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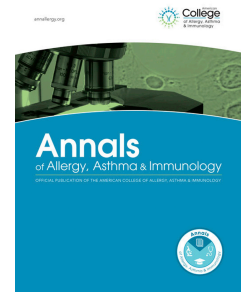
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**Con: OIT is safe/better than food avoidance**

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**Abbreviations:** CI = confidence interval. CM = cow's milk. FA = food allergy. FALQL-PF = Food Allergy Quality of Life Questionnaire-Parent Form. IgE = immunoglobulin-E. OIT = oral immunotherapy. QoL = quality of life. RR = relative risk. SU = sustained unresponsiveness.

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*To the editor,*

Food allergy (FA) is well-recognized as a major public health problem, affecting 8% of children and 5% of adults in the industrialized countries.<sup>1</sup> Despite the relatively high prevalence of this disorder, there is unfortunately no definitive cure. For a long time, the classical approach for the management of IgE-mediated FA has been strict food avoidance and the prescription of epinephrine auto-injector in case of accidental reaction. Regular oral food challenges (OFC) are performed in order to assess spontaneous tolerance acquisition. Food oral immunotherapy (OIT) was first described at the beginning of the 20<sup>th</sup> century and proposed as an alternative option. However, only in the past 10 years it has regained major interest, with an increased number of clinical trials, leading to its recommendation in European guidelines in 2018.<sup>1</sup> Nonetheless, integrating OIT as an option for the management of food-allergic patients is still highly debated with American guidelines only recommending this approach in research trials, and most clinicians continuing to prefer food avoidance. *Of note, similar restrictions are recommended in other national guidelines, such as those from Japan or Australia ([www.allergy.org.au](http://www.allergy.org.au))*<sup>2</sup>. In this review, we will highlight the advantages of the classical management, i.e. food avoidance, over food OIT (Table 1).

Physicians always hope to change the natural course of diseases, and allergists are not an exception. The natural evolution of FA following food avoidance has been investigated in multiple large cohorts of patients and it has been shown that a subgroup of patients will outgrow spontaneously their FA. Thus, 50% and up to 80% of hen's egg (HE) allergic patients become tolerant by 2-3 years of age and by 6 years, respectively.<sup>3</sup> Similarly, more than half of cow's milk (CM), soy and wheat allergic children become tolerant by 4-5 years of age.<sup>1,3</sup> Considering these data, food avoidance remains the reference for management of food-allergic children younger than 4-5 years of age. Indeed, it is generally accepted that an interventional treatment, i.e. food OIT, is not necessary below this age as natural tolerance

will occur in the majority of children with common food allergies (i.e. CM, HE, wheat and soy).

For older children, food OIT is increasingly proposed, mainly for CM, HE and peanut.<sup>3</sup> A recent meta-analysis evaluated the efficacy of food OIT in comparison to strict food avoidance/placebo.<sup>4</sup> OIT leads to desensitization in 76.9% of the included patients, while only 8.1% became spontaneously tolerant with food avoidance or placebo (relative risk (RR) of desensitization = 0.14, 95% CI 0.08 - 0.24).<sup>4</sup> However, these positive results must be interpreted with caution. Indeed, OIT protocols are not standardized: duration of the up-dosing phase, maintenance dose levels and duration of treatment vary significantly across these studies. Hence, it is difficult to compare these data and draw final conclusions, particularly with recommendation of a standardized protocol. Moreover, these studies evaluate mainly the capacity to desensitize the patients, which provides some advantages (i.e. mainly protection against accidental allergen ingestion and addition of nutritional values). However, the protection offered by desensitization is temporary and the subject must maintain regular ingestion of the food (usually daily) to retain the protection. In addition, the level of protection during active OIT is variable as subjects may react to doses of allergen that have been tolerated for up to months. Long-term follow-up studies of desensitization after OIT have shown that most subjects who are desensitized experience frequent reactions to continuing allergen exposure in the years after desensitization with most losing their protection because they stop taking the food regularly. This raises doubts regarding the feasibility to maintain a desensitized state in the longer term.<sup>5,6</sup> On the other hand, immune tolerance acquisition remains the final objective for FA treatment. Indeed, we want our patients to be able to ingest any amount of allergen, at any time after discontinuation of OIT, without any clinical reaction (complete resolution of food allergy with definitive immune tolerance). Because it is difficult to evaluate if OIT can induce a true complete immune

