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REVIEW

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Eosinophilic esophagitis and inhalant antigens: Pointing out the roles of allergic rhinitis, immunotherapy and biologic treatment

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ABSTRACT

Eosinophilic esophagitis (EoE) and allergic rhinitis (AR) usually represent the latest manifestations of the atopic march, sharing a common type 2 inflammation response. A relevant prevalence of AR in EoE cohorts has been widely confirmed. An increasing literature assessed the involvement of aeroantigens in EoE pathogenesis, focusing foremost on the seasonality of new diagnoses, symptoms, and response to therapy. Unfortunately, no diriment direction has been achieved, probably due to the retrospective design of the studies so far available, which chose surrogate markers of EoE activity (mostly the date of new diagnosis) which may be affected by geographical, logistic and personal factors, probably not dependent by the disease itself. EoE exacerbations reported in the context of the pollen levels (preferably pollen counts) may represent a more reliable marker. AR might promote the onset and the re-exacerbation of EoE through mechanisms that are both local (ie, massive exposure to airborne antigens mediated by post-nasal drip) and systemic (type 2 inflammation). Furthermore, AR may facilitate EoE onset by predisposing to pollen food allergic syndrome (PFAS), and EoE patients with PFAS reported higher rate of AR, thus suggesting a bond among these 3 conditions whose causative relationship have still to be ascertained. In addition, because of its shifting activity from Th2 to Th1 inflammation, several case reports focused on the effect of allergen immunotherapy (AIT) employed to treat AR in EoE patients. Also in this instance, no certainties could be guaranteed, although sublingual immunotherapy (SLIT) is more frequently reported to exacerbate EoE, while SCIT is mostly described as a remission adjuvant. The real life experience reported from our allergy service appears to confirm such hypothesis. Finally, a watchful eye should be reserved to monoclonal antibodies as a potential future option for concomitant EoE and AR. In light of all this, an attentive evaluation of allergic history of EoE patients should be relevant. Future perspectives should be addressed on prospective studies targeted to shed light on causative relations among airborne antigens, AR and EoE, and to viable comprehensive treatments.

Keywords: Allergic rhinitis, Eosinophilic esophagitis, Inhalant antigens, Subcutaneous immunotherapy, Sublingual immunotherapy

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INTRODUCTION

Eosinophilic esophagitis (EoE) and allergic rhinitis (AR) are considered stages of the atopic march, eventually occurring as late manifestations after atopic dermatitis, immunoglobulin (Ig)E mediated food allergy and allergic asthma.[1,2] Despite the term, "atopic" reminds to IgE-mediated hypersensitivity, such immunoglobulin is a mediator of some, but not all, atopic diseases. More properly, all of these conditions share an impaired barrier integrity of the epithelium, causing the entry of antigens, often acting as allergens, with a secretion of alarmins (ie, thymic stromal lymphopoietin - TSLP, interleukin – IL -15, IL-33). These cytokines lead to an abnormal type 2 inflammatory response, involving T helper 2 cells (Th2), innate lymphoid cells (ILC2) and pivotal interleukins, such as IL-4, IL-5, and IL-13 that promote tissue damage in skin, airways and gastrointestinal tract through several pathways.[1,3]

The prevalence of EoE is about 40 cases/100,000 inhabitants/year, rapidly arising overtime,[4] and with higher rates seen among males, aged 5–14 years and 20–45 years.[5] Compared to EoE, the prevalence of AR is much higher, reported from 5% to 50% worldwide, with an increasing trend with age until young adulthood.[6]

EoE is a chronic non-IgE-mediated disease, driven by food and environmental antigens stimulating a type 2 immune response, resulting in inflammation, remodeling and motility dysfunction of the esophagus.[5] Clinical manifestations may differ according to the age. Adults commonly report recurrent dysphagia, food bolus impaction, and heartburn, and they frequently apply compensating behaviors such as avoidance of hard textured foods, imbibition, cutting of the food in small pieces, and prolonged time of the meal. Children, instead, more often present with feeding problems, abdominal pain, vomiting, and consequent failure to thrive.[7] After the exclusion of other plausible causes, the diagnosis is based on clinical history and histologic findings (≥15 eosinophils/high power field – eos/hpf) on 6 esophageal biopsies from at least 2 different esophageal sites.[5]

