline blood absolute eosinophil count may identify patients who would benefit from a slower oral immunotherapy dosing regimen and decrease the occurrence of oral immunotherapy–induced gastrointestinal and eosinophilic responses.

BACKGROUND: We recently described that oral immunotherapy (OIT)-induced gastrointestinal symptoms were associated with peripheral eosinophilic responses (termed OITIGER).
OBJECTIVE: To identify treatment outcomes after dose modification and risk factors for developing OITIGER.
METHODS: Treatment modifications in patients with OITIGER (n = 65) including cumulative dose reductions or treatment suspension were individualized and based on the severity of symptoms and an associated absolute eosinophil count (AEC, eosinophils/μL) of more than 900. Multivariate analysis for risk factors associated with OITIGER was performed in milk-OIT subjects.
RESULTS: Treatment modifications reduced the cumulative daily dosage load by a median of 50% (interquartile range, 50%-67%) in 43 of 65 (66.1%) patients, deferred dose increases in 2 of 65 (3.1%) patients, or temporarily suspended treatment in 18 of 65 (27.7%) patients. Two patients (3.1%) had no treatment intervention. Symptoms and eosinophilia abated on dosage modification, allowing for resumption of dose increases (n = 34) or reinitiation of treatment (n = 9) after a median of 29 (interquartile range, 20-56) and 19 (interquartile range, 17-44) days, respectively. OITIGER reoccurred during treatment in 10 of 54 (18.5%) patients, which resolved after further dose modification. In long-term follow-up (>3-26 months), 31 of 32 patients were asymptomatic with stable AECs. Patients with OITIGER had a higher OIT failure rate ($P = .004$) and were less likely to reach full desensitization ($P < .001$), as compared with asymptomatic patients (n = 684). Multivariate analysis identified several risk factors for OITIGER: starting dose more than 120 mg ($P < .001$; odds ratio, 7.14), second-month dose more than 4-fold over the starting dose ($P = .037$; odds ratio, 2.18), and baseline AEC more than 600/μL ($P = .002$; odds ratio, 3.2).
CONCLUSIONS: OITIGER is transient or reversible in most subjects, and its occurrence is related to OIT starting dose, its rate of increase, and baseline AECs. **(J Allergy Clin Immunol Pract 2019;■:■-■)**

Key words: *Oral immunotherapy; Eosinophilic esophagitis; Cow's milk allergy*

INTRODUCTION

Oral immunotherapy (OIT) is an emerging therapy being investigated as an alternate treatment to strict food avoidance for patients with IgE-mediated food allergies. One of the most concerning issues leading to the debate as to its widespread use as a treatment program are the adverse events during the home-treatment phase. These can be divided into IgE-mediated and non–IgE-mediated reactions. IgE-mediated reactions requiring epinephrine may occur in up to 15% of patients,[1] whereas less severe reactions may occur more frequently.[2-4] In long-term

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Abbreviations used
EoE- Eosinophilic esophagitis
IQR- Interquartile range
OIT- Oral immunotherapy
OITIGER- Oral immunotherapy—induced gastrointestinal and eosinophilic responses

follow-up studies of milk-OIT, the frequency of reactions was reported to decrease over time.[5] Non—IgE-mediated reactions may be harder to clearly define because symptoms resembling the clinical presentation of pediatric eosinophilic esophagitis (EoE)[6] such as abdominal pain and vomiting overlap with gastrointestinal IgE-mediated adverse events. The overall prevalence of EoE after the initiation of OIT varies widely from a low of 2.7%[7] to a report that up to 30% of patients in OIT experience gastrointestinal symptoms that resemble EoE.[8] Nevertheless, most patients do not have a biopsy performed, limiting confirmation of the diagnosis and calling into question the true incidence.

We recently reported on patients experiencing non-IgE gastrointestinal symptoms during OIT.[9] By restricting the criteria to multiple episodes (≥3 different days per month) of abdominal pain or vomiting unrelated temporally to dosage administration, we were able to separate these adverse events from the IgE-mediated reactions. In almost all these patients, a significant increase in their peripheral blood eosinophil count occurred with the onset of symptoms, and a decrease in their peripheral blood eosinophil count was noted when symptoms subsided. We termed these gastrointestinal symptoms during OIT as OIT-induced gastrointestinal and eosinophilic responses (OITIGER).[9] Recently, OIT has been recognized as a factor that can contribute to the development of EoE,[10] consistent with our previous report that in 3 patients with OITIGER in whom esophageal biopsies were performed, increased esophageal eosinophil counts were observed.[9] It is still possible however that patients consenting for biopsy represent a select group because of the severity of their symptoms.

