Efficacy and Safety of Oral Immunotherapy in Children with Cow's Milk Allergy

Jessica L. Swansbrough

Pacific University
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Abstract

**Background:** One of the most common food allergies found in children is cow’s milk allergy. Currently the only treatment is a strict avoidance diet and to carry self-injectable epinephrine pens. Unfortunately this current protocol does not prevent against accidental ingestion of cow’s milk protein, which is easily hidden in many foods and could lead to life threatening allergic reactions. Specific Oral Immunotherapy (OIT) can allow these children to become desensitized to cow’s milk protein (CMP) and decrease their risk for serious reactions.

**Method:** Exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science using the keywords: children, immunotherapy and cow’s milk allergy. All eligible articles that met inclusion criteria were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

**Results:** Four articles met inclusion criteria for this systematic review. A randomized control trial, used 60 children with a history of severe allergic reactions to cow’s milk. In the OIT group, 36% of the children became completely tolerant (daily intake of 150 mL whole milk), 54% were partially tolerant (intake of 5-150mL). All of the children in the treatment group experienced allergic symptoms, 16% required IM epinephrine. A randomized double-blinded placebo controlled trial, contained 20 children with IgE-mediated cow’s milk allergy. After OIT the mean cumulative dose causing a reaction was 5 140 mg (240 mL). All the children in the active group experienced mild to moderate adverse reactions, 25% required IM epinephrine. A randomized, controlled, single-blinded trial had 30 children randomized into active group (cow’s milk) and control group (soy milk). Ten of 13 children were able to tolerate 200mL cow’s milk. Two children stopped the study due to severe allergic reaction. A prospective, observational study, including 105 milk-allergic children. 81.9% successfully achieved a minimum milk intake of 200 mL a day. 19% failed the protocol due to severe reactions (12%) or for personal reasons (7%). Multiple adverse reactions occurred during the protocol, 2.8% requiring IM epinephrine. None of the children in each control group became tolerant to cow’s milk and none required IM epinephrine.

**Conclusion:** Oral immunotherapy is a promising treatment option for children with cow’s milk allergy. Before this treatment can be used in clinical practice, further studies are needed to answer remaining issues of the degree of protection, risk of reactions and best fit protocols.

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**First Advisor**
Annjanette Summers PA-C

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Efficacy and Safety of Oral Immunotherapy in Children with Cow’s Milk Allergy

Jessica MacDonald

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR

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Faculty Advisor: James Ferguson, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Jessica MacDonald is a native of Southern California where she majored in Biological Sciences at the University of California, Irvine. After completion of her undergraduate degree, she worked as a medical assistant for an Integrative Medicine office in Irvine, Ca. Her journey through PA school has been supported by her loving husband and son. Post-graduation she is interested in pursuing a career in Pediatrics and Neonatal Care.
Abstract

**Background:** One of the most common food allergies found in children is cow’s milk allergy. Currently the only treatment is a strict avoidance diet and to carry self-injectable epinephrine pens. Unfortunately this current protocol does not prevent against accidental ingestion of cow’s milk protein, which is easily hidden in many foods and could lead to life threatening allergic reactions. Specific Oral Immunotherapy (OIT) can allow these children to become desensitized to cow’s milk protein (CMP) and decrease their risk for serious reactions.

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**Conclusion:** Oral immunotherapy is a promising treatment option for children with cow’s milk allergy. Before this treatment can be used in clinical practice, further studies are needed to answer remaining issues of the degree of protection, risk of reactions and best fit protocols.

**Keywords:** Children, immunotherapy, desensitization, cow’s milk hypersensitivity
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To my husband, Words do not describe the gratitude, respect and amazement I have for and in you. Through long days, late nights and a thousand miles away from family, you kept our house a home. Supporting me in every way possible and always putting our son first. Thank you for making my dreams your own and doing whatever it took to bring them to life. I love you always!