AR is an IgE-mediated inflammatory response of the nasal mucosa to allergens inhaled by sensitized subjects. The clinical features are barely specific, including sneezing, rhinorrhea, and nasal congestion. Depending on the period of exacerbation, it is possible to make a coarse classification in seasonal AR, usually exacerbated by outdoor allergens, and perennial AR, mainly associated to indoor year-round exposure.[8] The diagnosis of rhinitis is based on history, complemented with physical examination and nasal endoscopy if necessary, while the definition of the allergic etiology requires more specific investigations, foremost skin prick tests (SPTs) and the measurement of serum allergen-specific IgE (sIgE).[4]

In the last years, a few trials performed on animal models proved the inhalation of antigens as consistent with the onset of EoE. A milestone about this concept is represented by the study of Mishra et al, that established a causative role for aeroantigens in the pathogenesis of EoE. They showed, in fact, that intranasal challenges with *Aspergillus fumigatus* on sensitized mice with allergic airway inflammation promotes a marked eosinophilic infiltration in esophagus.[9] Rajavelu et al reported that intranasal instillation of peanut antigens in previously sensitized mice induced thickening and disruption of epithelial mucosa, esophageal eosinophilia and mastocytosis, and eosinophilic microabscesses, all typical of EoE.[10] Other findings proved a type 2 cytokine expression induced by inhalant antigens in patients affected by EoE. *A. fumigatus*, ragweed and house dust mites (HDM) were found to induce a significant higher IL-5 production (also IL-13 in the case of HDM) in peripheral blood mononuclear cells of patients with EoE.[11] Consistent evidences were reported in a recent study on mice knock out for Sharpin gene, therefore prone to inflammatory response: after a repeated intranasal exposure to *A. fumigatus*, they showed an eosinophilic inflammation of esophagus, lung and skin, and increased IL-4 and IL-13 expression. On the contrary, no elevation of allergen specific IgE-levels was detected, thus confirming that IgE probably do not play a key role in EoE, as already predictable from the scarce effectiveness of the anti-IgE monoclonal antibody Omalizumab. Rather, elevated IgE might be considered as an associated marker to EoE.[12,13]

In light of all this, a proliferation of literature aimed to prove or deny the link between

Reference	Patients with EoE	Age group	Seasonality		Symptoms	Response to therapy	Notes
			Peak of EoE diagnosis	Esophageal eosinophilia			
Wang 2007, Indiana US[18]	234	Children	–	Lower in winter	–	–	–
Iwanczak 2011, Poland[19]	84	Children,	Spring	–	–	–	–
Elitsur 2013, West Virginia, US[20]	95	Children	NS	–	–	–	–
Sorser 2013, Michigan US[21]	49	Children	Fall	–	NS	–	–
Schlegel 2014, Texas US[22]	81	Children	NS	–	–	–	–
Ram 2015, Pennsylvania US[23]	160	Children	Fall	Higher in spring	Spring (↑ flares)	–	- Selected population (suspected as inhalant-induced EoE) - inhalant-related flares more recurrent in older children (4–10 years vs < 4 years)
Fahey 2017, New York City, US[24]	36	Children,	Winter	–	Summer (↑ onset)	–	Association of symptoms onset with grass pollen peak
Pesek 2017, Arkansas, US[25]	123	Children	NS	–	–	NS	↓ response to PPI was significant related to perennial allergens sensitization

(continued)

Reference	Patients with EoE	Age group	Seasonality		Symptoms	Response to therapy	Notes
			Peak of EoE diagnosis	Esophageal eosinophilia			
Hommeida 2018, Minnesota US[26]	73	Children	NS	–	–	–	Mean delay of about 400 day between onset of symptoms and diagnosis
La Orden Izquierdo 2019, ES[27]	254	Children	–	–	–	–	Weak association between peak of diagnosis and *Platanus* pollen count, but not for other pollens
Larsson 2010, SE[28]	24	Children, adults	–	–	Fall (↑ FBI)	–	
Prasad et al. 2011, Minnesota US[29]	78	Children adults	Summer/fall	–	–	–	–
Frederickson 2014, Iowa, US[30]	193	Children, adults	NS	–	–	–	–
Warners 2017, NL[31]	2161	Children, adults	NS	–	–	–	–
Arias, Lucendo 2018, ES[32]	117	Children, adults	NS			–	
Reed 2019, North Carolina, US[33]	14	Children, adults	–	Higher in summer/fall	–	–	Significant worsening of EREFS score during seasonal flares