There was reluctance to continue or reintroduce treatment in these patients because of the risk of reemergence of symptoms and long-term consequences.[11] Our early observations however were that after cessation of OIT treatment, symptoms resolved[1] and peripheral blood eosinophilia reversed toward baseline.[9] Furthermore, the overwhelming majority of patients with OITIGER who resumed OIT treatment did not redevelop symptoms,[9] a finding consistent with that in a smaller OIT study in milk-OIT[12] and recently confirmed in a large retrospective long-term follow-up study of peanut-OIT.[13] The use of this large cohort (794 total number of patients of which 65 met the criteria of OITIGER) allowed comparisons between treatment interventions and clinical outcomes. Herein, we describe the treatment modifications, clinical outcomes in those resuming treatment, and the risk factors associated with OITIGER during OIT treatment.

METHODS

OIT program

An open-label OIT program at a single hospital center (Shamir Medical Center, formerly Assaf Harofeh Medical Center, Israel) has been previously described.[1] Briefly, patients older than 4 years with evidence of IgE-mediated food allergy by either a positive skin prick test result and/or specific serum IgE and evidence of a recent clinical reaction by a positive oral food challenge or clinical history of a reaction after accidental ingestion in the past year were enrolled. A total of 794 patients (614 milk-OIT, 130 peanut-OIT, 41 egg-OIT, and 9 sesame-OIT) enrolled from April 2010 until October 2015, at which time the data were analyzed. Informed parental (for patients <18 years) or patient (for patients ≥18 years) treatment consent was obtained from all participants. Helsinki committee approval for the publication of patient data was obtained.

Patients followed an individualized dose escalation treatment protocol, which consisted in the first round of a 4-day induction to determine the maximal tolerated starting dose.[1] This dose, which was a dose below the eliciting dose on challenge, was then consumed twice daily at home for 24 days. In approximately the first one-third of patients, the dose increase for the subsequent rounds was up to the maximum dose tolerated below the eliciting dose. When it was appreciated that symptoms may be related to the dosage administered, dose escalations were limited to 4-fold (second round), 3-fold (third round), and 2-fold (fourth and fifth rounds) increases over the previous round, respectively. Starting from the sixth round, the maximum monthly dose escalation was 50% from the previous dose. Patients returned to increase the maximum dose tolerated for home therapy every 28 days. Successful outcomes were defined by consumption without adverse reactions of a protein dose goal of 7,200, 3,000, 12,000, and more than 4,000 mg for the milk-, peanut-, egg-, and sesame-OIT programs, respectively. After a month of therapy at the goal dose, patients were instructed to decrease to 4,500, 1,200, 6,000, and 3,000 mg for the milk-, peanut-, egg-, and sesame-OIT programs, respectively. Partial desensitization was defined as being able to tolerate a daily dose greater than 180, 300, and 240 mg protein for milk, peanut, and sesame, respectively. Anticipatory home-treatment guidance to patients and parents was given. No dose increases were allowed at home. Patients were asked to report daily, either by email or by using an online web-based program, whether they tolerated their daily dose(s).[14] In cases of abdominal complaints, if not explicitly stated, patients were queried regarding the timing of symptoms to dose administration. Peripheral absolute eosinophil counts (AEC, eosinophils/μL) were obtained before treatment, and patients/caregivers instructed to measure AEC before each visit, as well as when gastrointestinal symptoms that were not related to the timing of the administration of the dose occurred.