tolerance, the term “sustained unresponsiveness” (SU) has been proposed. SU is actually considered as the best reflection of complete allergen tolerance: it is usually considered as acquired when an oral food challenge with consistent amount of allergen (notably more than a standard serving food) is successful 4 to 8 weeks after OIT discontinuation.<sup>3</sup> In their meta-analysis, Nurmatov et al. found that SU is reached in 31.8% of patients after OIT and 11.1% after food avoidance/placebo (RR = 0.29, 95% CI 0.08 - 1.13).<sup>4</sup> Despite this relative risk in favor of OIT, considering the confidence interval above 1, the benefit is not clearly demonstrated. Moreover, these results are based on only 4 studies, including small numbers of patients (i.e. 113 patients with OIT and 81 patients with food avoidance/placebo) considering the relatively high prevalence of FA. It should be pointed out that some studies perform OFC to low cumulative doses at 4 to 8 weeks after allergen elimination, which only demonstrates sustained desensitization, and clearly differs from SU.<sup>4</sup> In addition, it is important to note that SU is not a perfect marker of future definitive immune tolerance, as it takes only a picture of the tolerance at 4 to 8 weeks after OIT discontinuation. Thus, evidences for true efficacy of OIT (definitive immune tolerance) remain poor and larger placebo-controlled studies are needed to clearly conclude to the superiority of OIT over food avoidance.

Nowadays, the evaluation of chronic treatment efficacy is increasingly associated with an economic consideration. Because food OIT needs regular medical visits, especially during the up-dosing phase, or due to side effects, the medical cost of OIT is logically higher than food avoidance. In our current system of health cares, this is a major point that needs to be taken into account when taking the decision to start a new treatment. However, there is actually no clinical study clearly evaluating the medical costs of food OIT, in comparison with food avoidance.<sup>4</sup>

Although patients avoiding the incriminated food might experience a severe anaphylactic reaction upon accidental ingestion, these reactions can also occur during OIT

treatment. Thus, the expected reduced severity of reactions during study exit OFC after OIT should be balanced with the overall higher incidence of reactions during OIT and the fact that severe reactions are experienced more frequently with OIT than food avoidance. Indeed, it has been found that epinephrine is used in up to 25% of the patients during the up-dosing phase of OIT and is generally used more often during OIT than during food avoidance (respectively 23 per 100 patients per year vs 0, RR = 5.8, 95% CI: 1.6 – 21.9).<sup>7</sup> Moreover, LeBovidge et al. observed that 52 weeks after OIT onset, children and their parents reduced their perception of the risk of severe reaction and death due to accidental ingestion.<sup>8</sup> This might increase the risk of accidental ingestion and occurrence of severe allergic reactions. Another major concern with food OIT is the occurrence of eosinophilic esophagitis (EoE) which might be considered as a severe side effect. Its prevalence is estimated at 5.3% (2.7-14%) of patients receiving OIT.<sup>9,10</sup> The imputation of OIT in EoE development is supported by the fact that EoE appearing during OIT often resolved after its discontinuation.<sup>9</sup> In a study on 35,528 food allergic patients, the prevalence of EoE during OIT was reported up to 3-fold higher than in the food allergic patients avoiding the culprit food.<sup>10</sup> This potential complication is associated with significant symptoms which might have a considerable impact on the QoL. All of these potential severe side effects during OIT should be clearly explained to the patients and their family, and taken into account when deciding between food avoidance and OIT.