Ekre 2020, SE[34]	100	Children, adults	Fall	–	Summer, fall (↑ FBI)	–	- Higher FBE in summer/fall also in patients with seasonal allergic symptoms - Slight delay of the peak of incidence of FBE compared to the peak of inhalants
De Rooij 2021, NL[35]	4061	Children, adults	NS	–	–	–	–
Moawad 2009 Maryland, US[36]	127	Adults	Spring	NS	–	–	Positive correlation of EoE diagnosis with mean grass pollen count (not trees and weeds)
Almansa 2009, ES[37]	41; 37*	Adults	Spring	–	–	–	*Different cohorts of patients with EoE
Elias 2015, Minnesota, Iowa, Wisconsin, US[38]	372	Adults	Winter	Higher in winter	–	–	No seasonality of diagnosis in subgroups sensitized to aeroallergens or with a history of allergy
Jensen 2015, US[39]	14,524	Adults	Summer	Higher in summer	Spring, summer (↑ chest pain)	–	–

(continued)

Reference	Patients with EoE	Age group	Seasonality		Symptoms	Response to therapy	Notes
			Peak of EoE diagnosis	Esophageal eosinophilia			
Philpott et al. 2015, AU[40]	85	Adults	–	–	Grass pollen season (↑ recurrent FBi)	–	–
Sengupta 2015, Massacchussets, US[41]	47	Adults	–	–	Summer (↑ FBI)	–	–
Letner 2017, Massacchussets, US[42]	90**	Adults	Spring (birch pollen season)	–	–	–	** Patients with concomitant EoE and PFAS
Molina-Infante 2018, ES[43]	137	Adults	NS	–	–	–	–
Visaggi 2023, IT UK[44]	58	Adults	–	–	–	↓ during pollen season (EREFS, histologic)***	***Evaluation of response to SFED in patients sensitized to birch/grass pollen compared to non-sensitized

Table 1. (Continued) Seasonality of new diagnosis, eosinophilia severity in esophageal biopsies, symptoms and response to therapy in children and adult patients with eosinophilic esophagitis. Seasons were defined as spring (March, April and May), summer (June, July and August), fall (September, October and November) and winter (December, January and February). *Abbreviations and symbols: AU = Australia; EoE = eosinophilic esophagitis; EREFS = EoE endoscopic reference scores; ES = Spain; FBI = food bolus impaction events; IT = Italy; NL = Netherlands; NS = no significant association; PFAS = pollen food allergic syndrome; PPI = proton pump inhibitors; SE: Sweden; SFED = six food elimination diet; UK = United Kingdom; US = United States of America; ↑ = increase; ↓ = decrease*

aeroantigens and EoE has been stated, describing them as elicitor factors in pre-existing conditions or as sole drivers.[14,15] In this regard, a recently proposed aetiological classification supported the role of inhalant antigens, listing them together with food antigens and allergen immunotherapy as EoE triggers.[15]

This review is aimed to inspect the involvement of inhalant antigens/allergens in the onset and progression of EoE, going through the literature available about this argument. Starting from a detailed examination of the effect of the different seasons on EoE, a particular regard is reserved to the connecting points existing between EoE and AR and the role played by the different types of allergen immunotherapy (AIT). In this respect, also a real life experience from our allergy service is described. Lastly, monoclonal antibodies potentially involved in the treatment of both EoE and AR are examined.

SEASONALITY

The beginning

A first attempt to explore the concurrence of inhalant antigens in the pathogenesis of EoE was described by a case report by Fogg et al dealing with a young woman affected by asthma and allergic rhino-conjunctivitis that experienced different EoE exacerbations during pollen seasons and remissions during winter months. Such a clinical variation, was confirmed over the years by several esophageal findings: the biopsies performed in 3 pollen seasons of different years showed a moderate-to-severe EoE ($\geq$15 eos/hpf in 1 case, and $\geq$50 eos/hpf in 2 cases), while the 2 performed during winter seasons revealed mild inflammation ($<$15 eos/hpf).[16] Comparable findings were reported in a case series of 3 men that began to experience the typical clinical aspects of EoE (ie, solid-food dysphagia and chest pain) after a massive exposure to inhalants (grass pollen in 1 case, and mold and dust in others).[17]

Leaving aside individual events, several studies have interested on the role of airborne antigens in the manifestation of EoE, by examining the seasonality of new diagnosis, eosinophilia severity in esophageal biopsies, symptoms and response to therapy trends[18–43] (Table 1).