Treatment approach

The approach to the symptomatic patient was individualized and based on the severity of symptoms and an associated AEC, which was more than 900 eosinophils/μL of blood surrounding the occurrence of symptoms. Treatment modifications included decreasing the cumulative dose administered or suspending OIT until the symptoms subsided and eosinophil counts returned toward baseline. In 2 asymptomatic patients in whom the AEC increased to more than 2,500 eosinophils/μL during OIT, dosing was immediately reduced as in symptomatic patients. In both cases, the AEC reduced more than 100% within 2 months after the dosage change. Because their clinical response may have been affected by their dosing change, these 2 patients were excluded from subsequent analyses. In 1 patient with a 3.5-fold increase in AEC (from 220 to 760), symptoms were severe enough that the physician instructed a dose adjustment. Decreases in the cumulative dose ingested relative to the protocol were achieved by either keeping the monthly increase on hold or by decreasing from twice-a-day to once-a-day dosing and/or reducing the dose. In cases in which the food advancement

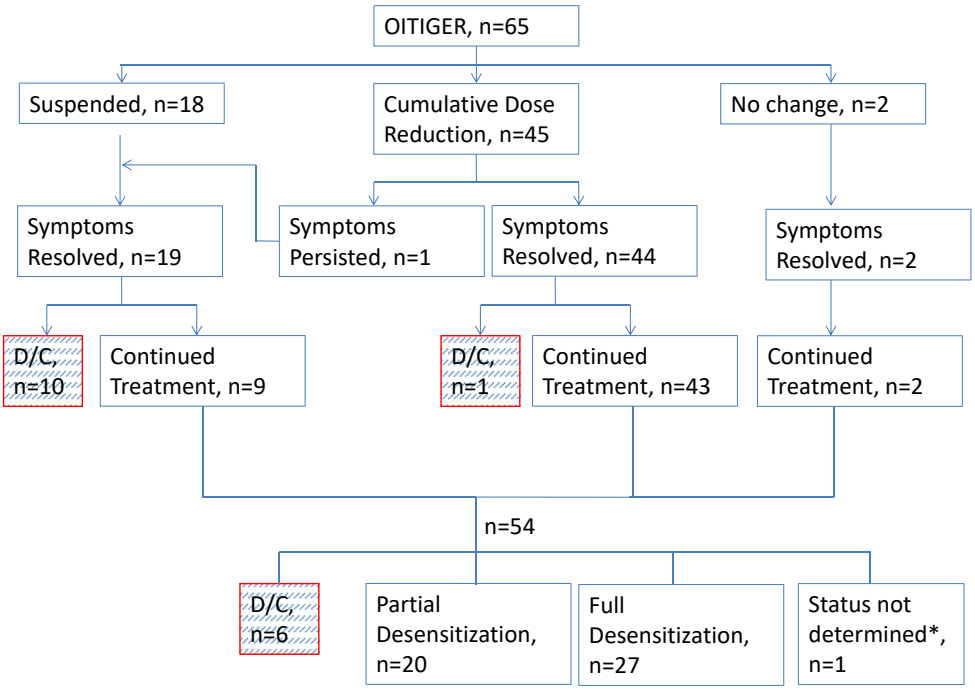

FIGURE 1. Consort flow diagram. Flow diagram of treatment interventions and clinical outcomes in patients with OITIGER. *D/C*, Discontinuation of treatment. Fourteen of 17 patients discontinued treatment because of symptoms, whereas 3 of 17 patients were noncompliant to the treatment protocol. *Status not determined because the patient is still in the escalation phase.

was slowed, monthly increases resumed after complete resolution of symptoms and eosinophils normalized to baseline. In 2 patients with OITIGER with AEC between 900 and 2,500 eosinophils/μL, dosage reduction was not implemented. No treatments with proton pump inhibitors or H1- or H2-receptor antagonists were given to patients.

Statistical analyses

Statistical analyses were performed using SPSS software version 16 (SPSS, Inc, Chicago, Ill). Categorical variables were analyzed using the Fisher exact test and are presented as percentages. Continuous variables were analyzed by *t* test if normally distributed or Mann-Whitney test if abnormally distributed. ANOVA was used to analyze the difference between the means. A *P* value of less than .05 was considered significant.

RESULTS

Treatment interventions

Sixty-five (n = 55, milk-OIT; n = 9, peanut-OIT; n = 1, egg-OIT) of 794 OIT participants met the criteria of OITIGER.[1] Treatment interventions with the goal to eliminate symptoms and decrease the eosinophilia were achieved by reducing the cumulative dose received relative to the prescribed protocol in 45 of 65 (69.2%) patients (Figure 1). In 18 of 65 (27.7%) patients, treatment was suspended. In 1 more patient, the treatment was suspended after symptoms persisted despite the cumulative dose reduction (Figure 1). No changes were implemented to the prescribed OIT treatment in 2 patients (Figure 1).