Moreover, food OIT has been associated with mild to moderate reactions to continuing allergen exposure in a significant proportion of treated patients, more frequently than reactions due to accidental ingestion with food avoidance.<sup>4</sup> While severe side effects expose the patient to a lethal risk, mild side effects are unpleasant and may lead to treatment discontinuation. Based on 7 controlled studies, Nurmatov et al. found that local allergic reactions were reported in 54.3% of the patients receiving OIT, 10.7% of the patients receiving a placebo and 0% of patients avoiding the culprit food (RR of not experiencing a

reaction in controls vs OIT subjects = 2.14, 95% CI 1.47 - 3.12).<sup>4</sup> In addition to these local symptoms, mild to moderate systemic reactions have been reported. In Hague et al.'s study, 29.6% of patients having stopped the OIT protocol did it because of gastrointestinal (GI) symptoms/intolerances and 26.5% due to other systemic allergic symptoms.<sup>11</sup> Based on five studies, Nurmatov et al. found that 16.1% of patients receiving OIT experienced a systemic reaction, versus 2.6% of patients receiving placebo, and no patient in the avoidance group (RR of not experiencing a reaction in controls vs OIT subjects = 1.16, 95% CI: 1.03 - 1.30).<sup>4</sup> The Cochrane meta-analysis reports an increased risk of generalized urticaria or erythema (relative risk RR = 12.1, 95% CI: 3.0 – 49.1), GI symptoms (abdominal pain, vomiting and diarrhea) (RR = 16.6, 95% CI: 4.1 – 66.9) and non-severe bronchospasm (RR = 10.0, 95% CI: 2.4 – 41.4) during OIT, in comparison to food avoidance.<sup>7</sup> All of these allergic reactions occur more frequently during up-dosing phase, but also during maintenance phase.<sup>6</sup> While the majority of reactions will occur in the absence of any known cofactors, 13% of the reactions are associated with co-factors ((e.g. exercise, viral illness, asthma, menstruation, alcohol).<sup>12</sup> During OIT, the patient is continuously exposed to the allergen and has to adjust the treatment when a cofactor appears. However, all these co-factors are unpredictable, except exercise and drug exposure. Thus, compared to food avoidance, OIT exposes clearly to an increase risk of mild to moderate side effects that might decrease the adherence to the treatment, and of severe allergic reactions that might induce a lethal risk.

In addition, it has been shown that aversion of the incriminated food is relatively common in children treated with OIT. In a retrospective study including 427 patients treated with OIT, Hague et al. reported that among 98 patients (22.9%) who stopped the protocol, 40% did it because of taste aversion.<sup>11</sup> This feeling might be increased by the fact that decision to start OIT is often initiated by the parents, because children have difficulties to really appreciate the benefits/drawbacks of this treatment at a younger age. When children

grow up, they might then disagree with this relatively heavy treatment. This highlights the importance of involving the patient and not only the parents when deciding to start OIT.

Quality of life (QoL) plays an increasingly important role in patient care. For a long time, it has been shown that QoL of allergic patients avoiding the incriminated food(s) is altered in different domains. In particular, the risk of accidental reactions can have a major impact, particularly on physical, emotional and global QoL, and on psychosocial health.<sup>13</sup> In addition, allergic children have more school absenteeism than healthy children.<sup>13</sup> **Of note, the impact of epinephrine auto-injector prescription is not clear, shown to be able to increase,<sup>13</sup> but also decrease the QoL.<sup>14</sup>** From another point of view, continuous ingestion of the incriminated food during OIT may also alter patient QoL. A few studies evaluated the evolution of QoL in patients treated by OIT. Recently, Rigbi et al. analyzed the evolution of the Food Allergy Quality of Life Questionnaire-Parent Form (FALQL-PF) score in allergic patients receiving OIT.<sup>15</sup> They showed a significant improvement of FALQL-PF score upon reaching OIT maintenance phase, with additional improvement 6 months later. However, a worsening of the FALQL-PF score was reported in one third of the patients in the initial phase of treatment.<sup>15</sup> Thus, they found that patients with the highest QoL score at baseline deteriorate initially their global score, while those with the worst QoL score improve it. This decrease of QoL might alter the compliance during this crucial initial period of OIT treatment, which might already be low in teenagers. This information is important for OIT programs and food avoidance may remain the treatment of choice for these patients with a relatively high QoL at baseline.<sup>15</sup> **One suggested benefit from desensitization is improvement in QoL as reported from the parent's perspective, with improvement primarily in parental anxiety, however there remains no convincing evidence that QoL improvement is greater in active OIT vs placebo groups. Moreover,** it is questionable whether it is justified to induce frequent allergic reactions in children during OIT for the purpose of reducing anxiety in patients and

