*Short Communication*

# Sustained Unresponsiveness in Oral Immunotherapy for Cow's Milk Allergy

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**Abstract: Background:** We aimed to investigate the efficacy and safety of home-based oral immunotherapy (OIT) in children with cow's milk (CM) allergy (CMA) and to examine whether sustained unresponsiveness (SU) could be achieved after cessation of OIT. **Methods:** Children with CMA, aged 3–10 years, were enrolled in the OIT ($n$ = 8) and the control ($n$ = 8) groups. Patients increased the dose of heated milk daily at home during the build-up phase. During the maintenance phase, 100 mL of unheated milk (UM) (3.0 g of CM proteins) was administered daily to the patients for 12 months. Oral food challenge (OFC) tests were performed with a total dose of 200 mL of UM after the build-up phase and four weeks after cessation of CM following the maintenance phase. **Results:** All patients in the OIT group achieved desensitization after completion of the build-up phase. After 12 months of the maintenance phase and four weeks of the CM restriction period, OFC was performed in six patients in the OIT group. Among them, five (83.3%) patients obtained SU, while none of the patients in the control group achieved tolerance ($p$ = 0.003). During OIT, adverse reactions were reported in seven (87.5%) patients. Anaphylaxis occurred in three (37.5%) patients in the OIT group and in four (50.0%) patients in the control group ($p$ = 1.000). There were no serious adverse or life-threatening events during OIT. **Conclusions:** Home-based milk OIT is an effective and safe treatment method for SU and desensitization to CMA.

**Keywords:** cow's milk allergy; desensitization; immunotherapy; immune tolerance; sustained unresponsiveness

## 1. Introduction

The prevalence of cow's milk (CM) allergy is estimated to be 2.5–3.8%, and it is one of the most common causes of food allergies (FA) and anaphylaxis [1–3]. Strict avoidance of all causative foods containing CM is challenging for patients and their family members. Moreover, only half of pediatric patients tolerate CM allergy (CMA) at the median age of 8.7 years [3,4]. Given these difficulties, the guidelines recommend oral immunotherapy (OIT) for 4- to 5-year-old children with CMA to induce tolerance or sustained unresponsiveness (SU) [5,6]. However, up to 20% of discontinuation rate was reported in patients undergoing OIT due to various discomforts and fears associated with adverse reactions during OIT [7–9].

A recent study used heated milk (HM) for OIT to reduce the frequency and severity of adverse reactions, and HM-OIT induced immunological changes more safely than previous trials using unheated milk (UM) [10]. However, since the CM heating process in the maintenance phase was inconvenient, we developed a protocol using UM in the maintenance period after a home-based up-dosing period using HM. In this study, we aimed to investigate the efficacy and safety of home-based OIT using this modified protocol in children with IgE-mediated CMA, and to examine whether SU could be achieved after four weeks of OIT cessation following the 12-month maintenance phase in real-world practice.

## 2. Materials and Methods

### *2.1. Study Population*

We enrolled patients aged 3–10 years who were diagnosed with CMA and whose parents provided consent for their children to receive OIT. Diagnosis of FA was based on convincing history within a year plus positive serum specific IgE (sIgE ≥ 0.35 kU/L) or a positive oral food challenge (OFC) test. We classified the reported allergic reactions according to the affected organs as follows: (1) skin or mucosal symptoms; (2) gastrointestinal symptoms; (3) respiratory symptoms; and (4) anaphylaxis [11]. For the control group, we selected patients who were diagnosed with CMA between January 2014 and December 2019, and matched for age, sex, levels of sIgE to CM, symptoms after exposure to CM, and duration of the follow-up period. This study was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Korea (IRB No. 2012-09-026, 2014-01-160, 2020-02-163, and 2020-05-135).

### *2.2. OIT Protocol*

For OIT, patients were challenged with 0.1 (3 mg of CM protein), 0.5, and 1 mL of HM every 20 min at the hospital. The daily intake of HM at home started with half of maximum tolerated volume, increased by 0.1 mL daily until 2.0 mL of HM was reached. Thereafter, patients were asked to take HM in 5% daily increments from 2.0 mL until 100 mL of HM (3000 mg of CM protein) was reached. To prepare HM, a sufficient amount of CM was placed in a microwave oven and heated at 700 W for 80 s [12,13].