In all patients, symptoms completely resolved after treatment interventions and the AEC returned toward baseline. Among the 19 patients in whom the treatment was suspended, 9 restarted OIT after a median duration of 19 days (interquartile range [IQR], 17-44 days). An oral food challenge was performed before continuation of OIT treatment to determine their new current tolerated dose.

Treatment by cumulative dose reduction included several categories. In 43 of 45 of these patients, the cumulative dosage was decreased by a median of 50% (IQR, 50%-66.7%), whereas in 2 of 45 patients, dose increases were suspended for 2 and 3 months, respectively. As above, 1 of these patients required treatment suspension to resolve symptoms. An additional patient, after symptoms resolved, refused to take the dose, leaving 43 patients from this group continuing treatment. For 34 of 43 of these patients, dose increases were restarted after a median of 29 days (IQR, 20-56 days). Among these, 12 of 34 (35%) received twice-a-day dosing and 22 of 34 (65%) received a dose once a day. In 9 of 43 patients, including 1 who developed OITIGER at the fully desensitized dose, after consultations between physicians and patients/caregivers, the decision was made to remain at the reduced dose and increases were not restarted for the remainder of OIT.

Clinical outcomes in patients with OITIGER

The clinical outcome of patients with OITIGER during OIT, as compared with the asymptomatic group, is depicted in Figure 2. Patients with OITIGER had a poorer outcome and were less likely to reach full desensitization ($P < .001$) and had a higher OIT failure rate ($P = .005$) (Figure 2). Nevertheless, approximately 73% of patients with OITIGER were able to achieve at least a partial desensitization that may protect against incidental exposures. Among the 17 patients who stopped treatment, 14 stopped because of symptoms, whereas in

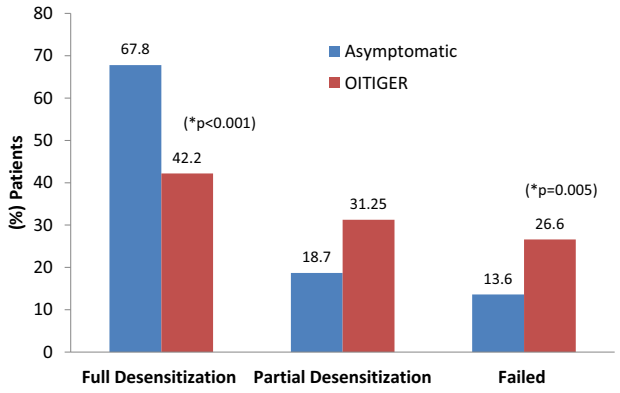

FIGURE 2. OIT treatment clinical outcomes of patients with OITIGER vs asymptomatic patients. Treatment outcomes for asymptomatic patients (n = 684) vs patients with OITIGER (n = 64). Significant differences noted between the patient groups in terms of the percent reaching full desensitization ($P < .001$) and failing ($P = .005$). A total of 43 asymptomatic patients and 1 patient with OITIGER still in the escalation phase were excluded.

3 patients it was not related to symptoms and patients were noncompliant. The duration of treatment for those reaching full desensitization was significantly longer in patients with OITIGER than in the asymptomatic group (median, 295 [IQR, 190.5-472.5] vs median, 229 [92.75-357], respectively; $P = .014$). In general, patients requiring complete suspension of treatment fared poorer relative to those in whom the dose was lowered, likely reflecting the severity of their disease (52.6% vs 16.3% failing, for suspended vs slowed group, respectively; $P = .003$).

Of the 54 patients continuing OIT after resolution of their symptoms, 27 (50.0%) reached full desensitization, 20 (37.0%) reached partial desensitization, and 6 (11.1%) discontinued treatment. In the latter, in 4 patients the symptoms returned. In the other 2 patients, stoppage was unrelated to symptoms: one who stopped before tonsillectomy and 1 with psychological issues with the treatment. The status of 1 patient is not determined because the patient is in the escalation phase. After resolution of symptoms, OITIGER reoccurred in 10 of 54 (18.5%) patients but in 5 of these cases full desensitization was achieved, and in another, partial desensitization, after further modification.

