



Letter

Life-threatening anaphylaxis to egg and milk oral immunotherapy in asthmatic teenagers

Oral immunotherapy (OIT) is a promising treatment for food allergy. However, life-threatening reactions to doses during OIT are a significant concern. We aimed to characterize patients who required admission to the intensive care unit (ICU) at our hospital for life-threatening anaphylaxis while undergoing OIT to cow's milk (CM) or egg.

Since 2006, 130 children 5 to 18 years old had undergone OIT within our department as standard treatment (80 to CM,¹ 50 to egg²) using OIT protocols from the Spanish Society of Pediatric Allergy, as previously described.^{1,2} Briefly, OIT induction took place during a 48-hour admission in the hospital, during which doses were doubled hourly (from 0.3 to 75 mg of CM protein for CM OIT; from 0.08 to 33 mg of raw egg white protein for egg OIT). Afterward, patients had their last tolerated dose once daily at home. Weekly increases, up to 6 g of CM protein or 2.5 g of raw egg white protein, were given in an outpatient setting for 16 weeks. This final dose was given daily in the maintenance phase. Uncontrolled asthma according to the Global Initiative for Asthma (GINA) guideline was an exclusion criterion for starting OIT. Patients and their families were provided with emergency medication, including epinephrine auto-injectors, antihistamines, steroids, and salbutamol.^{1,2} The OIT protocol was approved by the hospital ethics committee and written informed consent was obtained from parents and adolescents at inclusion.

In this series, 34.6% of patients (45 out of 130) were on steps 3 to 4 of asthma treatment and 10% were adolescents (9 boys and 4 girls, 13–18 years old). Twenty-two children required intramuscular epinephrine for anaphylaxis to OIT doses (60 injections).

Three cases with life-threatening anaphylaxis to OIT were identified. All 3 were teenagers with asthma receiving treatment according to GINA steps 3 to 4.

Case 1, a 15-year-old boy, was 17 months into CM OIT (maintenance phase). He developed immediate dyspnea and dizziness after his 6-g dose of CM protein, which rapidly progressed to hypotension, unconsciousness, and respiratory arrest. Generalized erythema was noted at this time. He required immediate intubation and ventilation by emergency medics and received 2 doses of intramuscular epinephrine (0.5 mg each). He was subsequently admitted to the ICU for invasive ventilation (28 hours) with intravenous salbutamol, steroids, magnesium, and ketamine. His underlying asthma had been poorly controlled for 9 months, with a need for salbutamol 2 to 3 times per week. His compliance with preventer medication and medical visits was poor. He had recently started smoking. In the week before the reaction, he had experienced an acute exacerbation requiring daily salbutamol but had not sought medical review. His compliance with the OIT protocol was

suboptimal (refusing daily doses owing to a dislike of milk and the need to remain at home for observation). In addition, the reaction might have been exacerbated by fasting and mild exercise (walking).

Case 2, a 14-year-old boy, experienced vomiting, urticaria, severe bronchoconstriction, and hypotension with decreased consciousness and hypoxemia immediately after taking 3.5 g of CM protein at home, 5 months into OIT (induction phase). Despite timely administration of his epinephrine auto-injector by his father, he required 2 further doses (0.3 mg each), volume expansion, inotropes, intravenous salbutamol, steroids, and invasive ventilation for 48 hours. Of note, during the previous 3 days, he had deceived his parents and skipped his OIT doses (100 mL of milk [3 g of CM protein]). He disliked milk, so his parents gave him 100 mL of custard (Danet; Danone SA, Barcelona, Spain) with a higher CM protein content (3.5 g/100 mL). This resulted in a 0.5-g increase in dose. He had persistent asthma, which became partly controlled since commencing OIT, with suboptimal compliance with medication. He also had experienced anaphylaxis after a dose increase 4 weeks previously, which resolved with 0.3 mg of intramuscular epinephrine and salbutamol; his OIT was decreased by 50% at that stage and subsequent increases were performed every 2 weeks, according to the protocol.¹