In the case of an allergic reaction during OIT at home, emergency kits were provided with a copy of the emergency action plan. The severity of allergic reactions was classified according to the Consortium of Food Allergy Research (CoFAR) grading system [14]. Patients were instructed to take antihistamines if they exhibited any symptoms other than anaphylaxis. If the patients exhibited anaphylaxis, they were given a self-injection of epinephrine. After the build-up phase, patients received OFC with UM and maintained 100 mL of UM (3000 mg of CM protein) at least four times a week for 12 months.

### *2.3. Evaluation*

Desensitization was defined as the lack of a reaction during the OFC with a cumulative volume of 200 mL of CM (6000 mg of CM protein) after the build-up phase. SU was defined as unresponsiveness to 6000 mg of CM protein after 4-week avoidance of CM following the maintenance phase. OFC tests were performed with a total volume of 200 mL CM under the supervision of pediatric allergists. The patients received CM in increments of 0.1, 1, 10, 30, and 60% of the total amount every 20 min.

In the OIT group, the patients underwent blood tests before the start of OIT and after the maintenance phase. The levels of sIgE to CM and casein, and specific IgG4 (sIgG4) to casein were measured. Serum sIgE and sIgG4 levels were determined using ImmunoCAP (Thermo Fisher Scientific Inc., Waltham, MA, USA).

### *2.4. Statistical Analysis*

Statistical analysis was performed using SPSS version 27.0 (IBM Corp, Armonk, NY, USA). Data are presented in the median and range. Categorical variables between groups were compared using the Fisher's exact test. The Wilcoxon signed-rank test was performed to compare the total IgE, sIgG4, and sIgE levels before and after treatment in each group. Levels of sIgE antibodies above 100 kU/L and sIgG4 antibodies above 30 mg/L were assigned values of 101 kU/L and 31 mg/L, respectively, for the analyses. A $p$ value of less than 0.05 was significant.

## 3. Results

### *3.1. Clinical Outcomes*

Eight patients each were enrolled in the OIT and control groups (Table 1). All patients in the OIT group achieved desensitization to UM (200 mL) after the completion of the build-up phase (Figure 1A). After 1 year of the maintenance phase and 4 weeks of the CM restriction period, the OFC test using UM (200 mL) was performed in six patients in the OIT group to assess SU. In the OIT group, two patients (25.0%) could not undergo the OFC to assess SU because they did not want to restrict cow's milk intake due to their high preference for dairy products and concerns about the possible recurrence of allergic symptoms. As a result, five (83.3%) patients obtained SU, while none of the patients in the control group achieved immune tolerance during the same period ($p$ = 0.003;

Figure 1 A,B). One patient who showed wheals and mild cough in the OFC after a 4-week restriction of CM increased the amount of UM according to the OIT protocol and maintained UM without further adverse reactions. Two patients who refused OFC for the assessment of SU also consumed CM *ad libitum* (Figure 1B).

**Table 1.** Baseline clinical characteristics of subjects.

| Variables | OIT Group (n = 8) | Control Group (n = 8) | *p* Value |
|---|---|---|---|
| Sex (male, *n*) | 5 (62.5) | 5 (62.5) | 1.000 |
| Age (year) | 6 (3–10) | 6 (4–7) | 0.645 |
| Comorbid conditions | | | |
| Atopic dermatitis | 6 (75.0) | 8 (100.0) | 0.467 |
| Allergic rhinitis | 4 (50.0) | 6 (75.0) | 0.608 |
| Asthma | 3 (37.5) | 2 (25.0) | 1.000 |
| Family history of allergic diseases | 3 (37.5) | 2 (25.0) | 1.000 |
| Additional FAs | 6 (75.0) | 6 (75.0) | 1.000 |
| Egg white | 5 (62.5) | 5 (62.5) | 1.000 |
| Wheat | 2 (25.0) | 1 (12.5) | 1.000 |
| Peanut | 2 (25.0) | 5 (62.5) | 0.315 |
| Tree nuts | 3 (37.5) | 5 (62.5) | 0.619 |
| Symptoms of allergy | | | |
| Skin & mucosa | 5 (62.5) | 7 (87.5) | 0.569 |
| Gastrointestinal | 0 (0.0) | 1 (12.5) | 1.000 |
| Respiratory | 1 (12.5) | 1 (12.5) | 1.000 |
| Anaphylaxis | 5 (62.5) | 5 (62.5) | 1.000 |
| Eosinophil count (/mm$^3$) | 337 (61.2–687.3) | 406 (120.5–1102.7) | 0.414 |
| Total IgE (kU/L) | 502 (33.4–2101) | 359 (93–2709) | 0.573 |
| sIgE to CM (kU/L) | 12.2 (2.3–30.7) | 11.6 (2.4–28.4) | 0.959 |