To my parents:  Thank you for your endless support and for always being my biggest fans. For never letting me doubt myself or give up on a dream, no matter the challenges I would face. For always being in arms reach, in case I might fall; just to spring me forward again. We’ve made our dreams come true, love your Baby Girl!
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Table 1: Characteristics of Reviewed Studies and Summary of Findings

List of Abbreviations

CM(P)........................................................................................................Cow’s Milk (Protein)
OIT................................................................................................................Oral Immunotherapy
SOTI...............................................................................................................Specific Oral Tolerance Induction
DBPCFC..................................................................................................Double-blind, placebo-controlled food challenge
NNT..............................................................................................................Number Needed to Treat
RCT............................................................................................................Randomized Controlled Trial
Efficacy and Safety of Oral Immunotherapy in Children with Cow’s Milk Allergy

BACKGROUND

Cow’s milk allergy is the most common food allergy affecting young children, with a prevalence of 2 to 4.5% of the general population. For the most part, cow’s milk (CM) allergy is thought to be temporary, with most children outgrowing the allergy by age 3. However, studies have shown that more than 19% of the children have ongoing CM allergy into their school age years, with 11% still allergic at age 8. Children with immunoglobulin E (IgE) mediated cow’s milk allergy can develop symptoms of urticaria, angioedema, rhinitis, conjunctivitis, gastrointestinal disorders and generalized anaphylaxis, usually occurring within 2 hours of exposure and this can be severe enough to cause a fatal outcome.

Unfortunately, the current first line treatment of CM allergies is avoidance of all milk containing products and the use of self-injectable epinephrine pens as rescue medication. For most, let alone a young school age child, an elimination diet can be difficult and even impossible at times, especially with the number of processed foods made today, making accidental exposures more frequent and leaving children at high risk for severe and possibly fatal allergic reactions.

A recent meta-analysis has shown promising results for the use of oral immunotherapy (OIT) for children suffering from IgE-mediated cow’s milk allergy. In general, the process of oral immunotherapy involves administering small, increasing doses of cow’s milk for a period of time until a maximum tolerance dose is met. This is
followed by a maintenance phase where that maximum tolerated dose is consumed daily. The actual mechanism behind immunotherapy is still unclear, but immunological changes involving immunoglobulins E and G4 have been used as markers, leading to the use of multiple names (oral desensitization, specific oral tolerance induction (SOTI) or oral immunotherapy) to describe the same concept. For most children, the higher the level of specific IgE to cow’s milk found in the serum at time of diagnosis, the less likely the child will come to spontaneously tolerate it over time and the more benefit from oral immunotherapy can be gained. Recent reviews have described multiple studies that have used different protocols and study designs to evaluate the efficacy of oral immunotherapy in CM allergy. The results have ranged from minimal tolerance that will protect against accidental exposures to full tolerance with unrestricted diets. However, these results come with a price. Every time a child is purposely given cow’s milk during the OIT process, it puts them in harm’s way of a potentially serious allergic reaction. It is still unclear whether these results show temporary or long-term tolerance for these children. So the question remains, is OIT for cow’s milk allergy safe enough, and is the outcome worth the potential risk, to make OIT a part of routine clinical practice?

**METHODS**

An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, Web of Science and EBMR Multifile databases, using the keywords: children, immunotherapy, cow’s milk hypersensitivity and desensitization. The search was then specified to articles written in the English language and containing only human participants. Titles and abstracts were screened for information evaluating
the efficacy and safety issues of oral immunotherapy for children with cow’s milk hypersensitivities. All eligible articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).14

**Inclusion Criteria**

Randomized Control Trials (RCTs) published after 2007, containing all relevant key terms and conducted on children of various ages (2-18 years-old) were included. Recent studies published in 2012 focusing on the relevant data above; that have not been critically appraised in previous reviews were also included.

**Exclusion criteria**

Randomized Control Trials before 2007 or conducted using children of a specific age were not included. Studies that evaluated data on other food allergies besides or as well as cow’s milk protein were not included. In addition, studies were not included if they did not address the safety issues surrounding the use of oral immunotherapy.

**RESULTS**

The initial search yielded a total of 89 articles for screening. Once duplicates were removed, the search was reduced to 45 articles. After a thorough review of full texts for relevant data using the method previously stated, the search was narrowed to six randomized control trials. One RCT was excluded because it was conducted using only 2 year-old children.15 A second RCT was excluded for using results for both cow’s milk and egg hypersensitivity16 and a third RCT was also excluded for using a narrow age range for children (ages 1-7) and for additionally conducting the study on children with egg hypersensitivity,17 leaving three articles that met inclusion criteria. An additional
A search was performed on the remaining non-RCTs for studies published in 2012 pertaining to the topic on hand, that were not already included in recent reviews. One observational article was found that met the inclusion criteria. Characteristics of the included studies can be found on Table 1.

