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The Efficacy and Safety of Epicutaneous Immunotherapy for Milk Allergy: A Systematic Review

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Abstract

Introduction: *Cow's milk allergy (CMA) is rising among children and adults, affecting 2-3% of children in affluent countries. Currently, the only standard of care is dairy restriction. However, epicutaneous immunotherapy (EPIT) is being studied as a potential treatment involving transdermal administration of an allergen to induce tolerance. EPIT has been proven safe for managing other food allergies in children and adolescents, but its efficacy for CMA is yet to be determined.*
Methods: *A systematic search of four databases (PubMed, ScienceDirect, SCOPUS, and clinicaltrials.gov) was conducted in September 2022 by three independent reviewers. Additional studies were found by manual reference browsing. All published articles and randomized controlled trials (RCTs) that assessed the effect of EPIT on CMA in children and adolescents aged ≤18 years were included. The search terms used were "epicutaneous immunotherapy" or "immunotherapy" or "EPIT"; "milk allergy" or "cow's milk allergy" or "CMA" or "CMPA"; "children" or "young" or "kids."*
Results: *Six studies were included after a systematic search of 123 studies, with three RCTs evaluating the safety and efficacy of EPIT in children with CMA and three meta-analyses and reviews on EPIT for CMA. The findings were inconclusive but suggested the possibility of treating cow's milk allergy.*
Discussion: *EPIT shows promise in treating food allergies, including CMA. Evidence is lacking to determine its efficacy for CMA. More clinical trials with different dosages and longer follow-ups are needed. Results should be interpreted with caution due to limited studies.*

Introduction

Cow milk allergy (CMA) is a potentially severe and life-threatening condition in children and adults. Although potentially powerful in young children, it is frequently outgrown in the first 3–4 years of life. Vanderplas et al. (2008) mentioned that the primary allergens associated with CMA are caseins, representing approximately 80% of the proteins in cow's milk. It is the most common food allergy in childhood, with 5-15% of infants having CMA-like symptoms and 0.5% of breastfed infants exhibiting consistent clinical responses as CMA. Newborns with CMA often experience cutaneous symptoms within the first month of life (50-70%), followed by gastrointestinal symptoms (50-60%) and respiratory symptoms (20-

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30%). Symptoms may appear immediately or hours after consuming milk (Vandenplas et al., 2008).

Observational studies have shown that patients with cow's milk allergy have a high innate tolerance and frequency rate. Kripak et al., (2007) described tolerance as "no reactions in the past 12 months and a cow's milk IgE level < 3 kU/L". Unfortunately, as of today, treatment is currently unavailable for the population that does not develop tolerance. The only option is the avoidance of allergens. Consequently, affected children face unforeseen reactions that can negatively affect their quality of life and be potentially life-threatening.

Epicutaneous treatment is a viable treatment option for food allergies. EPIT develops immune tolerance by exposing the skin to controlled amounts of a specific allergen through the regular application of a patch or tape. This repeated exposure modulates the immune system, reducing symptoms and severity of food allergies to increase the individual's tolerance and reduce sensitivity over time. (Xiong et al., 2020) The EPIT uses a patch to apply an allergen to the skin. This delivery method enables administration in an environment without medical supervision, such as at the patient's home. Therefore, it is more convenient than receiving care in a hospital. Recent clinical studies have demonstrated the safety and efficacy of EPIT for managing food allergies in children and adolescents. (Rutault et al., 2016) However, the efficacy of this treatment for CMA has not been established yet. As the prevalence of cow's milk allergy (CMA) in children and adults is rising, it is vital to apply proper interventions to stop allergic responses and avoid unnecessary dietary restrictions. This systematic review intends to summarize the safety and efficacy of EPIT in patients with CMAs.

Materials and Methods

Search strategy

An online search was conducted in the PubMed, ScienceDirect, SCOPUS, and clinicaltrials.gov databases from January 2000 until September 2022 with the research question: "Efficacy and safety of epicutaneous immunotherapy in children aged three months to 18 years diagnosed with cow's milk allergy" following the PICOS criteria (population, intervention, control, outcome, and study design): (i) population: children/adolescents ($\leq$18 years) with cow's milk allergy (CMA); (ii) intervention: epicutaneous immunotherapy; (iii) control: standard of care (dietary restriction)/placebo; (iv) outcome: milk allergy desensitization (efficacy) and safety of the intervention; (v) study designs: randomized controlled trials and observational studies, systematic reviews, and meta-analyses.

