Prevalence of Eosinophilic Esophagitis in Sublingual Immunotherapy Tablet Clinical Trials is Similar to the Background Prevalence in an Atopic Population

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Introduction

- Eosinophilic esophagitis (EoE) is an allergen-mediated inflammatory condition of the esophagus
- The prevalence of EoE in the general population is approximately 0.1%[1] and is observed to be higher in adults than children
- Patients with EoE often have comorbid allergic disease (i.e., allergic rhinitis, asthma, eczema, food allergy), known as atopy[2]
- The presence of atopic disease is known to increase the risk of developing EoE[1,3]
- There is currently limited prevalence data for EoE in atopic populations, although recent studies have estimated the prevalence of EoE in atopic populations as 8.0-16.5% in adults and 0.2% to 5% in children[1,4,5]
- Sublingual immunotherapy (SLIT)-tablets are an effective treatment for allergic rhinitis with or without conjunctivitis (AR/C)
- Reports of EoE associated with SLIT-tablets are rare[6,7]

Objective

- To assess the prevalence of EoE in subjects with atopic disease treated with SLIT-tablets in clinical trials

Methods

- Qualifying SLIT-tablet trials for the analysis were those having an intentional focus on EoE as described in their protocols or during conduction of the trial
- All subjects included in the trials were atopic, having AR/C and/or asthma
- 4 house dust mite SLIT-tablet trials, 1 ragweed SLIT-tablet trial, and 1 tree* SLIT-tablet trial fit the criteria for analysis (**Table 1**)

Table 1. Trial characteristics

Trial	No. Randomized		Age Range, y	Duration of Treatment
	SLIT-Tablet	Placebo		
HDM trial 1 (MT-06)	654	338	18–65	12 mo
HDM trial 2 (P001)	741	741	≥12	12 mo
HDM trial 3 (MT-11)	270	263	5–17	24–30 mo
HDM trial 4 (MT-12)	727	731	5–11	12 mo
Ragweed trial (P008)	513	509	5–17	6–7 mo
Tree* trial (TT-06)	473	479	5–17	12–13 mo

HDM, house dust mite.

*Birch homologous group

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Results

- In clinical trials including 3,378 atopic subjects treated with SLIT-tablet, 2 cases of EoE were reported, corresponding to a prevalence of 0.06%
- No EoE cases were reported in placebo-treated subjects
- Details of the 2 cases are shown in **Table 2**

Table 2. Details of EoE cases

SLIT-Tablet Received	Subject Characteristics	Medical History	Timing of Onset of EoE Symptoms	Symptoms/ Signs	Treatment	Diagnostic Findings	Outcome
HDM	34 y, female with HDM allergic rhinitis and HDM allergic asthma	Occasional heartburn, dysphasia, stomach discomfort	Day 99 of treatment	Pharyngeal pruritus with meals, difficulty swallowing	PPI Fluticasone	Gastroesophageal biopsy of thickened mucus membrane, no EOS count performed	Continued treatment, not recovered at end of treatment
HDM	10 y, male with HDM allergic rhinitis and conjunctivitis and HDM allergic asthma	None	Day 6 of treatment	Episodes of nausea and vomiting over 3 weeks; on day 31, vomiting episodes followed by hospitalization	PPI	Gastroscopy with biopsy from the supracardial esophagus; EOS predominating (50 EOS per high-power field) No evidence of GERD on 24-hour pH esophageal metry	Discontinued SLIT-tablet on day 30; vomiting recovered 6 days after last SLIT-tablet dose

EOS, eosinophils; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

Discussion

- Potential unmasking: Case 2 could be considered potential unmasking of EoE given the early onset of the symptoms of EoE after treatment initiation
  - EoE is not an acute process, although there is little data on time to initial onset
  - Some studies have shown that at least a quarter of patients with IgE-mediated food allergy may have pre-existing, subclinical EoE.[8,9] One such study assessed patients with allergy and anaphylaxis to cow's milk and found that at baseline, 38% had esophageal eosinophilia, 29% of whom were asymptomatic and 24% had non-specific symptoms[9]

Limitations

- The trials included in this analysis were variable in the treatment duration, age range, and SLIT-tablet received
- Although some of the trials excluded subjects with a history of or existing EoE, no validated tools were used to detect non-symptomatic EoE during screening; therefore, prevalence was used as the outcome of this analysis

References

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Conclusions

The prevalence of EoE reported in SLIT-tablet trials is similar to the background population and does not appear to be higher than expected in an atopic population. The safety profiles of SLIT-tablets are under continuous surveillance through routine pharmacovigilance. Therefore, based on the small number of cases from controlled clinical trials, a direct association between SLIT-tablets and EoE cannot be confirmed.