**Longo et al Study**

This randomized control trial evaluated the efficacy of specific oral tolerance induction (SOTI) in children with very severe cow’s milk allergy. The authors selected 60 children from Trieste, Italy, aged 5-17 with milk-specific IgE levels greater than 85 kUA/L (80% >100 kUA/L), a positive history of at least one severe allergic reaction when accidentally exposed to milk products (reaction classified as 4 and 5 on Clark’s classification) and positive double-blind, placebo-controlled food challenge test to the lowest doses (0.8 mL of whole milk). The children were computer randomized into two groups: 30 children, the treatment group, were started on OIT immediately, while the remaining 30 children, control group, were kept on a milk-free, elimination diet and both groups were followed for one year. The OIT protocol had a rush phase and a slow increase phase. For the rush phase the children were admitted to the hospital for 10 days and received rapid increases in milk dosage. Doses were administered at 1-hour intervals on the first day and 2-hour intervals on days 2-10, with a maximum dose of 20 mL of whole milk on day 10. The slow increasing phase was performed at home with increasing dosages of 1mL every other day. Parents were instructed on proper protocol in case a reaction was to occur. The primary outcome was the ability of a child to tolerate 150 mL or more of whole cow’s milk as a single dose. SOTI was considered a failure if a child
did not tolerate at least 5 mL of whole cow’s milk in a single dose after one year or if the child discontinued SOTI due to severe side effects.\textsuperscript{7}

After 1 year, in the treatment group, 11 (36\%) of the 30 were able to consume a daily intake of 150 mL of whole cow’s milk or more, plus additional dairy products. 16 (54\%) were able to tolerate between 5-150 mL at a single dose and 3 (10\%) dropped out of the study because of continuous allergic symptoms. In the control group, none of the children gained spontaneous improvement and were unable to tolerate 5 mL of whole cow’s milk at the end of the year. Adverse reactions in the SOTI group were very common, but mostly mild. A total of 5 children experienced an anaphylactic response requiring intramuscular (IM) epinephrine compared to none in the control group (NNH = 7). In the control group, 6 (20\%) children had mild reactions, none requiring IM epinephrine. The study found that specific IgE measured at 6 and 12 months showed a significant decrease in 15 (50\%) of 30 in the SOTI group and IgE levels in the control group were essentially the same.\textsuperscript{7}

Longo et al\textsuperscript{7} showed for the first time, that OIT can be effective in children suffering from a severe food allergy. In this study 36\% of the children that underwent OIT were able to ingest cow’s milk and dairy products without restrictions after 1 year, compared to none in the control group (P<.001, NNT = 3). An additional 54\% of children gained partial tolerance. Although they did not reach a unrestricted diet, the authors stress the importance of partial tolerance as the ability to still prevent accidental exposure to a small amount of cow’s milk (NNT = 2).\textsuperscript{7}
The authors found the limitations of the study to include the insufficient data to estimate the risk of fatal anaphylaxis during OIT compared to the risk of fatal anaphylaxis after accidental exposure in untreated children. It is also unclear as to whether the treatment offers a long-lasting immunity shift or if a daily maintenance dose is required. For these reasons, the authors recommend that SOTI be restricted until larger RCTs are conducted with longer follow-up; despite the promising results found.\(^7\)

**Skripak et al Study**

This study was the first randomized, double-blind, placebo-controlled trial\(^8\) to evaluate whether milk OIT is safe and efficient in desensitizing children with CM allergy. The authors enrolled 20 children from East Coast U.S. medical centers, aged from 6-17 with a known history of IgE-mediated milk allergy (>0.35 kU/L), a positive skin prick test to milk extract and a positive double blinded, placebo controlled food challenge test to a cumulative amount of 2.5 g or less of milk protein. The children were randomized in a 2:1 ratio to a milk (treatment group=13) or placebo OIT (control group=7). The oral immunotherapy involved 3 phases: 1 day of build-up in-office with an initial dose 0.4 mg of milk protein and a final dose of 50 mg, an 8 week in-office dose increase to a maximum of 500 mg and then a daily maintenance dose at home for 3-4 months.\(^9\)

