

Sustained Unresponsiveness Induced by Oral Immunotherapy Is not a Complete Symptom-Free Condition; a Prospective Case Series

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Strict food avoidance is the only standard treatment for food anaphylaxis. Incidental exposure, cross-contamination, incomplete adherence, nutrient, and psychological deprivations in parallel to significant quality of life impairment led to many attempts to find alternative therapies.[1]. During OIT, gradually increasing doses from very small amounts are given to the patient at specified intervals until a predetermined final dose is reached (build-up phase). If the patient reaches this final dose, the subject has to take this maintenance continuously in a regular daily schedule (maintenance phase). Adverse reactions are the main limitation of oral immunotherapy. The first easiest and more feasible achievement is the reduction of anaphylaxis risk after accidental exposures, and the most ambitious target which is not always achieved, the Sustained unresponsiveness (SU).[2, 3].

During desensitization, food tolerance is maintained as long as food intake is regular, while in SU, food tolerance is maintained even if the patient does not eat the food for a certain period of time.[2, 4]. Currently, the immunologic mechanisms or prognostic factors in success or failure of OIT and the achievement of SU are not fully understood. Therefore, we designed this study to assess the possible reactions of patients with anaphylaxis after the achievement of SU. In summary, desensitization was performed based on weekly increasing doses from the very little amount to the final dose of 100 mL of cow's milk equivalent to 4 g of protein [5]

Throughout the maintenance phase, individuals were required to consume 100 mL of cow's milk daily. Patient characteristics, immediate reactions during desensitization, and long term complications like eosinophilic esophagitis development due to desensitization have already been published.[6]. All of the participants or their parents signed a written informed consent form and the Ethics Committee of Iran University of Medical Sciences approved this study (IR.IUMS.FMD.REC.1397.333). Twenty-one patients who met the inclusion criteria, including cow's milk anaphylaxis, successful OIT with more than 48 months of the maintenance

phase, complete adherence to maintenance phase protocol was allocated to this study. After 4 weeks of complete dairy avoidance, they underwent an open oral food challenge (OFC) briefly, started with a dose of 1 cc of milk and increased to a cumulative dose of 100 mL at 20-minute intervals.[7]. From these 21 patients: 11 had allergic rhinitis (52%), 6 atopic dermatitis (28%), 5 asthma (24%), 1 urticaria (4%), 2 contact dermatitis (10%), and 13 of them had other food allergies (62%). Eight out of 21 individuals who could pass the OFC were diagnosed as SU and approved for this study.

In order to reassure patients that higher doses have no reactions, they were asked to drink the double and triple the maintenance dose in the hospital under our supervision in the first week. All of them consumed this amount of milk without any reaction and then they were allowed to take any amount of cow's milk (independent to dose) or regardless of timing (independent to daily manner). In the other manner they were asked to use dairy products as ad libitum feeding program. They were given a 24-hour contact number to report any symptoms immediately, and we followed them weekly by phone for 6 months. Any kind of Reactions, the severity of symptoms, relieving drug, the interval of usage, amount of milk consumption, and the existence of cofactors such as exercise, fever, and infection were monitored. All of them showed a significant decrease in specific IgE and significant increase IgG4 to cow's milk after the OIT. Seven of eight participants showed some reactions after cow's milk consumption. Reactions were mild and only oral antihistamines were used for treating the reactions. All of the symptoms were appeared along with cofactors. Cow's milk consumption without cofactors was safe independent of the amount and interval of the consumption. Exercise in the first hour after drinking milk was the most common trigger. Table 1.

In this prospective cohort study, only 8 cases out of 21 patients, passed the OFC after 4 weeks of cessation of dairy consumption and were diagnosed as SU.[2]. There are two different definitions in OIT. Desensitization refers to a temporary state of unresponsiveness of the adaptive immune system to a specific antigen, which is dependent on continuous use of the predetermined amount of that food, while sustained unresponsiveness is defined as persistent unresponsiveness to that antigen, irrespective of amount and consumption continuity[2, 4]. It is estimated that about 30 to 90% of individual who undergo OIT are able to achieve desensitization state[2, 8] but the rate of SU is unknown and is reported between 28 to 36 % in limited trials[4, 8], it is suggested longer

maintenance phase and higher amount of daily use may have some role in SU development[2]. In this study, 8 of 21 (38%) patients developed SU. The success rate of SU induction was not our aim. We wanted to provide more information about possible reactions related to milk ingestion after SU achievement. The main question was: Can we really give assurance to patients with anaphylaxis that they are completely safe in the exposure to the culprit food, regardless of the dose and continuity of consumption? To the best of our knowledge, it is the first time to follow these individuals after SU development; however, this important question is asked without a clear response.[2, 9, 10] Allergic reactions are the main side effects during OIT in both escalation and maintenance phases. It is important to consider that in the maintenance phase of desensitization, patients may show severe reactions to previously tolerated doses in association with exercise, viral infection, dosing on an empty stomach, menses, and asthma exacerbation. It is hypothesized that these factors may increase intestinal permeability, thereby leading to loss of protection to the previously tolerated dose, even when the maintenance dose has been achieved regularly[2]. Our study showed these factors could affect the unresponsiveness state even when SU has developed; however, none of our patients showed severe reactions. The present study showed the dose and continuous consumption of food allergen were not involved in the reaction after SU development but aggravating factors are still important.

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Conflict of interest

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Table 1. Clinical and laboratory data

Patient	Gender	Anaphylaxis history	Maintenance Duration (month)	OIT				Reaction without cofactor	Reaction with cofactor	Type of reaction	Number of reactions	Relieving drug for treatment	Type of cofactor
				SIgE (kUA/L)		sIgG (mg/mL)							
				Before	After	Before	After						
1	Male	Yes	50	35.96	19	9.36	15.25	No	Yes	LU	4	H	Exercise
	12												
2	Male	Yes	48	48	0.63	17	29	No	Yes	LU	6	H	Exercise, UPI
	11												
3	Male	Yes	56	12.86	1.9	10.71	16.52	No	Yes	GU	3	H	Exercise
	15												
4	Female	Yes	64	9.49	4.06	4.85	48	No	Yes	Rh, U	7	H	Exercise, Fever
	9												
5	Male	Yes	48	28	2.35	65	>100	No	Yes	N, LU	3	H	Exercise
	23												
6	Male	Yes	52	23.5	2.44	43	87.66	No	No	-	-	-	-
	17												
7	Male	Yes	49	12	8.05	11	85	No	Yes	LU, GU	8	H	URI
	9												
8	Female	Yes	53	88	25	2.35	56	No	Yes	TI, LU	2	H	Exercise

Abbreviation: **GU:** Generalized urticarial, **H:** Anti histamine (H1 blocker), **N:** Nausea, **OIT;** Oral immunotherapy, **Rh=** Rhinorrhea, **TI:** throat itching, **UPI:** Upper respiratory infection

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