Case 3, a 13-year-old boy, developed severe bronchoconstriction and hypotension with hypoxemia and dizziness followed by generalized urticaria 1 hour after his weekly dose increase (1.8 g) in month 4 of egg OIT (induction phase). Immediate treatment was administered: 3 consecutive doses of intramuscular epinephrine (0.3 mg each), nebulized salbutamol, intravenous hydroxyzine, and intravenous saline. He required noninvasive ventilation in the ICU for 8 hours. Fasting and mild exercise (walking) might have acted as cofactors. In addition, he recognized that he had noticed dyspnea for 10 minutes without warning his parents or the staff before his reaction progressed. He had persistent asthma (partly controlled with daily budesonide, formoterol, and montelukast).

Additional patients' characteristics, causes, and circumstances for these life-threatening reactions are presented in Table 1. All patients recovered from their reaction. None had required previous ICU admission from asthma or food-induced anaphylaxis.

All 3 patients described shared common features: teenage years, persistent asthma with suboptimal control, high milk- or egg-specific IgE levels, and risk-taking behaviors, including poor compliance to OIT and/or to asthma management plans. One case of a life-threatening reaction to OIT published to date shared several of these characteristics.³

Asthma, especially poorly controlled asthma, is the factor most commonly associated with fatal and near-fatal anaphylactic reactions to foods.^{4,5} We defined uncontrolled asthma as an

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Table 1
Patients' characteristics, causes, and circumstances of life-threatening reactions to OIT

Patients' characteristics, causes, and circumstances	Case 1	Case 2	Case 3
Age (y)	15	14	13
Sex	Male	Male	Male
Food involved	Cow's milk	Cow's milk	Raw egg white
Eliciting dose (g protein)	6	3.5	1.8
Dose increase coinciding with reaction	No	Yes	Yes
OIT stage	Maintenance phase (17th month)	Induction phase (5th month)	Induction phase (4th month)
Previous need for epinephrine during OIT	Yes	Yes	No
Last OIT-related reaction	Abdominal pain 3 wk previously	Anaphylaxis on dose increase 4 wk previously	Vomiting + abdominal pain 8 wk previously
Reaction type at challenge before OIT	Urticaria + wheeze + dizziness	Urticaria + rhinitis	Urticaria + abdominal pain + rhinitis
Specific IgE levels before OIT (kU/L)	Casein IgE >100	Casein IgE 195	Egg white IgE 75
Underlying asthma	Yes	Yes	Yes
Treatment step ^a	Step 4	Step 3	Step 4
Control level ^a	Uncontrolled	Partly controlled	Partly controlled
Risk-taking attitudes and poor compliance ^b	Yes	Yes	Yes
OIT compliance	Doses skipped, exercise and fasting not avoided, epinephrine auto-injector not carried	Doses skipped, alternative dairy product used, higher dose given in error	Fasting and exercise not avoided, denial of symptoms when reacting
Asthma control	Poor treatment compliance, smoking, no medical advice sought despite worsening	Suboptimal treatment compliance	None

Abbreviation: OIT, oral immunotherapy.

^a Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31:143–178.^b These concepts refer to patients' actions that may have contributed to an increased severity of OIT-related reactions. These actions contravened the OIT protocol and asthma management recommendations that had been agreed to by the patients.

exclusion criterion for OIT, but not partly controlled asthma, which affected cases 2 and 3. This fact highlights that asthma must remain strictly well controlled throughout OIT. Otherwise, OIT should be discontinued or not commenced. However, bronchoconstriction was the most common reaction to CM OIT in this series of 80 patients.¹ This raises the question as to whether OIT, especially CM OIT, might contribute to asthma destabilization. Reactions involving the bronchial tract should be regarded as potentially life-threatening.