The study showed, 19 children completed the treatment, 12 in the active group and 7 in the placebo group. At the baseline double blinded placebo controlled food challenge both groups mean milk threshold dose was 40 mg. After oral immunotherapy the mean cumulative dose to cause a reaction in the treatment group was 5 140 mg (P = .002), while all patients in the placebo group still reacted at 40 mg (P = .0003). Four children in the treatment group were able to tolerate the entire 8 140 mg compared to
none in the control group (NNT = 4), while 8 other children were able to tolerate partial doses of 1 340-8 140 mg compared to none in the control group (NNT = 2). Milk specific IgE levels did not change significantly in either group, but the milk IgG levels increased significantly in the active group (P = .002). All the children in the active group experienced mild to moderate adverse reactions. Adverse reactions were more common in the treatment group than in the control group (35% to 1%) with most common being local and gastrointestinal reactions and 90% required no treatment. IM epinephrine had to be administered to 4 children of the treatment group compared to none in the control group (NNH = 4).  

The authors found that milk OIT was effective in increasing the reaction threshold to milk in all children that were treated. However, limitations of the study noted by the authors include, the unclear concept as to whether the children are fully tolerant or simply temporarily desensitized and at risk for future reactions. Also, the authors note that allergic reactions with OIT were common and not optimal for therapy, even though most did not require treatment and those that did responded well to medications. The authors recommend the uncertainty of safety and long-term efficacy be further evaluated before OIT is considered for clinical practice.  

**Pajno et al Study**

This randomized, single-blind, placebo controlled trial focused on establishing a patient-friendly desensitization protocol using a weekly up-dosing schedule. The authors enrolled 30 children, aged 4-13 years-old from allergy units of two hospitals in Italy, with IgE-mediated CM allergy confirmed by double blinded, placebo controlled food challenge test and positive skin prick test. The children were equally randomized to
desensitization with CM (treatment group) or soy milk (control group). Soy milk was used as the control, doses and treatment remained blinded to the investigators and physicians. However, the study was not blinded to the children and their parents because of the distinctive difference in taste between whole cow’s milk and soy milk. The oral immunotherapy protocol consisted of weekly outpatient visits, set-up for an 18-week regimen. At weekly intervals, increasing amounts of CM (or soy milk) were given, starting with 1 drop of a 1:25 dilution and doubling every week in the clinic to reach a 200 mL maximum at the end of the 18 weeks. A daily dose equal to the most recent weekly increased amount was given to each child at home.9

The study had 2 dropouts from the treatment group and 1 from the control group early in the protocol due to personal family reasons, leaving 13 children in the treatment group and 14 children in the control group. After the 18 weeks, 10 (77%) of the 13 treatment children achieved full tolerance (200 mL) to CM, compared to none in the control group (NNT = 2). One child obtained partial tolerance (5-100 mL) to CM, compared to no children in the control group (NNT = 14). The authors state 3 children experienced severe reactions needing IM epinephrine in the treatment group, compared to no severe reactions among the control children (NNH = 5). The study found no significant changes in specific IgE levels following OIT treatment, but the study did note significant increases in specific IgG4 levels in children that were treated with OIT (P = .003). A follow-up at 6 months after completion of the study showed no clinical changes in the patients that continued to tolerate CM.9

Pajno et al9 argue that the proposed protocol is as safe and effective than previously mentioned studies, but more practical and patient-friendly because it does not
requiring hospitalization or long treatment periods. The authors mention that the significant increase in IgG4 levels shows an induced consistent immunologic change in children treated with OIT. However, the authors found the limitations of the study to include whether these immunologic changes correlate to a permanent or temporary desensitization. Pajno et al recommend the proposed outpatient weekly up-dosing protocol be the new choice of regimen for children with IgE-mediated CM allergies.9

Sanchez-Garcia et al Study

This prospective open-label observational study10 focused on the efficacy of milk oral immunotherapy. The authors enrolled 105 children, aged 2-18, with IgE-mediated CM allergy (> 0.35 KU/L) from Nino Jesus Paediatric Hospital in Madrid, Spain. Children were not randomized to treatment and control groups and placebo was not used. The OIT protocol contained an induction phase and a maintenance phase. The induction phase consisted of increasing milk doses weekly in the clinic under medical supervision and continuing the tolerated dose at home daily, until a total dose of 200 mL of whole milk was met. Children were treated with a daily dose of antihistamines during the induction phase. Once the child achieved the daily intake of 200 mL of milk, the maintenance phase was started. The child was instructed to consume 200 mL or more of milk and dairy products daily until the end of the study.10