Data were represented as number (%) or median (range). Abbreviations: OIT, oral immunotherapy; FA, food allergy; sIgE, specific IgE; CM, cow milk.

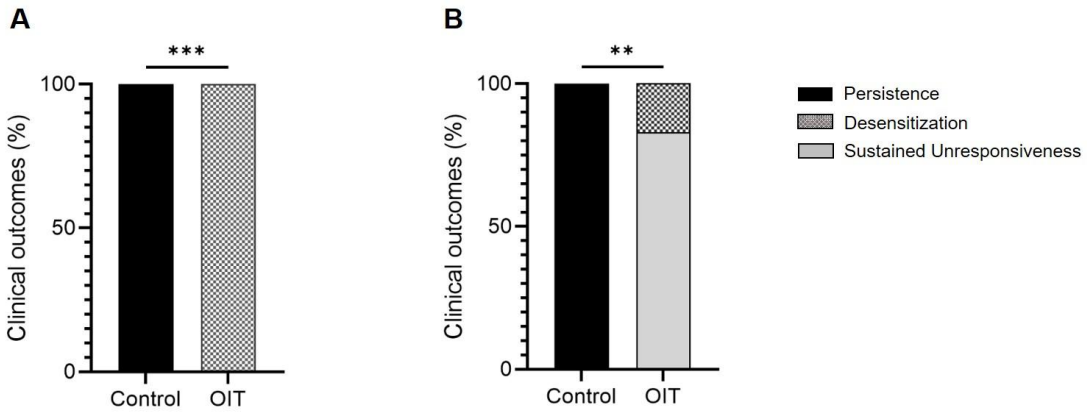


**Figure 1.** Clinical outcomes in the oral immunotherapy and control groups after the build-up (**A**) and maintenance (**B**) phases. ****** $p < 0.01$, ******* $p < 0.001$.

### *3.2. Adverse Reactions during OIT*

During OIT, adverse reactions occurred in 87.5% of patients (7 patients and 72 events), and five children experienced three or more episodes (Table 2). In the control group, allergic reactions accidently occurred in 62.5% of patients (five patients and nine events), but none of the patients had more than three episodes. There were no differences in the number of patients with allergic symptoms between the OIT and control groups ($p = 0.569$). Moreover, no difference was found in the number of patients who experienced anaphylaxis (CoFAR grade 2) between the OIT (3/8, 37.5%) and control (4/8, 50.0%) groups ($p = 1.000$). No patients reported significant adverse reactions of CoFAR grade 3 or required psychiatric intervention for anxiety in either group ($p = 1.000$). The most common allergic symptoms in both groups were skin or mucosal allergic reactions (50.0% vs. 75.0%, $p = 0.608$). Mild adverse reactions (CoFAR grade 1) occurred more frequently in the OIT group than in the control group

(55.6% vs. 91.7%, $p = 0.011$), whereas anaphylaxis occurred more frequently in the control group than in the OIT group (44.4% vs. 8.3%, $p = 0.011$).

