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

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Abstract

Cow's 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 IgG4 serum levels. Currently, there are no treatments beyond strict allergen avoidance. The patient's quality of life 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), subcutaneous 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.

Statement of the Problem

- **Increasing** prevalence of cow's milk allergy in children
- **ONLY** treatment option is strict avoidance
- Accidental exposures resulting in **life threatening reactions**

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), Keet et al. (2012), Kim et al. (2011), Nadeau 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, anti-IgE pharmaceuticals).
- **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. Keet et al. (2012), Kim et al. (2011), Salmivesi et al. (2013), and Pajno (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) are required. A decline in CM threshold occurs in participants previously desensitized without maintenance therapy Skripak et al. (2008).
- **Are there adjunctive therapies used with oral immunotherapy to decrease the frequency and severity of adverse reactions due to therapy?** Five studies have reviewed the impact of adverse reactions in the development of OIT for CMA: Skripak et al. (2008), Keet et al. (2012), Kim et al. (2011), Nadeau et al. (2011) and Lucendo et al. (2014). Researchers noticed an increase in adverse reactions with OIT. Skripak et al. (2014) observed a statistically significant increase between OIT and placebo (p = .02). Adverse multisystem reactions occurred more frequently in those receiving OIT compared to placebo or SLIT (Keet et al., 2012). Omalizumab allowed a safer, rapid desensitization and is continuing to be researched.

Applicability to Clinical Practice

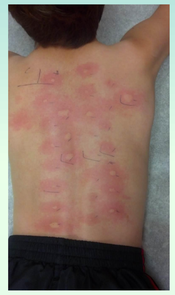
- **Lifestyle modifications**, strict cow's milk avoidance, continue to have possibilities of unintentional exposures resulting in IgE-mediated reactions.
- **Educate** family on new research to improve patient's quality of life both physical and psychological.
- **Raising the CM threshold** in CMA patients has the potential to reduce emergent medical expenses considerably.
- Involves long term **maintenance therapy**
- **Safety** from adverse reactions continues to preserve the absence of OIT in the clinical setting.

Cow's Milk Allergy Facts

- **2-7.5%** of children <1 year of age have CMA (Ludman et al., 2013)
- **2 %** of adults in developed countries have CMA (Sackeyfio et al., 2011)
- **39%** of children with food allergies will have a severe reaction once every four years (Umetsu, 2014)
- **125,000** emergency room visits yearly (Levy et al., 2014)
- **15,000** food induced anaphylaxis episodes yearly (Levy et al., 2014)
- Economic impact is estimated at **25 billion dollars** per year in the United States (Umetsu, 2014)
- **Physical and Psychological burden**
- **53-57%** of children outgrow CMA by 5 years of age
- CMA is more likely to persist in children with asthma or allergic rhinitis (Ludman et al., 2013)
- **No cure**, current treatment is strict avoidance of cow's milk

How is Cow's Milk Allergy Diagnosed?

- **Double-blind, placebo-controlled food challenge** (DBPCFC)→GOLD STANDARD
- **Reoccurrence of symptoms** after ingestion of the suspected food and resolution of these symptoms when strict avoidance is maintained
- **Skin prick testing** (SPT) with >3 mm wheal (Sensitive: 95% NPV, 50% PPV)
- **Serum food-specific IgE levels** with Phadia ImmunoCAP assay (95% clinical reactions)

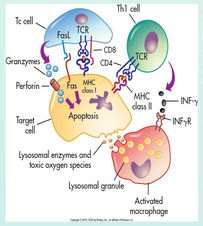


Pathophysiology

	Innate Immunity		
Characteristics	**Barriers**	**Inflammatory Response**	**Adaptive (Acquired) Immunity**
Level of defense	First line of defense against infection and tissue injury	Second line of defense; occurs as a response to tissue injury or infection	Third line of defense; initiated when innate immune system signals the cells of adaptive immunity
Timing of defense	Constant	Immediate response	Delay between primary exposure to antigen and maximum response, immediate against secondary exposure to antigen
Specificity	Broadly specific	Broadly specific	Response is very specific toward "antigen"
Cells	Epithelial cells	Mast cells, granulocytes (neutrophils, eosinophils, basophils), monocytes (macrophages), natural killer (NK) cells, platelets, endothelial cells	T lymphocytes, B lymphocytes, macrophages, dendritic cells
Memory	No memory involved	No memory involved	Specific immunologic memory by T and B lymphocytes
Peptides	Defensin, cathelicidins, collectins, lactoferrin, bacterial toxins	Complement, clotting factors, kinins	Antibodies, complement
Protection	Protection includes anatomic barriers (i.e., skin and mucous membranes), cells and secretory molecules or cytokines (e.g., lysozymes, low pH of stomach and urine) and ciliary activity	Protection includes vascular response, cellular components (e.g., mast cells, neutrophils, macrophages, secretory molecules or cytokines, and activation of plasma protein systems	Protection includes activated T and B lymphocytes, cytokines, and antibodies

