

Sustained Unresponsiveness Induced by Oral Immunotherapy Is Not a Completely Symptom-Free Condition: A Prospective Case Series

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Strict food avoidance is the only standard treatment for food anaphylaxis. Many attempts have been made to find alternative therapies through investigation of incidental exposure, cross-contamination, incomplete adherence, nutrients, and psychological deprivations in parallel to significant impairment of quality of life [1]. During oral immunotherapy (OIT), gradually increasing doses start with very small amounts at

specified intervals until a predetermined final dose is reached (build-up phase). If the patient reaches this final dose, he/she has to maintain therapy following a regular daily schedule (maintenance phase). Adverse reactions are the main limitation of oral immunotherapy. The first, easiest, and most feasible achievement is to reduce the risk of anaphylaxis after accidental exposures, and the most ambitious target, which is not always achieved, is 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]. The immunologic mechanisms and prognostic factors involved in the success or failure of OIT and 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. Desensitization was performed based on weekly increasing doses from a very small amount to the final dose of 100 mL of cow's milk, which was 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 such as eosinophilic esophagitis due to desensitization have been reported elsewhere [6]. The participants or their parents signed a written informed consent form, and the Ethics Committee of Iran University of Medical Sciences approved the study (IR.IUMS.FMD.REC.1397.333). The study population comprised 21 patients who met the inclusion criteria, including cow's milk anaphylaxis, successful OIT with a maintenance phase of more than 48 months, and complete adherence to the maintenance phase protocol. After 4 weeks of complete dairy avoidance, they underwent a brief open oral food challenge, starting with a dose of 1 mL of milk, which was increased to a cumulative dose of 100 mL at

Table 1. Clinical and Laboratory Data

Patient	Sex	History of Anaphylaxis	Duration of Maintenance, mo	OIT				Reaction Without Cofactor	Reaction With Cofactor	Type of Reaction	Number of Reaction	Reliever Medication	Type of Cofactor
				sIgE, kU _A /L		sIgG, mg/mL							
				Before	After	Before	After						
1	Male 12	Yes	50	35.96	19	9.36	15.25	No	Yes	LU	4	H	Exercise
2	Male 11	Yes	48	48	0.63	17	29	No	Yes	LU	6	H	Exercise, URI
3	Male 15	Yes	56	12.86	1.9	10.71	16.52	No	Yes	GU	3	H	Exercise
4	Female 9	Yes	64	9.49	4.06	4.85	48	No	Yes	Rh, U	7	H	Exercise, fever
5	Male 23	Yes	48	28	2.35	65	>100	No	Yes	N, LU	3	H	Exercise
6	Male 17	Yes	52	23.5	2.44	43	87.66	No	No	-	-	-	-
7	Male 9	Yes	49	12	8.05	11	85	No	Yes	LU, GU	8	H	URI
8	Female 16	Yes	53	88	25	2.35	56	No	Yes	TI, LU	2	H	Exercise

Abbreviations: GU, generalized urticaria; H, antihistamine (H₁ blocker); N, nausea; OIT, oral immunotherapy; Rh, rhinorrhea; TI, throat itching, URI, upper respiratory infection; U, urticaria; LU, local urticaria.

20-minute intervals [7]. Of these 21 patients, 11 had allergic rhinitis (52%), 6 atopic dermatitis (28%), 5 asthma (24%), 1 urticaria (4%), 2 contact dermatitis (10%), and 13 other food allergies (62%). Eight of the 21 individuals were diagnosed as having SU and included in this study.

In order to reassure patients that higher doses do not induce reactions, they were asked to drink double and triple the maintenance dose in the hospital under our supervision during the first week. All of them consumed this amount of milk without reaction and were then allowed to take any amount of cow's milk (independent of dose) regardless of timing (independent of daily manner of consumption). They were also able to use dairy products in an ad libitum feeding program and were given a 24-hour contact number to report any symptoms immediately. We followed the patients weekly by phone for 6 months and recorded reactions, severity of symptoms, reliever medication, interval of usage, amount of milk consumption, and presence of cofactors such as exercise, fever, and infection. All patients experienced a significant decrease in specific IgE and significant increase in IgG4 to cow's milk after the OIT. Seven of the 8 participants experienced a reaction after consuming cow's milk. Reactions were mild and were treated only with oral antihistamines. All of the symptoms appeared along with cofactors. Cow's milk consumption without cofactors was safe, independently of the amount and interval of the consumption. Exercise in the first hour after drinking milk was the most common trigger (Table).

In this prospective cohort study, only 8 of 21 patients passed the oral food challenge after 4 weeks of cessation of dairy consumption and were diagnosed as having SU [2]. OIT is characterized by 2 different definitions. 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 SU is defined as persistent unresponsiveness to that antigen, irrespective of amount and continuity of consumption [2,4]. It is estimated that about 30% to 90% of individuals who undergo OIT are able to achieve desensitization [2,8]. The rate of SU is unknown, although it is reported to be between 28% and 36% in limited trials [4,8]. A longer maintenance phase and increased daily use may have some role in the development of SU [2]. In this study, 8 of 21 patients (38%) developed SU. Our study did not aim to determine the success rate of induction of SU. We attempted to provide more information about possible reactions related to milk ingestion after achievement of SU. Our main intention was to determine whether we can really assure patients with anaphylaxis that they are completely safe on exposure to the culprit food, regardless of the dose and continuity of consumption. To our knowledge, this is the first report of such patients being followed after they developed SU. However, the question of whether patients will be safe on exposure remains unanswered [2,9,10]. Allergic reactions are the main adverse effects during OIT in both the escalation and the maintenance phase. It is important to consider that in the maintenance phase, patients can experience 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 at the previously tolerated dose, even when the maintenance dose has been achieved regularly [2]. Our study showed that these factors could affect the state of unresponsiveness, even when SU has developed. Nevertheless, none of the patients

studied experienced severe reactions. The present study showed that the dose and continuous consumption of a food allergen were not involved in the reaction after development of SU, but that aggravating factors are still important.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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