Data Collection

We conducted database searches in PubMed and SCOPUS to identify reports, studies, clinical trials (Figure 1), systemic reviews, and meta-analyses written in English from 2000 to 2022. The search terms used were "epicutaneous immunotherapy," "immunotherapy," "EPIT," "milk allergy," "cow's milk allergy," "CMA," "CMPA," "children," "young," and "kids" (details of the search strategy can be found in Figure 1). We included all English-language articles published at the time of the review. Additionally, relevant studies were identified by reviewing cited references in retrieved papers and one meta-analysis (Xiong L et al., 2020). This strategy is presented in Appendix 1. The selection of studies was conducted according to the PRISMA guidelines.

Selection Criteria

Studies that met the criteria for the mini-review were: (1) intervention: EPIT, regardless of the number of sessions; (2) condition: cow's milk allergy or CMA; and (3) population: studies that included subjects aged less than 18 years.

Two groups of reviewers (group A = x reviewers, group B = y reviewers) conducted the literature review. Titles and abstracts were screened to remove duplicates, and studies that did not qualify due to language and studies with interventions other than EPIT were excluded (n=35). Each paper was thoroughly reviewed to identify relevant studies or papers for this mini-review. Discussion between the four reviewer's groups resolved disagreements on study inclusion.

The specific criteria were as follows: (1) participants diagnosed with milk allergy younger than 18 years of age based on the clinical history and laboratory tests; (2) EPIT was administered to the intervention group; (3) placebo or allergen avoidance in the control group, and (4) at least one of the primary or secondary outcomes was reported.

Results

The search yielded 123 studies. After the screening, 39 records were retrieved via database, and the identification of 2 articles via manual reference browsing. Out of these, 35 were excluded based on the inclusion/exclusion criteria, mainly due to wrong therapy or wrong food allergy. The analysis included the remaining three review studies and three randomized clinical trials. Table 1 describes the main features of the clinical trials, and Table 2 summarizes the

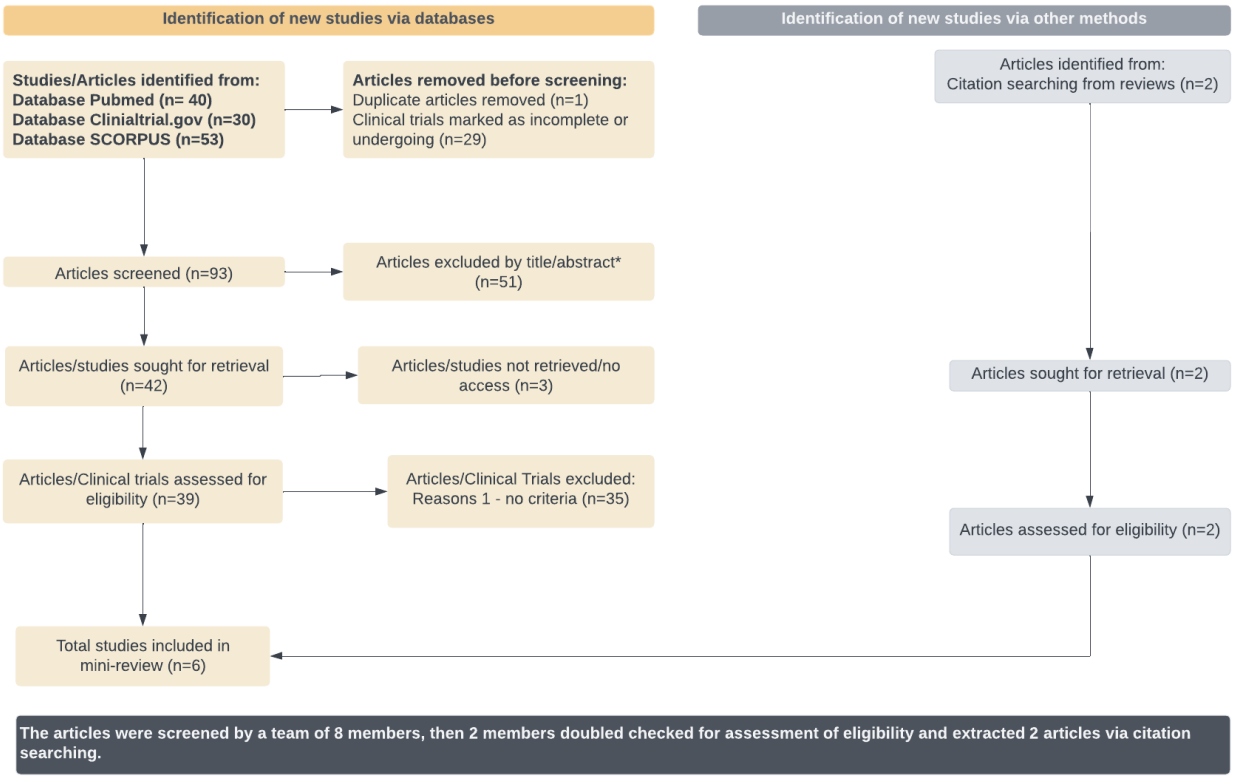

Figure 1: *PRISMA Flowchart of the articles selection process.*

corresponding data. The studies that evaluated the effects of EPIT on children and adolescents with milk allergies were considered.