Of the 105 children in the study, 86 (81.9%) reached full tolerance of a daily dose of 200 mL of milk. 19 (19.1%) children did not meet the 200 mL daily intake and failed treatment due to either moderate or severe reactions or for personal reasons. The authors did not make it clear if any children achieved partial tolerance. The authors reported 3 children had severe reactions requiring IM epinephrine (2.8%). The study did obtain
results showing a significant decrease in specific IgE to milk (P = 0.007) and casein (P = 0.001) levels in children treated with OIT.\textsuperscript{10}

The authors found the limitations of the study to include long-term follow-up for those children who were successful with OIT. The authors state it is still unclear as to which type of protocol (rush or slow up dose) gives maximum results with the fewest adverse reactions. The authors recommend that milk OIT should be implemented as a routine treatment for a child suffering from IgE-mediated CM allergy, but only by experienced allergist, specializing specifically in food allergy immunotherapy and where proper rescue medication is available. However, Sanchez-Gracia et al state, before this is possible further studies on accurate biomarkers to test response of OIT need to be done, as well as an international position paper.\textsuperscript{10}

**DISCUSSION**

The eligible studies\textsuperscript{7-10} found that children with cow’s milk allergies who received oral immunotherapy had a higher rate of achieving tolerance to cow’s milk than children who used elimination diet alone. The magnitude of the treatment effect was very large, however, the confidence behind this data is still somewhat lacking, as demonstrated by the moderate level of quality of evidence found (refer to Table 1).

**Clinical Relevance**

The primary outcome when initiating oral immunotherapy is for the child to reach full tolerance to cow’s milk. Full tolerance by definition in the included articles is the ability to consume a minimum 150 mL of whole CM in a single dose with no allergic symptoms. The Longo et al\textsuperscript{7} study results yielded much lower tolerance rates compared
to other studies\(^9-10\) (36% vs. 80%). However, this is most likely due to the fact that their study only included children with severe cow’s milk allergy (>85 kUA/L) and therefore, less likely to become tolerant.\(^11\) In addition, when considering the children that gained partial tolerance (5-150 mL) the success rate increases to 27/30 (90%). This becomes a crucial point when considering children with life threatening CM allergy because even providing the smallest amount of protection can prevent against an accidental exposure and potentially save a life. The Skripak et al\(^8\) study also displayed lower tolerance rates (33%) than the other studies.\(^9-10\) This can be explained by the authors using an equivalent of 240 mL of whole cow’s milk as the maximum goal at the end of the induction phase compared to the 150 mL maximum used by most studies. In other words, 75% of the children were able to consume 125 mL of CM before having a reaction and overall, 100% of the children were able to achieve at least partial tolerance, which once again becomes a key aspect when considering accidental exposures.

Pajno et al\(^9\) was the first to use a weekly up-dosing immunotherapy protocol and the most recent study by Sanchez-Garcia et al\(^10\) used a very similar set-up, requiring no hospitalization and only a time restraint average of 4.5 months. Both studies had over an 80% full tolerance outcome, interpreted to mean that the “patient-friendly and easy-to-use”\(^9\) regimen should be recommended as the preferred protocol of choice for OIT. Sanchez-Garcia et al\(^10\) also demonstrated that “high risk” children with severe cow’s milk allergy, that failed regular protocols, can still achieve full tolerance through the use of the slow up dose weekly protocol by extending the length of the induction phase.
In all the included studies,\textsuperscript{7-10} less than 20% of the children had to discontinue treatment due to severe allergic reaction. However, almost 100% of children in each trial did experience mild to moderate adverse reactions. Most of the reactions required no medication and future reactions in those children were minimized by decreasing the rate of oral desensitization. On average, the studies\textsuperscript{7-10} showed that one in four children treated with OIT would require use of IM epinephrine and therefore would have experienced a life threatening reaction during the therapy, compared to their control groups, where no child on elimination diet alone required IM epinephrine. This raises huge concern when considering OIT and whether it is worth putting children in high risk situations to prevent that same situation, which may or may not ever happen. On the other hand, if the choice was given, most parents would choose to have their children exposed to severe allergic reactions under direct supervision of a medical provider with all necessary rescue medications within arm’s reach, as opposed to a reaction occurring in some unknown location with no safe guards. In a recently published article, Barbi et al\textsuperscript{19} evaluates adverse effects during OIT. The study found that out of 192 children only 5 (2.6%) experienced a severe allergic reaction (Clark Scale 5)\textsuperscript{18} that required IM epinephrine. These results support the concept that even though adverse reactions are common and frequent during OIT, most are easily manageable. The concept of oral immunotherapy may appear simple to parents of milk allergic children and a process that they can easily do at home; however, each study stresses the dangers and the potential of a fatal outcome, surrounding the protocols. Oral immunotherapy needs to be treated with the up most respect and performed only under direct medical supervision to prevent accidental and unnecessary harm to a child.
Limitations of Study