Type IV cell-mediated hypersensitivity reactions are:

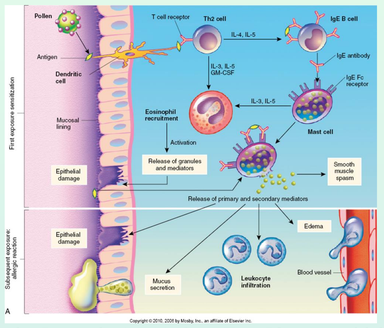
- Initiated by haptens that react with normal self-proteins in the skin and remain contained to the point of contact at which a cell-mediated immune response occurs.
- Cytotoxic T lymphocytes (Tc cells) or lymphokine-producing Th1 cells directly kill foreign or abnormal cells as well as activate other cells to assist.
- Cow's milk protein, Type IV cell mediated reaction, results in tissue destruction in the gastrointestinal tract and contact dermatitis.



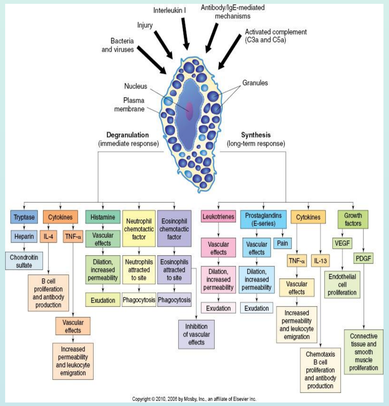
Type	Name of Reaction	Rate of Developement	Class of Antibody Involved	Principal Effector Cells Involved	Complement Participation	Examples of Disorders
I	IgE-mediated	Immediate	IgE	Mast cells	No	Seasonal allergic rhinitis
II	Tissue-specific	Immediate	IgG IgM	Macrophages in tissues	Frequently	Autoimmune thrombocytopenic purpura, Graves disease, autoimmune hemolytic anemia
III	Immune complex-mediated	Immediate	IgG IgM	Neutrophils	Yes	Systemic lupus erythematosus
IV	Cell-mediated	Delayed	None	Lymphocytes Macrophages	No	Contact sensitivity to poison ivy and metals (jewelry)

The human body has 3 mechanisms of self defense:

1. Barriers
2. Inflammatory Response
3. Adaptive (Acquired) Immunity



Adaptive Immunity is critical to a **Type I hypersensitivity** response to cow's milk by utilizing antibodies as memory cells which recognize the cow's milk antigen as foreign, prompting an IgE-mediated reaction involving both antigens, antibodies, and ultimately mast cell degranulation.



Literature Review

- **Oral Immunotherapy vs Placebo.** Skripak et al. (2008) performed a 23 week RCT in 20 children ages 6-21 with IgE-mediated Cow's Milk Allergy (CMA) to desensitize 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= .002) in the Oral Immunotherapy (OIT) group in addition to a 76% increase in IgG4 (p = .002). Adverse reactions were statistically significant (p=.02) with OIT group having more reactions.
- **Cow's Milk Oral Immunotherapy vs. Sublingual Immunotherapy.** Keet et al. (2012) performed a 66 week study in 30 children ages 6-11 with IgE-mediated CMA evaluating the safety and efficacy of sublingual immunotherapy versus oral immunotherapy. OIT participants tolerated the 8g CM challenge at T5 (p = .002) compared to the SLIT group. Adverse reactions were not statistically significant between the SLIT vs OIT groups (p = .73), however multisystem reactions were (p = <.001) 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 1-2 g.
- **Heated Milk Used to Accelerate Tolerance.** Kim et al. (2011) conducted a 37 month study of 88 children ranging in age from 8-75 months old (6 ¼ years) and demonstrated accelerated heated CM tolerance and increased CM threshold in 74% of the study participants. Researchers observed a significant difference (p= .04) between adverse reactions between baked milk-tolerant and baked-milk reactive during DBPCFC in the follow up period.
- **Anti-IgE Therapy (omalizumab) Plus Oral Immunotherapy.** Nadeau et al. (2011) performed a phase I 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 was limited by size, not having a placebo group, phase I study, and length of study.
- **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 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 IgG4.
- **What Is the Maintenance Therapy to Maintain Tolerance.** Salmivesi 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. Pajno et al. (2013) studied daily vs twice weekly maintenance therapy in a 12 month study with 38 children ages 4-13 years with no statistical significance between dosing regimens (p= .08).

Acknowledgements

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