Seasonal trend of new EoE diagnosis

As already stated in a systematic review of Lucendo et al,[45] the rate of new diagnosis of EoE does not follow a seasonal distribution. Several studies, in fact, did not report a significant peak of diagnosis in 1 season compared to the rest of the year,[20,22,26,30–32,35,43] and the studies that achieved a statistical significance are discordant.[19,21,23,24,29,34,36,37,42] In few trials, the temporal distribution of eosinophilia severity in esophageal biopsies has been assessed but, considering them as a whole, no diriment direction has been achieved.[18,23,33,36,38,39] A variety of reasons may be recognized to explain such a discrepancy, for instance the differences in inclusion criteria of patients with EoE, first and foremost the intensity of their treatment during the period of observation. Another limitation is the small size of most of the cohorts investigated and, in view of this, a cross-sectional study involving more than fourteen thousand of EoE adults from a US national database may take on a certain relevance. In this trial a consistent, though weak, higher relation between esophageal eosinophilia and summer months was highlighted, particularly in July.[39] On the other hand, 2 Dutch studies involving cohorts of thousands of children and adults did not achieve any significant correlation.[31,35] Another issue is represented by the timing of EoE diagnosis. Due to the retrospective design of the entirety of the trials, the date of histologic diagnosis was frequently identified as a surrogate marker for EoE activity, thus probably contributing to increase the contrasting evidences. Seasonality and pollination, in fact, are not static concepts; rather they are conditioned by climatic and geographical factors.[46] In addition, the date of diagnosis is often affected by personal (ie, compensating behaviors, targeted treatment) and logistic factors (ie, accessibility to the point of care, waiting time for esophagogastroduodenoscopy – EGDS). Several studies at least agree on a lower incidence of EoE in winter months (in a case with significant reduction of esophageal eosinophilia).[18,23,34,36] Nonetheless, Fahey et al recorded a higher rate of EoE diagnosis in winter but, if the time of symptoms onset is considered, such an increase might be

explained with the contemporaneity with grass pollen peak.[24] In light of this, compared to the date of histologic diagnosis, one may postulate that EoE exacerbations reported in the context of the pollen levels (preferably of the effective pollen count of the period) represent a more reliable marker to investigate the seasonal activity of the disease. To our knowledge, only three studies correlated the rate of EoE diagnosis to pollen counts, reporting a significant association with grass and *Platanaceae* pollens higher levels.[27,36,47]

Seasonal trend of EoE symptoms

Contrasting evidences were found also about the hypothesis of a seasonal pattern of symptoms, but most of the studies described a distribution more focused on the major pollen seasons (spring and summer).[21,23,24,28,34,39-41] Regarding the type of clinical presentation, this trend is confirmed for both the periods of symptoms onset and flares.[23,24,39] Interestingly, a trial conducted on a selected children population suspected to have inhalants-induced EoE re-currences found the inhalant-induced flares as significantly more recurrent in older children (4–10 years vs $<$ 4 years).[23]

Due to esophageal dismotility, another typical condition caused by EoE is food bolus impaction (FBI);[28,34,41] hence, several retrospective studies employed data of patients needing food bolus extraction to investigate the seasonal pattern of these events. A significant increase of FBI events was reported during summer and fall.[28,34,41] This suggested a slight delay between the period of major pollen exposure and the worsening of esophageal dismotility that might reflect the need of time of eosinophilic inflammation to reach a sufficiently advanced state for the obstructive event to occur.[28] A possible role of trigger for inhalant antigens is supported also by the study of Phillpot et al that found a significant higher rate of recurrence of FBI events during the grass pollen season.[40]

Seasonal trend of response to therapy

Trials assessing the response to therapies in EoE patients throughout the seasons are rare. Six-food elimination diet (SFED), which is the avoidance of foods containing milk/dairy, wheat, egg, soy, nuts, and seafood/shellfish, is an acknowledged first-line therapy in EoE. It is reasonable to assume that environmental or foods antigens not usually included in this diet might constitute overlooked triggers in a subset of non-responders EoE patients.[42] A study performed on 58 adults with active EoE that underwent to at least 6 weeks of SFED without pharmacological treatment showed that patients sensitized to grass and/or birch pollen had significantly lower response rates during the pollen season compared with outside of the pollen season, and also compared with non-sensitized controls.[44] Regarding pharmacological treatments, Pesek et al did not find a significant association between seasonal allergens sensitization and histologic response to proton pump inhibitors (PPI)