In long-term follow-up after treatment resumption (>3 months to 26 months), the AEC of patients with OITIGER returned toward baseline (Figure 3, *A*). An additional patient after initial recovery from OITIGER redeveloped nausea, abdominal pain, and vomiting, and concurrently the AEC progressively increased to more than 9,000 eosinophils/μL (data not shown). No complaints of dysphagia were noted. The treatment was discontinued, which led to a return of the AEC to 1,600 eosinophils/μL and a subsiding of the patient's symptoms. Although there was an increase in the AEC from baseline after the introduction of allergen in the asymptomatic group (measured in patients whose updosing lasted at least 7 months), the AEC then remained stable throughout OIT treatment (Figure 3, *B*). In contrast, as a group, the AEC of patients with OITIGER steadily increased in the first 90 days of treatment (Figure 3, *B*).

We next examined for factors contributing to treatment failure in patients with OITIGER as compared with patients with OITIGER who continued therapy and reached a partial or full desensitization. No significant differences were noted in the age, sex, asthma status, starting dose, fold increase in dosing, and epinephrine treatment during induction (Table I). Patients who failed treatment were more likely to be treated for milk as compared with peanut ($P < .015$) (Figure 4). All reported gastrointestinal symptoms (nausea, abdominal pain, or vomiting) were increased in the treatment failure groups, though differences were not statistically significant (Table I). The treatment failure group did not have an increase in baseline eosinophils or an increase in eosinophil number versus those who reached full or partial desensitization. In contrast, the failure and partial desensitization groups had a significantly higher frequency of epinephrine treatments at home ($P < .035$; Figure 4), suggesting that failure in these patients is additionally related to the higher frequency of anaphylactic-type reactions. Consistent with this, during milk-OIT, patients with OITIGER receiving epinephrine at home (n = 10) had a median starting dose of 22.5 mg (IQR, 16.9-56.3 mg), which was lower than that for patients with OITIGER who did not receive epinephrine at home ($P = .012$). This latter group (n = 45) had a median starting dose of 75 mg (IQR, 22.5-480 mg).

Risk factors for OITIGER

We evaluated the risk factors for the development of OITIGER, specifically in milk-OIT because this group constituted most patients and each food group required a different minimal dosage to enter OIT (>12 mg for milk vs >1 mg for peanut and egg). In univariate analysis, in addition to the differences in baseline and maximum-AEC reached (data not shown), patients who developed OITIGER during the first month of milk-OIT (n = 18) had a significantly higher median starting dose than those who were asymptomatic (480 mg [IQR, 45-960] vs 45 mg [22-120], respectively; $P < .001$) (Table II). Furthermore, patients who developed OITIGER during rounds 2 to 7 and presented with clinical signs of vomiting (n = 27) had a significantly greater escalation in dosing from their starting dose to round 2, as compared with asymptomatic milk-OIT patients (median, 4.0 [IQR, 3.0-4.4] vs median, 4.0 [2.7-4.1], fold increase, respectively; $P = .027$) (Table II). Using multivariate analysis, a starting dose of more than 120 mg of milk protein was associated with the development of OITIGER in the first treatment round ($P < .001$), with an odds ratio of 7.14 (95% CI, 2.4-21.3) (Table II). In addition, a dose increase after a month of treatment of greater than 4-fold over the starting dose increased the risk of reactions ($P = .037$; odds ratio, 2.18; 95% CI, 1.05-4.52). Finally, a baseline AEC of more than 600 was associated with OITIGER development ($P = .002$; odds ratio, 3.2; 95% CI, 1.50-6.6).

