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Sustained milk consumption after 2 years post-Milk Epicutaneous therapy for Eosinophilic Esophagitis

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Author contribution:

JMS-study design, writing manuscript, interpreting data; ABM-writing manuscript, study visits, data interpretation; CAL-writing manuscript, study design, interpreting data; DB-writing manuscript, regulatory coordinator, coordination and collection of data, study visits; MOL-writing manuscript, collection of data, study visits; TBW-writing manuscript, collection of data and study visits, AC-interpreting data, collection of data, study visits, regulatory items

To the Editor:

Eosinophilic Esophagitis (EoE) is an allergic disease of the esophagus without any curative therapy. Typical symptoms of EoE are feeding difficulties, vomiting, abdominal pain and dysphagia and vary by age, with a diagnosis confirmed on esophageal biopsy with> 15 eosinophils/high power field (eos/hpf).[1]

The two treatment options for pediatric EoE[2] are: 1) topical swallowed steroids, which is effective in inducing EoE remission in 50-90% of patients, depending on the dose, formulation and medication used; 2) dietary elimination of the causative allergen/s which is effective in 50-70% of patients with selective food elimination, and 95% with elemental diets[3]. Cow's milk (CM) is the most common food allergen causing disease in up to 65% of patients.[4] When either treatment is discontinued, inflammation and symptoms recur.[3]

Epicutaneous immunotherapy (EPIT) is an investigational immunotherapy using low dose allergen exposure through the skin to induce desensitization. In the randomized controlled clinical trial,*Study of Efficacy and Safety of Viaskin® Milk for CM-induced EoE (SMILEE Study)* , 20 pediatric participants with CM-induced EoE were randomized to receive EPIT with Viaskin® Milk (n=15) or placebo (n=5)(details in appendix). After CM-induced EoE was confirmed, EPIT therapy was applied daily for 9 months during a CM-free

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period, followed by CM-containing diet for 2 months (Figure 1). At 11 months, subjects completed an upper endoscopy with biopsy to evaluate tissue eosinophilia as the primary endpoint. In the pre-defined per-protocol population (7 patients-Viaskin® Milk, 2 patients- placebo), Viaskin® Milk treated subjects had a lower number of eosinophils/high power field (eos/hpf) on biopsy (25.57 ± 31.19) compared to placebo (95 ± 63.64). After the blinded phase, 19 subjects were eligible to enroll in the open-label extension (additional 11 months of therapy) and had repeat endoscopy and biopsy. At the end of the open-label phase, 6/19 subjects had < 6 eos/hpf (32% response rate); 3/19 subjects had 7-14 eos/hpf for total response rate of 47%.[5]

As part of routine clinical care, we continue to follow all 19 subjects who completed the open-label extension (currently 2 years after the end of Viaskin® Milk therapy) to understand whether CM continued in their diet without symptoms. Four of 5 subjects who had <6 eos/hpf after milk introduction were able to continue with approximately 2 servings of CM/day without any symptoms (Table 1). One of these patients had a clinically indicated endoscopy and biopsy that had 0 eosinophils. Two subjects, who had 6-14 eos/hpf during the study, continued to tolerate CM, including one subject who continued to have 6-14 eos/hpf on repeat endoscopy. In addition, 4 subjects who had significant symptoms ingesting CM and had > 15 eos/hpf during the initial SMILEE study were able to add CM back into their diet without having symptoms, as either baked CM (n=2) or regular CM with concomitant swallowed steroids therapy (n=2).

The follow-up of this pilot study for the use of EPIT for milk-induced EoE suggests that the treatment effect can persist for 2 years after stopping therapy; six out of 7 patients in the responder and partial responder groups remain completely symptom-free while consuming an average of 2 servings/day of CM. In contrast to the current therapies of diet elimination or swallowed topical steroids where symptoms return when therapy is stopped, EPIT has demonstrated a persistent effectiveness. These findings align with EPIT's proposed mechanism of action, by directly targeting and reprogramming the immune response to allergen.[3] EPIT may induce true tolerance, as is observed in murine models, where Foxp3(+) CD25(+) CD4(+) T regulatory cells are induced and can transfer tolerance.[6] Further longer-term studies are needed to examine this possibility and confirm these unique findings.

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Sincerely,

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Table 1

Responder Status to Viaskin Patch after milk introduction and treatment	**Complete responders (< 6 eos/hpf)**	**Partial Responders (6-14 eos/hpf)**	**Non Responders (> 15 eos/hpf)**
N	6	3	10
Time from last application of Patch (yrs; mean + SD	2.0 + 0.2	2.0 + 0.1	
Current Milk consumption (servings/day; mean + SD)	2.1 + 0.4	2.75 + 0.4	2 subject on baked milk with nl bx 2 subjects on milk on swallowed steroids-nl bx 3 off milk 1-Biological therapy
Current Symptoms	4 - none 1 -minimal	2-none	
More recent endoscopy and biopsy (eos/hpf)	0 N=1	10 N=1	2
Lost to Follow-up	1	1	

Eos/hpf-eosinophils per high power field; Nl bx-normal biopsy; yrs-years, SD-standard deviation

Figure 1: Schematic Study diagram

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`image1.emf` available at https://authorea.com/users/356155/articles/479132-sustained-milk-consumption-after-2-years-post-milk-epicutaneous-therapy-for-eosinophilic-esophagitis

Figure 1 Legend:

Study schematic with 4 upper endoscopies with biopsy with the first confirming the diagnosis of eosinophilic esophagitis and the last 2 being research endoscopy determining endpoints of the study.

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