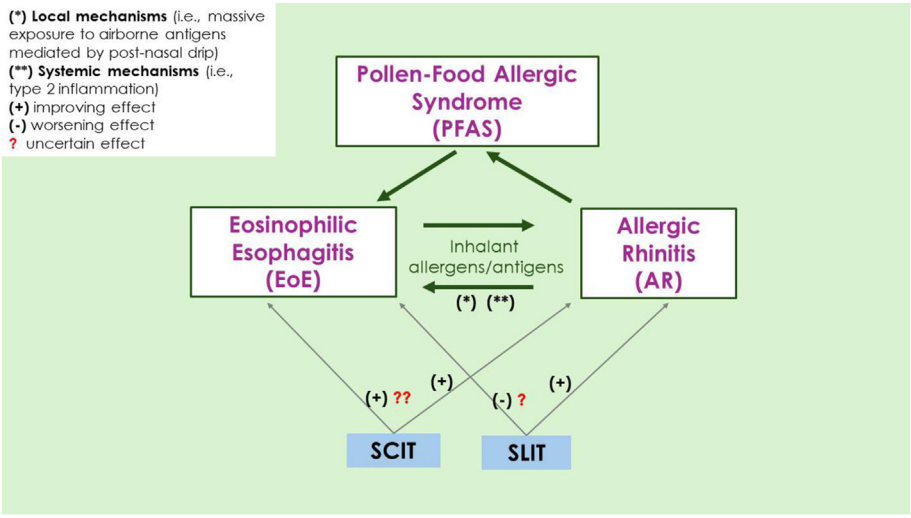

Fig. 1 Potential pathogenic mechanisms of EoE induced by concomitant AR.

AIT inducing EoE								
Reference	Sex	Age	Route of administration	Type of allergens	EoE symptoms after initiation of AIT	Esophageal histologic outcome (eos/hpf)	Remission of EoE after SLIT discontinuation	Further interventions
Miehlke 2013[60]	F	44	SLIT	Hazelnut, birch, alden	Dysphagia	164	Yes, in 1 month	–
Antico 2014[61]	F	23	SLIT	HDM, grass	Dysphagia, retrosternal discomfort	24[a]	Yes[a]	PPI
Benè 2016[62]	F	10	SLIT	HDM	Heartburn, vomiting, feeding disturbance, loss of weight	100	Yes, in 2 months	PPI
Rokosz 2016[63]	M	9	SLIT	HDM, grass, tree	Reflux, feeding disturbance	57	Yes, in 1 month	PPI, elemental diet
Kawashima 2018[64]	F	53	SLIT	Cedar	Dysphagia, vomiting	61	Yes, in 2 months	PPI
Wells 2018[65]	M	10	SLIT (two attempts) SCIT	Grass	Reflux, abdominal pain Reflux, vomiting	– –	Yes, in 3 weeks Yes, after months (2 hospitalizations)	Topical steroid Topical steroids, elemental diet
Fujiwara 2021[66]	M	43	SLIT	Cedar, HDM	Heartburn	88	Yes (no SLIT discontinuation, but switching from swallow to spit method)	–
	F	43	SLIT	Cedar, HDM	Dysphagia	29	Yes	–
	F	49	SLIT	Cedar	Dysphagia	80	Yes (no SLIT discontinuation, but switching from swallow to spit method)	Vonoprazan
	F	50	SLIT	Cedar	Dysphagia	NT	Yes	–
	M	53	SLIT	Cedar	Retrosternal discomfort	80	Yes	PPI
	M	36	SLIT	Cedar	Heartburn	36	–	–

(continued)

AIT inducing EoE								
Reference	Sex	Age	Route of administration	Type of allergens	EoE symptoms after initiation of AIT	Esophageal histologic outcome (eos/hpf)	Remission of EoE after SLIT discontinuation	Further interventions
Suto 2021[67]	M	40	SLIT	Cedar	Heartburn	≥70	Yes, in 1 week	Vonoprazan
Bauer 2023[68]	M	7	SLIT	HDM, tree, cat, dog, peanut, cashew, pistachio, sesame[b]	Feeding disturbance, loss of weight	22	Yes	Topical steroid
Yamagata 2023[69]	M	26	SLIT	Cedar	Dysphagia and heartburn	55	Yes, in 1 month (no SLIT discontinuation, but switching from swallow to spit method)	–

Table 2. (Continued) Case reports supporting the hypothesis of AIT-induced EoE. *Abbreviation: AIT = allergen immunotherapy; F = female; HDM = house dust mites; M = male; SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy; PPI = proton pump inhibitors.* [a]*The patient agreed to restart grass tablet SLIT, and after mild relapse of symptoms on the seventh day, she consented to undergo an esophagogastroduodenoscopy performed before the beginning of grass pollination. The histologic finding led to a further discontinuation of SLIT.* [b]*The patient previously reported also food allergies*