parents, particularly given that the level of anxiety and fear relating to likelihood of severe or fatal reactions is known to be greater than warranted. One might consider that alternative approaches to improve QoL and reduce anxiety in parents and patients may be safer and more cost effective than OIT. Finally, there is actually no long-term study evaluating the impact of OIT on QoL and especially during the maintenance phase at home. It would be important to evaluate this aspect as changes in life habits required in patients treated by OIT might clearly affect their QoL, such as limitations in physical activity after allergen ingestion, dietary restriction during fever or drug intake, or taste aversion.

In conclusion, OIT is increasingly proposed as a therapeutic option especially in Europe, for children older than 4-5 years of age with persistent IgE-mediated food allergy to CM, HE, and peanut. However, there remains serious concern regarding the safety of OIT and expert societies in other parts of the world continue to recommend that OIT should only be conducted in the setting of a clinical trial. If OIT is proposed, this point should be discussed extensively with the patient before initiating the treatment and regularly during its course. Furthermore, there is a lack of data long term and the initial improvement should be balanced with high rate of side effects associated with OIT. One major drawback of OIT is compliance, particularly in teenagers, which might affect the efficacy of the treatment and the risk of adverse reactions. While its efficacy in terms of desensitization seems to be demonstrated in many large studies, it is important to take into account the fact that there is currently no optimal standardized protocol. Indeed, several important points remain not-well defined, such as the optimal maintenance dose and duration of OIT to obtain a definitive immune tolerance, the need of epinephrine during the maintenance phase, the need and interval of follow-up visits and finally how to manage the patients in presence of co-factors such as viral infection. Moreover, data for cost-effectiveness analysis of OIT are needed in comparison to food

176 avoidance. Finally, the vast majority of published studies included mainly children with FA.  
177 Considering all these arguments, the superiority of OIT over food avoidance is not proved and  
178 the balance between the risk of OIT and its benefits, particularly when there is only  
179 desensitization, is essential before proposing this treatment. More studies are needed,  
180 particularly in adults with persistent FA.

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ACCEPTED MANUSCRIPT

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**Table 1.** OIT is better than avoidance: the con arguments.

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Efficacy of the treatment</b><br>- Food avoidance: the majority of patients outgrow their FA by 4 to 5 years of age<br>- OIT: leads to desensitization, but acquisition of persistent immune tolerance is not clearly demonstrated. No cost-effectiveness studies                                                                                                                                                                                                                                                     |
| <b>Side effects potentially leading to treatment discontinuation</b><br><b>(prevalence of anaphylaxis = 25%, of EoE = 5%)</b><br>- More local side effects during OIT than during food avoidance<br>- More mild to severe systemic side effects during OIT than during food avoidance<br>- Taste aversion might occur in a subgroup of patients during OIT<br>- More frequent use of epinephrine during OIT compared to food avoidance<br>- Eosinophilic esophagitis more frequent during OIT than during food avoidance |
| <b>Quality of life</b><br>- Long-term improvement of QoL after OIT not proved<br>- Potential initial QoL deterioration has been suggested in patients with a good QoL at baseline<br>- Necessity of regular medical visit (every 2 weeks)<br>- Necessity to maintain a regular food ingestion                                                                                                                                                                                                                            |

EoE = eosinophilic esophagitis. FA = food allergy. OIT = oral immunotherapy. QoL = quality of life.