**Table 2.** Comparisons of adverse reactions between the oral immunotherapy and control groups.

| | **Control Group (n = 8)** | **OIT Group (n = 8)** | ***p* Value** |
|---|---|---|---|
| Number of individuals with adverse events | | | |
| 1 or 2 episodes | 5 (62.5) | 2 (25.0) | 0.315 |
| ≥3 episodes | 0 (0.0) | 5 (62.5) | 0.026 |
| None | 3 (37.5) | 1 (12.5) | 0.569 |
| Number of individuals by severity of symptoms | | | |
| Mild (CoFAR grade 1) | 4 (50.0) | 7 (87.5) | 0.282 |
| Moderate (CoFAR grade 2) | 4 (50.0) | 3 (37.5) | 1.000 |
| Severe (CoFAR grade 3) | 0 (0.0) | 0 (0.0) | 1.000 |
| Number of individuals by type of allergic reaction | | | |
| Skin & mucosa | 4 (50.0) | 6 (75.0) | 0.608 |
| Respiratory | 0 (0.0) | 5 (62.5) | 0.026 |
| Gastrointestinal | 0 (0.0) | 2 (25.0) | 0.467 |
| Anaphylaxis | 4 (50.0) | 3 (37.5) | 1.000 |
| | Control group | OIT group | *p* value |
| Total number of reported adverse events | 9 | 72 | |
| Frequency of adverse events by severity | | | |
| Mild (CoFAR grade 1) | 5 (55.6) | 66 (91.7) | 0.011 |
| Moderate (CoFAR grade 2) | 4 (44.4) | 6 (8.3) | 0.011 |
| Severe (CoFAR grade 3) | 0 (0.0) | 0 (0.0) | 1.000 |
| Frequency of adverse events by type of reactions | | | |
| Skin & mucosa | 5 (55.6) | 52 (72.2) | 0.439 |
| Respiratory | 0 (0.0) | 12 (16.7) | 0.342 |
| Gastrointestinal | 0 (0.0) | 2 (2.8) | 1.000 |
| Anaphylaxis | 4 (44.4) | 6 (8.3) | 0.011 |

Values are presented as numbers (%). Abbreviations: OIT, oral immunotherapy; CoFAR, Consortium of Food Allergy Research.

During OIT, the possibility of adverse events per ingestion dose was 1.4% (72/5342). Adverse reactions occurred more frequently in the build-up phase than in the maintenance phase (2.5% [61/2412] vs. 0.4% [11/2930], respectively). However, there was no difference in the frequency of adverse reactions according to the severity and type between the OIT and control groups in the build-up and maintenance phases, respectively (all $p > 0.05$; Table 3).

**Table 3.** Comparisons of adverse reactions between OIT and control groups during the build-up and maintenance phases.

| **Build-Up Phase** | **Control Group** | **OIT Group** | ***p* Value** |
|---|---|---|---|
| Total number of reported adverse events | 5 | 61 | |
| Frequency of adverse events by severity | | | |
| Mild (CoFAR grade 1) | 3 (60.0) | 57 (93.4) | 0.061 |
| Moderate (CoFAR grade 2) | 2 (40.0) | 4 (6.6) | 0.061 |
| Severe (CoFAR grade 3) | 0 (0.0) | 0 (0.0) | 1.000 |
| Frequency of adverse events by type of reactions | | | |
| Skin & mucosa | 3 (60.0) | 45 (73.8) | 0.608 |
| Respiratory | 0 (0.0) | 11 (18.0) | 0.580 |
| Gastrointestinal | 0 (0.0) | 1 (1.6) | 1.000 |
| Anaphylaxis | 2 (40.0) | 4 (6.6) | 0.061 |
| **Maintenance phase (12 months)** | **Control group** | **OIT group** | ***p* value** |
| Total number of reported adverse events | 4 | 11 | |
| Frequency of adverse events by severity | | | |
| Mild (CoFAR grade 1) | 2 (50.0) | 9 (81.8) | 0.516 |
| Moderate (CoFAR grade 2) | 2 (50.0) | 2 (18.2) | 0.516 |
| Severe (CoFAR grade 3) | 0 (0.0) | 0 (0.0) | 1.000 |
| Frequency of adverse events by type of reactions | | | |
| Skin & mucosa | 2 (50.0) | 7 (63.6) | 1.000 |
| Respiratory | 0 (0.0) | 1 (9.1) | 1.000 |

| | | | |
|---|---|---|---|
| Gastrointestinal | 0 (0.0) | 1 (9.1) | 1.000 |
| Anaphylaxis | 2 (50.0) | 2 (18.2) | 0.516 |

Values are presented as numbers (%). Abbreviations: OIT, oral immunotherapy; CoFAR, Consortium of Food Allergy Research.