DISCUSSION

This is the largest cohort of patients in which the treatment modifications, clinical outcomes, and risk factors have been described for these recurrent non−IgE-mediated gastrointestinal symptoms during an individualized OIT regimen. We previously reported that these reactions, consisting of abdominal pain and vomiting, were not infrequent, occurring in approximately 8% of treated patients,[9] whereas others reported up to 13.7% during peanut-OIT.[13] Although patients with OITIGER undergoing

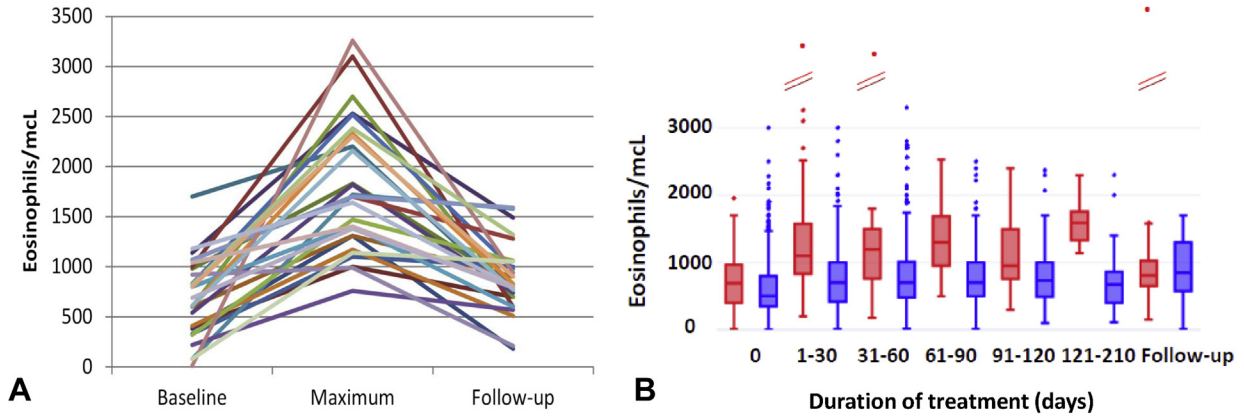

FIGURE 3. Blood eosinophil levels during OIT. (**A**) AEC of patients at baseline, maximum count, and after resumption of treatment from 3 to 26 months. Data for all 3 points were available for 31 patients. In 55 of 65 patients, peripheral eosinophilia coincided with symptoms. In 10 of 65 patients, the maximum AEC was the count taken before the onset of clinical symptoms. (**B**) Boxplots and outliers (*dots*) in OITIGER (red) and asymptomatic (blue) groups undergoing OIT. Differences in AEC between the OITIGER and asymptomatic groups were significant at baseline ($P < .05$) and at each assessed interval ($P < .001$), except at follow-up. N values for OITIGER/asymptomatic groups were 59/506, 47/403, 42/383, 39/287, 27/209, 8/92, and 32/21 for baseline, and treatment intervals (days) 1 to 30, 31 to 60, 61 to 90, 91 to 120, 121 to 210, and follow-up, respectively. AEC of outliers above hash marks in the OITIGER group at intervals 1 to 30, 31 to 60, and follow-up were 6400, 5620, and 9010, respectively.

TABLE I. Comparison of patients with OITIGER who failed vs those who reached full or partial desensitization

Parameter	Criterion	Failed (n = 17)	Full desensitization (n = 27)	Partial desensitization (n = 20)	*P* value
Demographic characteristics	Sex: male (%)	65	59	65	NS
	Age (mo)	91 ± 51	84 ± 37	88 ± 38	NS
	Asthma (%)	58.8	51.8	45	NS
OIT	Starting dose (mg)	352 ± 672	303 ± 411	131 ± 239	NS
Symptoms (%)	Nausea	37.5	33.3	20.0	NS
	Abdominal pain	81.2	70.4	70.0	NS
	Vomiting	82.4	66.7	70.0	NS
	Food impaction	0	0	0	NS
Eosinophils/μL (AEC)	Baseline	669 ± 296	698 ± 460	747 ± 297	NS
	Maximum	1989 ± 1559	1725 ± 642	1574 ± 516	NS
	Postintervention	791 ± 461	890 ± 360	745 ± 379	NS

NS, Not significant.
Categorical variables are presented as (%). Continuous variables are presented as mean ± SD.

our regular OIT protocol were more likely to fail as compared with an allergen-matched asymptomatic group, after interventions by either suspending or reducing their cumulative allergen load, half achieved full desensitization and more than two-thirds reached a partial desensitization. These findings are particularly important, because in the past OIT patients with OITIGER would be considered treatment failures and OIT discontinued. Given the demonstration that most of these patients can be treated using a slower dosing regimen, one can speculate that not only IgE-mediated responses but also the eosinophil-driven pathway can be modulated in these patients. Although the mechanism of desensitization during OIT for IgE-mediated responses is not completely understood, increases in IgG_4 and decreases in basophil reactivity are implicated.[15-17] Of interest, in mouse models of EoE, a heightened thymic stromal lymphopoietin-basophil pathway[18] was reported.