Dupont et al. (2010) evaluated EPIT for milk allergy in the first published trial. Patients aged between three and 15 years were included in the study. The patch was applied three times per week for 48 hours (at a dose of 1 mg of cow's milk protein). They described the most frequent symptom as local erythema, visible for 4–14 days. The frequency of adverse reactions in the active group was described as the number of patients with adverse effects (AE) and the frequency of responses for a total number of doses in the study as follows: skin disorders (5 of 10 patients; 93 of 470 doses), respiratory symptoms (2 of 10; 2/470), gastrointestinal symptoms (1 of 10; 16/470), and fever (1/10; 6/470). No severe reactions or the need for epinephrine was found during the study. In addition, one patient in each group received steroids for local eczema. The treatment was well-received by the patients. No treatment was interrupted due to an AE, and no child received epinephrine or visited the emergency department or hospital.

A second study (Rutault et al., 2016) with children and adolescents described three successive cohorts of six subjects who received 150 µg, 300 µg, or 500 µg cow's milk protein patches (versus placebo). The 18 subjects included in the study did not report any serious adverse events during the three weeks of treatment. The majority of the subjects (83.3%) reported local itching, redness (83.3%), or swelling (72.2%). Four adverse events (all of which were of mild or moderate intensity) were reported. The first report was published in an abstract format without describing adverse events at higher doses. Later, the results of 198 patients (phase II) were published on the DBV Technologies website.

Spergel et al. (2020) conducted a parallel-group phase II trial (EPIT or placebo) for patients aged 4–17 years diagnosed with milk-induced eosinophilic esophagitis (EoE). They used patches containing 500 µg of milk protein (Viaskin milk). The primary outcome was efficacy, measured as "maximum esophageal eosinophil counts." The safety outcomes have been reported. Although no difference was observed in the intention-to-treat population, the protocol revealed that the active treatment group had a lower mean eosinophil count (p=0.038). Therefore, the role of EPIT in treating EoE remains unknown.

Esposito et al. (2018) reviewed food allergies, including CMA. They concluded that despite the variability in the methods used to demonstrate the safety and adherence of EPIT, there was evidence of its efficacy and safety for food allergies. However, the review also highlighted the need for further studies

	Study			Participants			Intervention and Control	
		Design	Geographic	Sample Size	Age	Diagnosis	Treatment duration time	Intervention	Control
Spergel, 2020	RCT	Unicenter	USA	20	4-11 years	milk-induced Eosinophilic Esophagitis	9 months	milk patch 500 μg	placebo
Dupont, 2010	RCT	Bicenter	France	19	3 months-15 years	milk allergy	12 weeks	milk patch 1mg	placebo
Miles trial, 2018	RCT	Multicenter (17)	USA and Canada	198	2-17 years	milk allergy	12 months	milk patch 150μg, 300 μg, 500 μg	placebo

Table 1: *Summary of Clinical Trials based on study, participants, and intervention and control.*

to answer questions about dose and treatment time, which remained open after other clinical trials and studies.

Efficacy

Clinical and surrogate outcomes were used in these trials to determine desensitization. IgE levels, blood protein measurements (comprehensive metabolic panel), and skin prick tests were surrogate outcomes.

In the first study reported by Dupont (2010), the mean cumulative tolerated dose (CTD) escalation was 12 times higher in the active group than in the placebo group (8%) ($p = 0.13$). However, the study observation period was only three months, insufficiently producing meaningful results. Furthermore, meaningful results would take at least one year after the initiation of treatment. (Longo et al., 2008) As a result, more research is needed to determine the long-term therapeutic effects.

Xiong et al. (2020) conducted a meta-analysis to determine the safety and efficacy of EPIT for allergen-induced diseases. They included ten clinical trials, two of which were on cow's milk allergy (CMA), and their findings indicated that the efficacy of EPIT for CMA remains unknown. Compared to the placebo, the pooled data suggested that EPIT could significantly raise the reactivity threshold for peanuts or cow's milk (RR 2.34, 95% CI 1.69-3.23; I2 = 0%). In addition, the risk of local reactions was significantly higher for EPIT (RR 1.56, 95% CI 1.03-2.36; I2 = 82%) than placebo. EPIT significantly improved tolerance to allergic food in IgE-mediated cow's milk allergy (RR 2.33, 95% CI 1.68-3.22; I2 = 0%) according to subgroup analyses. However, tolerance improved significantly only in children aged 12 years (RR 2.85, 95% CI 1.92-4.24; I2 = 0%) compared to adults. They concluded that the efficacy of EPIT for CMA remained unknown and EPIT may cause more local skin reactions but no severe or systemic adverse effects. Nonetheless, these findings should be interpreted with caution because of the small number of studies and differences in EPIT time and dose.