Several previous findings support our main observation that teenagers with food allergy and persistent asthma may constitute particularly high-risk patients for OIT. First, asthma morbidity and mortality are increased in teenagers compared with younger children.⁶ Second, adolescents with asthma and food allergy report more severe asthma than those without food allergy.⁷ As with adolescents with other chronic illnesses, those with asthma show risk-taking behavior and poor treatment compliance, which may contribute to their poorer outcome.⁶ Similarly, risk-taking attitudes have been repeatedly reported in food-allergic teenagers—especially boys—such as eating allergen-containing products, not carrying epinephrine auto-injectors always, or not using them when needed.^{8–10} Thus, food-allergic adolescents and young adults are at highest risk of death of anaphylaxis to foods.⁵

Oral immunotherapy might be seen as a promising therapy to prevent potentially severe accidental reactions to foods. However, for some patients it may be a high-risk intervention.¹¹ Reactions to OIT are common, largely unpredictable, and inconsistent in some cases, probably because reactions are typically multifactorial.⁴ The risk may be partly controlled with different strategies, such as regular intake of a consistent dose, avoidance of potential cofactors, adequate control of underlying diseases, mainly asthma, and rescue medication availability at all times. Parents and patients are expected to adhere to these measures for the duration of OIT, including during maintenance.^{1,2} However, their experiences during OIT may influence their expectations, risk perception, and future actions, leading to risky attitudes in some cases. In addition,

dose adjustment after reactions does not guarantee safety of future doses.

In cases 1 and 2, several alarming signs that should have led to OIT discontinuation were not detected until the life-threatening reaction had occurred (asthma destabilization, skipping doses, not avoiding cofactors). Thus, strict supervision is needed, particularly in adolescents, to ensure compliance to OIT and asthma management and to monitor OIT-related reactions and asthma symptoms. A daily reporting system (eg, by the Internet) may be a useful intervention. However, it is debatable whether this close monitoring can be guaranteed long term outside the research setting.

In conclusion, teenagers with persistent asthma and high milk- or egg-specific IgE levels should be considered a particularly high-risk group for OIT. This can be partly attributed to their risk-taking behaviors and poor compliance. Asthma must remain strictly well controlled before and during OIT. The recognition of high-risk warning signs that should lead to OIT discontinuation (ie, asthma worsening, poor compliance) is essential to minimize risks. Close monitoring and age-appropriate patient-centered educational strategies should be developed to improve patient–clinician concordance in teenagers considering OIT. Much caution is needed to implement OIT outside the research setting.

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References

- [1] Vazquez-Ortiz M, Alvaro-Lozano M, Alsina L, et al. Safety and predictors of adverse events during oral immunotherapy for milk allergy: severity of reaction at oral challenge, specific IgE and prick test. *Clin Exp Allergy*. 2013;43: 92–102.
- [2] Vazquez-Ortiz M, Alvaro M, Piquer M, et al. Baseline specific IgE levels are useful to predict safety of oral immunotherapy in egg allergic children. *Clin Exp Allergy*. 2014;44:130–141.
- [3] Nieto A, Fernandez-Silveira L, Mazon A, Caballero L. Life-threatening asthma reaction caused by desensitization to milk. *Allergy*. 2010;65:1342–1343.
- [4] Pumphrey R. Anaphylaxis to foods in infancy and childhood—causes and circumstances. In: Wahn U, Beyer K, eds. *Symposia Proceedings: Food Allergy in Infancy and Childhood*. Heilbronn, Germany: SPS Verlagsgesellschaft GmbH; 2008:43–50.
- [5] Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*. 2001;107:191–193.
- [6] Couriel J. Asthma in adolescence. *Paediatr Respir Rev*. 2003;4:47–54.
- [7] Graif Y, German L, Livne I, Shohat T. Association of food allergy with asthma severity and atopic diseases in Jewish and Arab adolescents. *Acta Paediatr*. 2012;101:1083–1088.
- [8] Sampson MA, Muñoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. *J Allergy Clin Immunol*. 2006;117:1440.
- [9] Monks H, Gowland MH, MacKenzie H, et al. How do teenagers manage their food allergies? *Clin Exp Allergy*. 2010;40:1533–1540.
- [10] Marrs T, Lack G. Why do few food-allergic adolescents treat anaphylaxis with adrenaline?—Reviewing a pressing issue. *Pediatr Allergy Immunol*. 2013;24: 222–229.
- [11] Wasserman RL, Factor JM, Baker JW, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. *J Allergy Clin Immunol Pract*. 2014;2:91–96.