### *3.3. Change of Immunological Profiles during OIT*

In the OIT group, the levels of sIgE to CM and casein significantly decreased after the maintenance phase of OIT ($p$ = 0.017 and 0.012, respectively; Figure 2A,B). However, there was no significant change in the levels of sIgE to CM after a median of 25 months (range 20–28 months) compared with baseline measurements in the control group ($p$ = 0.093; Figure 2A). The differences in sIgE levels to CM were greater in the OIT group than in the control group ($p$ = 0.036; Figure 2C). The significant increase in levels of sIgG4 to found before and after OIT ($p$ = 0.017; Figure 2D).

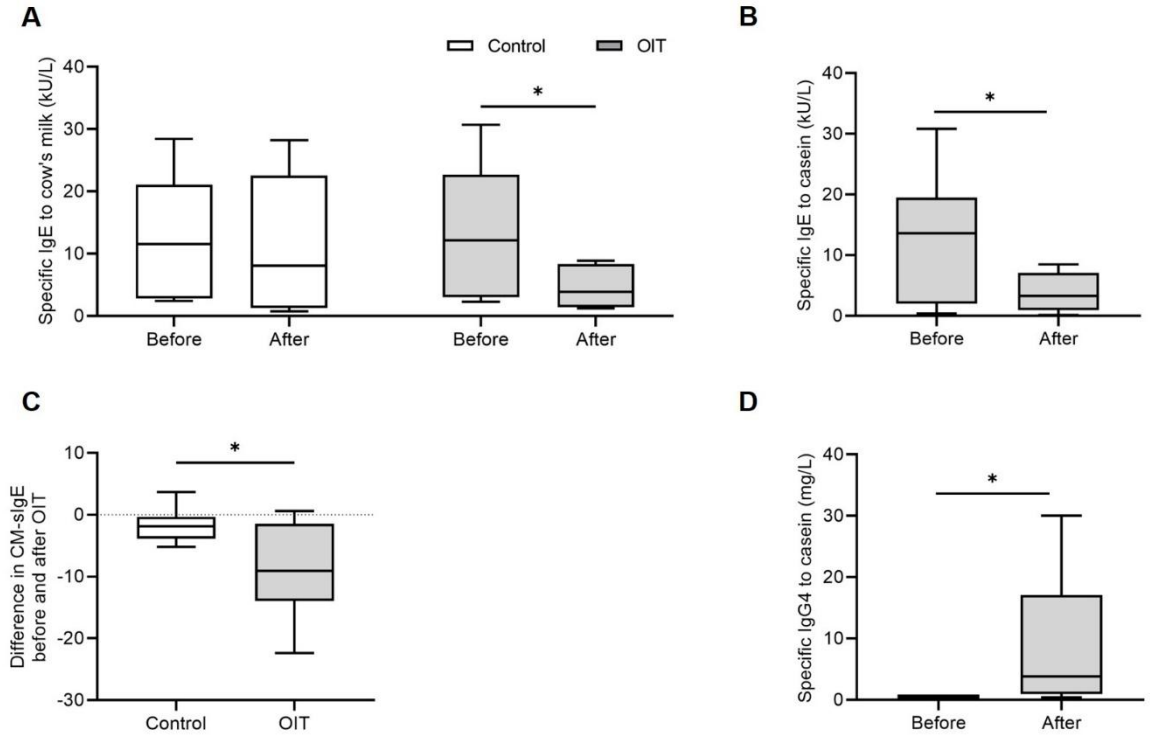


**Figure 2.** Changes in cow's milk- and casein-specific IgE levels (**A**,**B**), difference in cow's milk-specific IgE (**C**) and changes in casein-specific IgG4 levels (**D**) before and after oral immunotherapy. Abbreviations: CM, cow's milk. ***** $p < 0.05$.