Importantly, both the gastrointestinal symptoms and elevated blood eosinophil counts were reversible on modification of treatment. The treatment regimen did not include the use of proton pump inhibitors, as reported by others.[13] Treatment aimed to reduce the allergen load by either stopping the daily dose or by decreasing it from the daily administration of twice to once per day. After symptoms subsided, the escalating monthly doses were continued albeit at a slower pace. In more than 80% of patients in whom dosage escalation was resumed, symptoms did not reoccur. In the 10 cases in which it did, it was amenable to a second round of interventions in 6 of them. This contrasts to the general view that elimination must be continued to maintain symptom-free periods and histologic remission in patients with EoE.[19]

Although IgE itself is unlikely to play a role in the pathogenesis of EoE-type disease, the elevated frequency of OITIGER in these patients should not come as a surprise because the atopic phenotype is one of the predisposing mechanisms for EoE (for review, see O'Shea et al[10]). For example, using genome-wide association studies, significant associations between childhood food allergy and loci for atopic dermatitis and EoE were identified,[20] and it was

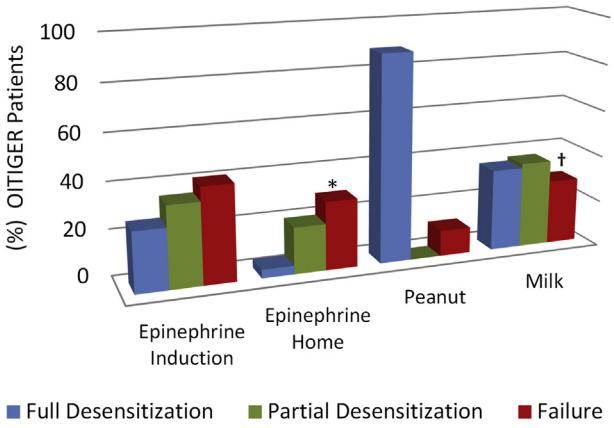

FIGURE 4. Treatment outcomes of patients with OITIGER. The % of patients with OITIGER reaching full desensitization, partial desensitization, or failure is depicted. *$P = .035$ for comparison of use of epinephrine at home in those who were fully desensitized vs the failure and partially desensitized combined groups. †$P = .015$ for comparison of treatment outcome failures for milk (27.8%) and peanut patients (11.1%).

TABLE II. Univariate and logistic regression analysis during milk-OIT

Univariate analysis

Parameter	Asymptomatic	OITIGER	*P* value
Dosing			
Starting dose (mg), median (IQR)*	45 (22-120)	480 (45-960)*	<.001
Fold increase in dose,† median (IQR)	4.0 (2.7-4.1)	4.0 (3.0-4.4)	.027

Logistic regression

Variable	Asymptomatic vs OITIGER, medians	OR (95% CI)	*P* value
Starting dose > 120 mg	30 vs 600	7.14 (2.4-21.3)	<.001
Fold change >4	3.3 vs 4.2	2.18 (1.05-4.52)	.037
Baseline AEC >600	390 vs 750	3.2 (1.5-6.6)	.002

OR, odds ratio.
AEC, eosinophils/μL blood.
*Comparison of the starting doses of asymptomatic patients (n = 469) and patients with OITIGER, who developed symptoms during the first round of milk-OIT (n = 18).
†(Round 2 dose/round 1 starting dose) in patient groups. Asymptomatic patients (n = 469) were compared with patients with OITIGER, who developed vomiting symptoms (n = 27), in rounds 2 to 7 during milk-OIT.