The included studies\textsuperscript{7-10} offered promising results for the future of oral immunotherapy. However, the evidence supporting these results is of moderate quality (GRADE)\textsuperscript{14} because of serious limitations, imprecision and possible publication bias. Only one of the three included RCTs was double-blinded,\textsuperscript{8} (high quality) while the other two were single-blinded or contained no blinding\textsuperscript{7,9} (moderate quality) and the observational study had no randomization or control (low quality). In addition, there is variability across the studies, involving timing, differences in protocol and the appropriate markers for immunotherapy. Brozek et al,\textsuperscript{13} a systematic review and meta-analysis for cow’s milk oral immunotherapy argues, that the evidence\textsuperscript{7-9} has very serious imprecisions due to very small sample sizes. The included studies\textsuperscript{7-10} were down-graded for this reason, but then upgraded because the magnitude of effect was large enough (RR = infinite) that a large sample size would not change the results. However, Brozek et al,\textsuperscript{13} argued a strong point regarding the presence of publication bias. Although it cannot be proven, it is highly possible that studies containing high adverse reactions have remained unpublished, leading to weak evidence where anaphylactic shock is concerned.

Recommendations for further studies include a standardized protocol, possibly similar to the patient-friendly regimen introduced by Pajno et al\textsuperscript{9} that focuses on minimizing allergic symptoms. Further studies should address the issue of “tolerance” vs. “desensitization” and whether a daily maintenance dose is required to maintain the acquired tolerance. Further double-blind, placebo-controlled RCTs need to be performed on large sample sizes, and adverse effects should be studied closely to minimize all bias.
CONCLUSION

Overall oral immunotherapy has a promising future as the treatment for children with cow’s milk allergies. Even if only partial tolerance is achieved the child and their parents will be able to live their lives without the constant fear of accidental exposure. The risk of experiencing a reaction during OIT protocols, although common, is much safer than the potential harm that can occur with an unexpected severe allergic response. Implications for the clinical practice is to recommend a standardized, patient-friendly, cost effective OIT protocol, for all children older than three with moderate to severe cow’s milk allergy, with a specific focus on young school age children, who are no longer under constant parental supervision and are therefore vulnerable to accidental exposure. Implications for the researchers are to conduct further studies to determine a standard protocol, that has maximum effects with the fewest adverse reactions and which is easy to perform and comply to, and to further evaluate the discussion of tolerance and desensitization to determine if a daily maintenance dose is required once tolerance is achieved. Researchers need to focus on discovering the mechanism behind oral immunotherapy, so a standardized biomarker can be used across studies to accurately display the effectiveness of the therapy. Until these further studies can be conducted and the true efficacy and safety of OIT determined, it is recommended that OIT for cow’s milk allergy only be used in scientific trials.
References


TABLE 1 Characteristics of Reviewed Studies, GRADE profile

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<thead>
<tr>
<th>Complete Tolerance to Cow’s Milk (&gt;150 mL/day)</th>
<th>Number of Patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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<td>Sanchez-Garcia et al(^4)</td>
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<table>
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<tr>
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<td>0/7</td>
<td>Infinity(^e)</td>
<td>NNT 2</td>
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<td>Pajno et al(^3)</td>
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<tr>
<th>Anaphylaxis (use of IM epinephrine injection)</th>
<th>Number of Patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
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<td>Longo et al(^1)</td>
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</tbody>
</table>

\(\text{No blinding in the Longo et al study}^1\) and the Pajno et al study\(^3\) was only single blinded. The observational trials had no randomization, control group or blinding

\(\text{All studies contain small sample sizes}\)

\(\text{RR} > 2 \text{ in the RCTs}\)

\(\text{Publication bias likely due to possible misinterpretation of severity of reaction}\)

\(\text{No participants in the controls that were able to tolerate the minimal amount of milk protein in food challenge}\)