Discussion

This study aims to review the latest updates and fill the knowledge gap in CMA using EPIT since no new RCTs have been published since the review by Esposito et al. (2018).

The studies conducted by Dupont et al. (2010), Rutauld et al. (2016), and Spergel et al. (2020) have made substantial contributions to the understanding of EPIT. However, despite the compelling data presented in these works, some important questions still need to be addressed to comprehend the implications of EPIT fully.

In order to deepen our understanding of this subject, it is crucial to carry out longer-term trials that assess the safety of EPIT and its efficacy. Additionally, future investigations should be designed more rigorously, incorporating a comprehensive review of the existing literature to ensure that all relevant data is considered. Only then can we truly understand the full potential of EPIT and its impact on the field.

The first published experiment found a "trend toward improvement in the cumulative tolerated dose in the active treatment group" (Dupont et al., 2010), but this did not show significance due to the short duration of therapy (3 months). Therefore, longer treatment times are needed to better understand EPIT's efficacy for CMA.

These research gaps call for the design of novel randomized clinical trials. Researchers must adopt a comprehensive strategy to evaluate the influx of new immunotherapies that address therapeutic gaps for different food allergies. No reports of anaphylactic cases emerged from any investigations due to the non-use of epinephrine. To compare the safety of different regimens, a uniform grading system is recommended to categorize the adverse effects of allergen immunotherapies. However, none of the studies evaluated the impact on the quality of life of the patients, the parents, or both, which is important to consider.

Despite the small number of studies, several of which had the same sponsor, researchers should per-

Main efficacy outcome		**Main Results**				
MILES trials, 2018	Oral Food Challenge (Cow milk protein - CMP): (1) a increase ≥ 10 fold in the cumulative reactive dose (CRD) at month 12 (as compared to the baseline value) plus reaching tolerance to at leat 144 of CMP (4.5 mL of milk) or (2) a CRD of CMP ≥ 1,44 mg (45 mL of milk) at month 12 of the food challenge		Responders Rate				300 µg dose was identified as the most effective tested dose for children (intent-to-treat (ITT), p=0.042
			Placebo group	150 µg	300 µg	500 µg	
		Overall	30.2%	36.7%	49%	36.2%	
		Children (2 to 11 years)	32.5%	34.2%	57.9%	38.9%	
		Adolescents (12 to 17 years)	23.1%	45.5%	18.2%	27.3%	
Spergel, 2020	Patients maximum esophageal eosinophil count on biopsy specimens, one week after milk reintroduction. (Maximum eos/hpf (400X) field from 4-mm hematoxylin and eosin-stained sections)		Mean (SD)				
			Placebo group		500 µg		
		Intent to treat analysis	48.20 (56.98)		50.1 (43.97)		No significant difference. Least square means difference 8.6 (95& CI, -35.36 to 52.56)
		Per-protocol analysis	95 (63.64)		25.57 (31.39)		Significant difference. Least square means difference -69.37 (95% CI, -117.47 to -21-28)
Dupont, 2010	Pilot Study		Mean (SD)				
			Placebo group		1 mg		
	Oral dood challenge (OFC). Measure by the increment in the cumulative tolerated dose, Per protocol analysis	Day 0	4. 36 (5.87)mL		1.77 (2.98)mL		No significant difference. P-value = 0.13
		Day 90	5.44 (5.88)mL		23.61 (28.61)mL		
	Serum Cow's milk protein-sIgE (measured in KUA/L)	Day 0	12.19 (17.02)		20.18 (23.27)		No significant difference. P-value = 0.68
		Day 90	20.99 (32.55)		19.48 (17.44)		

Table 2: *Randomized Clinical Trials findings on cow's milk allergy.*

form additional independent studies to confirm the results and increase the acceptance of such interventions. We encourage other researchers in the field to investigate the application of EPIT in children with CMA due to its high potential benefit for children's psychological and physical development. EPIT therapy shows promise, but additional studies are needed to determine the efficacy of EPIT that further in the future, will provide a clearer understanding of the treatment's effectiveness and inform decision-making for healthcare professionals and families.

Author Contributions

Conceptualization- LMAF, WNPG; HV; AM; Methodology - LAMF, WNPG, GG, VVV, HV, GMM, MA, GN, CH, RM, VAA, VC; AM; Writing – Original Draft Preparation- LMAF, WNPG, HV, GMM, MA; Tables - GMM; Writing – Review & Editing - LMAF, WNPG, HV, GG, RH, YMEKAH; Supervision- RH; Project Administration, PPCR; All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The original articles cited in this reference list are available through the provided DOI links in their respective publications.

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Conflicts of Interest

The authors declare no conflict of interest.

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