found that patients with EoE have higher rates of asthma[21] and food allergy.[22] On a cellular level, IL-5, IL-13, and type 2 cytokines all play central roles in EoE (for review, see Lucendo[23]). Interestingly, an increase in IgG_4 has been associated with pediatric EoE,[24] and OIT-induced desensitization is similarly associated with an increase in IgG_4.[15-17] It is therefore difficult to distinguish whether patients with OITIGER before OIT had a preexisting condition of subclinical EoE that was exacerbated by the initiation of treatment. Support for this notion is that in both peanut-allergic[25] and milk-allergic patients[26] baseline gastrointestinal eosinophilia was noted before the onset of OIT treatment. Alternatively, one cannot rule out that *de novo* induction by the introduction of allergen initiates the disease.[22] Decreasing the cell-mediated IL-4 and IL-13 axis during desensitization, for example, may lead to a reactive increase in the IL-5–mediated pathway, resulting in the increased blood AEC. A precedent for this hypothesis is the observation that after dupilumab treatment, which inhibits IL-4 and IL-13 from binding to their shared alpha component of their receptors, an increase, albeit transient, in the AEC was noted.[27] Esophageal biopsy before the initiation of treatment would provide important information regarding this question, but patients are reluctant to provide consent for baseline biopsies. Our finding that these patients have a heightened eosinophil-driven axis suggests minimally that they are predisposed to such phenomena. However, the fact that more than 80% of patients who continued treatment did not redevelop disease suggests that dose adjustment appears to modify this effect. One important limitation to the above is that 17 subjects in the OITIGER group discontinued treatment, and 14 of them did so because of symptoms. Thus, it is unclear whether symptoms would be reversible on dose modification in the latter subjects. A pivotal area of research, therefore, would be to differentiate those subjects who will progress to EoE from those who will eventually have resolution of symptoms.

A greater proportion of milk-OIT patients as compared with peanut-OIT patients were represented among patients with OITIGER who failed OIT. This result, however, may be a consequence of a poorer outcome due to IgE-mediated disease in general for milk-OIT[1] as compared with peanut-OIT.[28] Consistent with this view, patients with OITIGER who failed or were able to reach only partial desensitization required a significant increase in epinephrine treatments during home therapy, suggesting failure due to IgE-mediated symptoms. Thus, both IgE-mediated and eosinophil-mediated responses may be heightened in these individuals.

Our risk factor analysis suggests that the risk of developing disease may be related to the amount of allergen exposure in an individual prone to heightened eosinophil responses. Thus, it is likely that during OIT at least 2 predisposing factors are implicated for the development of OITIGER: (1) higher peripheral blood eosinophilia at baseline and (2) rate of escalation of OIT dosing. Our OIT program individualizes initial dosing on the basis of each patient's IgE-mediated sensitivity to their respective allergens, which, in the context of developing OITIGER, may be provocative in susceptible individuals. Our data would suggest that in high-risk cases, identified by the AEC, a slower dosing regimen and/or a limited starting dose may be beneficial in decreasing the risk of developing OITIGER and in increasing the number of successful OIT outcomes.

There are several limitations to this study. First, as described in the Methods section, on appreciation that symptoms may be related to the dosage administered, dose escalations were limited in each round. This change in protocol may have unintentionally created separate cohorts, having an impact on the results in terms of the number of subjects experiencing OITIGER. Second, the treatment program used for this study differs significantly from other research protocols. Thus, the applicability of the risk factors identified in this study to other protocols requires investigation. Specifically, dosing in the build-up phase is determined by each individual reaction dose threshold,[1] unlike other studies in which a fixed build-up schedule is predetermined.[29] Third, 17 patients discontinued treatment in our study. Thus, although symptoms resolved in all 17 patients, we have not demonstrated

that they would be able to restart OIT in this subgroup. Fourth, in 15% of patients, the maximum AEC was the count taken before the onset of clinical symptoms, although the onset of clinical symptoms may lag behind the increase in peripheral eosinophilia. Finally, because the modifications and/or cessation of dosing led to improvement in symptoms, patients and/or their parents were reluctant to undergo gastrointestinal endoscopies. Endoscopies at baseline, during symptoms, and on recovery are required to fully characterize this disease entity and response to treatment. Biopsies that have been presented to date may represent a select group that provided consent for endoscopy because of the severity of their symptoms.

CONCLUSIONS

The development of OITIGER during an individualized OIT treatment program can be treated in most subjects with modification of the cumulative dose received and treatment resumed when symptoms subside. Our data would suggest that in high-risk individuals, identified by their peripheral blood eosinophil count, a slower OIT dosing regimen may be beneficial for decreasing the risk of developing OITIGER.

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