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Oral Immunotherapy in IgE-Mediated Cow’s Milk Protein Allergy

Jody Bauer
University of North Dakota

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Cows' milk allergy prevalence in children has been increasing significantly over the last several decades. The diagnosis of a cow's milk allergy (CMA) can occur through several methods such as signs and symptoms, double blind oral food challenge, skin prick testing, IgE and IgG serum levels. Currently, there are no treatments beyond avoidance. The pathophysiology of quality is impacted with the fear of inadvertent exposure resulting in allergic reactions that may be life threatening. Recent studies have explored desensitization to CM using oral immunotherapy (OIT), sublingual immunotherapy, and sublingual immunotherapy (SLIT). Research has found that desensitization will decrease the risk of allergic response to accidental exposures with the hope of lifelong tolerance to CM. The findings indicate means of successful desensitization, lifelong tolerance through maintenance regimens, and methods of increasing safety during desensitization.

## Research Questions
- Does giving increasing doses of cow's milk (OIT) improve tolerance to exposure to cow's milk protein? Yes. Oral immunotherapy and SLIT improved CM tolerance in children with CMA determined by Skripak et al. (2008); Kert et al. (2012); Kim et al. (2011), Nadareishvili et al. (2011), and Levy et al. (2014). Researchers compared techniques of desensitization (OIT, SLIT, heated CM) and methods of adverse reaction reduction (heated CM, strict avoidance, continue to have CM-mediated hypersensitivity reactions.
- Are there methods to maintain long-term tolerance to cow's milk allergy? Currently, no medications or therapy plans have produced lifelong tolerance without maintenance therapy. Kert et al. (2012); Kim et al. (2011), Salive et al. (2013), and Pujo et al. (2013) researched approaches to maintain a high CM threshold and therefore long-term CM tolerance. Approaches to sustain desensitization through maintenance therapy (daily vs twice weekly) is required. A decline in CM threshold occurs in patients previously desensitized without maintenance therapy Skripak et al. (2008).

## Pathophysiology


### Adverse Reactions

- **Type I cell-mediated hypersensitivity reactions** or IgE-mediated reactions:
  - Initiated by hapten that react with normal self-proteins in the skin and remain contained to the point of contact at which a cell-mediated immune response occurs.
  - Cytotoxic T lymphocytes (TC cells) or lymphokine-producing TH cells directly kill foreign or abnormal cells as well as activate other cells to assist.
- **Cow’s milk protein, Type IV cell-mediated reactions, results in tissue destruction in the gastrointestinal tract and contact dermatitis.

### References

1. Levy, E. et al. (2014). Oral Immunotherapy vs Placebo, Skripak et al. (2008) performed a 25 week RCT in 20 children ages 6-21 with IgE-mediated Cow’s Milk Allergy (CMA) to determine children. Participants were escalated to a dose of 500 mg (15 mL of milk), the dose was maintained for 13 weeks followed by a Double Blind Placebo Controlled Food Challenge (DBPCFC). The increase CM threshold was statistically significant (p = 0.02) in the Oral Immunotherapy (OIT) group in addition to a 76% increase in IgG4 (p = 0.02). Adverse reactions were statistically significant (p = 0.02) with OIT group having more reactions.
2. Cow’s Milk Oral Immunotherapy vs Sublingual Immunotherapy, Kert et al. (2012) performed a 6 week study in 30 children ages 4-11 with IgE-mediated CMA evaluating the safety and efficacy of sublingual immunotherapy versus oral immunotherapy. OIT participants tolerated the IgG challenge at T3 (p = 0.02) compared to the SLIT group. Adverse reactions were not statistically significant between the SLIT vs OIT groups (p = 0.7), however, multimammatory reactions were (p = 0.01) with increased incidence in the OIT group. SLIT was limited by the route of administration and a maximum dose of 7 mg compared to the OIT group 1-2750 mg (220 mL milk).
3. Heated Milk Used to Accelerate Tolerance, Kim et al. (2011) conducted a 37 month study of 88 children ages 6-36 months (65%) and demonstrated accelerated heated CM tolerance and increased CM threshold in 74% of the study participants. Researchers observed a significant difference (p = 0.01) between adverse reactions between baked milk-tolerant and baked milk-reactive during DBPCFC in the follow up period.
4. Anti-IgE Therapy (omalizumab) Plus Oral Immunotherapy, Nadareishvili et al. (2011) performed a 1 phase study in 11 children ages 7-17 with IgE-mediated CMA to accelerate desensitization and decrease adverse reactions. Omalizumab was administered every 2-4 weeks for 9 weeks at which time cow’s milk was introduced with a desensitization goal of 1000 mg. The dose of CM was escalated weekly over the next 7.11 weeks with a goal of 7250 mg (220 mL milk). Adverse reactions were 1.6% of dose administrations. This study could not be limited by size, not having a placebo group, phase I study, and length of study.
5. Predictors of OIT Success, Levy et al. (2014) explored oral immunotherapy to predict successful desensitization and increase the cow’s milk protein threshold. Two hundred eighty eight participants with IgE-mediated CMA, ages 4-27 years (mean 7.5) over 10 months enrolled Levels of CM specific IgE and IgG4 were followed. Researchers found participants that successfully reached a desensitization goal of 7.2 g of CM were shown to have higher levels of IgE and IgG4.
6. What Is the Maintenance Therapy to Maintain Tolerance, Salive et al. (2013) explored further if successfully desensitized CMA participants could maintain desensitization with daily maintenance therapy for 3 years. Researchers found 79% of CMS participants maintained significant desensitization. Pujo et al. (2013) studied daily to twice weekly maintenance therapy in a 12 month study with 38 children ages 4-13 years with no statistical significance between dosing regimens (p = 0.18).

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