## 4. Discussions

This is the first study to confirm the long-term efficacy and safety of CM OIT and evaluate SU in Korean patients. We demonstrated the efficacy of home-based CM OIT with a desensitization rate of 100% and an SU rate of 87.5%. None of the patients experienced serious adverse reactions or psychological problems during OIT. Of note, anaphylaxis was more frequently reported in the control group than in the OIT group. Although this study cannot be compared to previous studies due to differences in the number of subjects, protocols, and food forms used for treatment, our results provided notable insights. OIT has been reported to induce desensitization and tolerance in 36.7–100% and 22.6–45% of patients allergic to CM, respectively [12,15,16]. The immunological profiles of patients in the present study also showed patterns similar to those in previous studies [17,18]. Taken together, our results suggest that home-based OIT using HM is an effective and safe method that can be used to induce tolerance acquisition and immunological changes in real-world practice.

A Cochrane systematic review reported adverse reactions and anaphylaxis in more than 90% of patients during milk OIT [19]. Moreover, 15.8% of children with CMA who started OIT discontinued the treatment because of acute or repeated adverse reactions [20,21]. Therefore, OIT protocols using HM or baked milk can ensure safe up-dosing. However, the baked milk OIT protocol demonstrated low UM desensitization rates of less than 70%, which does not fully resolve concerns about CM exposure in real life, despite a reduced frequency of adverse reactions (approximately 8–33%) [22–24]. To overcome these problems, Takahashi et al. used CM heated for 100

s in a 550 W microwave oven for OIT, similar to the present study [12]. However, that study used the rush protocol, in which patients were administered HM 2–4 times at 2-h intervals in a hospital setting. When it reached 200 mL, patients consumed 200 mL of HM for 2 months every day at home, switched to 200 mL of UM by shortening the time spent heating the CM in the microwave oven and maintaining it for 1 year. After 2-week off-treatment period, 22.6% of the participants passed the OFC test. Another Japanese study used modified HM (125 °C for 30 s and spray-drying for 3 s) during the build-up and maintenance phases and compared its efficacy with UM-OIT [10]. After completing 1 year of follow-up, 18% of patients in the HM group and 31% of patients in the UM group passed OFC tests with 25 mL of HM without statistical significance. Notably, the HM group showed a significantly lower incidence of moderate-to-severe adverse responses compared to the UM group during OIT [10]. However, the SU assessment was not conducted in that study, although it is recommended at least 2–4 weeks after discontinuation of OIT [25]. In this regard, the advantages of our protocol are that the up dosing was performed with HM, which is easy to prepare using microwaves, and HM was switched to UM in the maintenance phase to increase the desensitization rates and improve convenience. Furthermore, considering that there is no statistically significant difference in the occurrence of severe adverse reactions, such as anaphylaxis, between the control group and the OIT group, the OIT protocol using HM in our study can be considered a relatively safe treatment method.

This study has limitations stemming from the small number of subjects. Moreover, SU was not assessed in two patients who received OIT because some patients did not want to evaluate SU due to their high preference for dairy products and fear of recurrence of CMA in real-world practice. However, this is the first report on home-based CM OIT showing excellent desensitization and SU rates, and additional research is being conducted.

In conclusion, our home-based OIT using HM in the build-up phase and UM in the maintenance phase showed good desensitization and SU rates in patients. Thus, it can be safely used for the treatment of CMA in clinical practice.

**Author Contributions:** SK, MK, JihK: conceptualization, methodology, software; SK, MK, JiwK,: data curation, writing—original draft preparation; JiwK,, MJ, JYL: visualization, investigation; KA, JihK: supervision; MK, JihK: software, validation; MJ, JihK, KA: writing—reviewing and editing. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board by the Institutional Review Board of the Samsung Medical Center, Seoul, Korea (IRB No. 2012-09-026, 2014-01-160, 2020-02-163, and 2020-05-135).

**Informed Consent Statement:** Patient consent was waived due to the retrospective nature of the study, which involved an EMR chart review and posed no direct risk to participants, as approved by the institutional review board.

**Data Availability Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical restrictions.

**Conflicts of Interest:** The authors have no conflicts of interest to declare pertaining to this article.

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