AIT ameliorating EoE		Age	Route of administration	Type of allergens	Duration of AIT	Histologic esophageal remission	Symptomatic remission	Concomitant treatment
Reference	Sex							
De Swert 2012[70]	M	10	SCIT	Birch, grass	3 years	Yes (0 eos/hpf)	Yes (abdominal pain and diarrhea[a])	No
Ramirez 2013[71]	M	4	SCIT	HDM	At least 2 years	Yes ("rare eosinophils")	Yes (vomiting)	PPI and dietary elimination
Robey 2019[72]	–	–	SCIT	HDM, Cat, tree mix, grass mix, English plantain	–	No	No	Dietary elimination and topical Fluticasone (symptomatic and histologic remissions were achieved previous to SCIT with only topical Budesonide)
				HDM, Birch, Cedar, Maple, Timothy, Ragweed	–	No	Yes	Dietary elimination (symptomatic remissions were achieved previous to SCIT with only topical Fluticasone)
				Ragweed, Alternaria	–	Yes (3 eos/hpf)	No	Dietary elimination
				Dog, grass mix, Alternaria	–	–	No	Dietary elimination
				Cat, weed mix, Alternaria	–	Yes (3 eos/hpf)	Yes	Topical Budesonide (symptomatic and histologic remissions were not achieved previous to SCIT with only topical Fluticasone)
Iglesia 2021[73]	M	14	SCIT	Trees, grasses, weeds, HDM, molds, cat, dog	At least 18 months	Yes (5 eos/hpf)	Yes (dysphagia)	No

Table 3. Case reports supporting the hypothesis of AIT-improved EoE. *Abbreviation: AIT = allergen immunotherapy; F = female; HDM = house dust mites; M = male; SCIT = subcutaneous immunotherapy; SFED = 6 foods elimination diet; SLIT = sublingual immunotherapy; PPI = proton pump inhibitors.* [a]*The patient was affected by eosinophilic gastrointestinal disease involving not only the esophagus, but also duodenum and colon*

and swallowed corticosteroids.[25] By contrast, perennial allergens sensitization was associated to increased non-response to swallowed corticosteroids and SFED, in particular in patients aged 6–11 years, and in those sensitized to cockroach and molds.[25]

PATHOGENIC MECHANISMS OF EOE INDUCED BY CONCOMITANT AR

EoE and AR

AR might promote the onset and the re-exacerbation of EoE through both local and systemic mechanisms.[38] A massive inhalation of airborne allergens may exceed mucociliary clearance, enabling antigens to reach the esophagus, supported by nasal secretions and post-nasal drip typical of AR.[48] Moreover, in case of significant nasal obstruction, patients are forced to inhale through the mouth, with further topical exposure to inhalants that are bound by antigen-presenting cells. This may activate a type 2-mediated response with IL-5-mediated eosinophil recruitment in esophagus and release of inflammation mediators.[13,36] Regarding pollens, they might additionally induce a seasonal worsening due to the intrusion of pollen tubes into the impaired epithelial barrier, facilitating pollen deposition in virtue of esophageal pH and humidity resembling the stigma at pollination. This might prolong the time of adherence, together with a slowing of swallowing characteristic of the esophageal dysmotility, resulting in eosinophil build-up and eventually in the formation of eosinophil micro-abscesses.[49] All of these conditions enhance a local esophageal response in some ways similar to the oral allergy syndrome.[16] Furthermore, allergic patients may be also affected by an immune response that is systemic and leads to eosinophil migration to airways and esophagus, causing an up-regulation of the atopic inflammation of both districts[36] (Fig. 1).

Several studies confirmed the relevant prevalence of AR in EoE cohorts (17–93%),[21–23,25,37,50,51] with allergic airway diseases preceding or at most being concomitant with the development of esophageal symptoms.[1,50,51] A retrospective study performed on 139 children with EoE reported a bi-directional association between EoE and AR, both representing a disease risk factor for each other. Presence of AR, in fact, was related to a subsequent EoE diagnosis (hazard ratio – HR - 2.8, 95% CI – confidence interval - 2.0–3.9), as well as the presence of EoE was associated with following AR diagnosis (HR 2.5, 95% CI 1.7–3.5).[1]

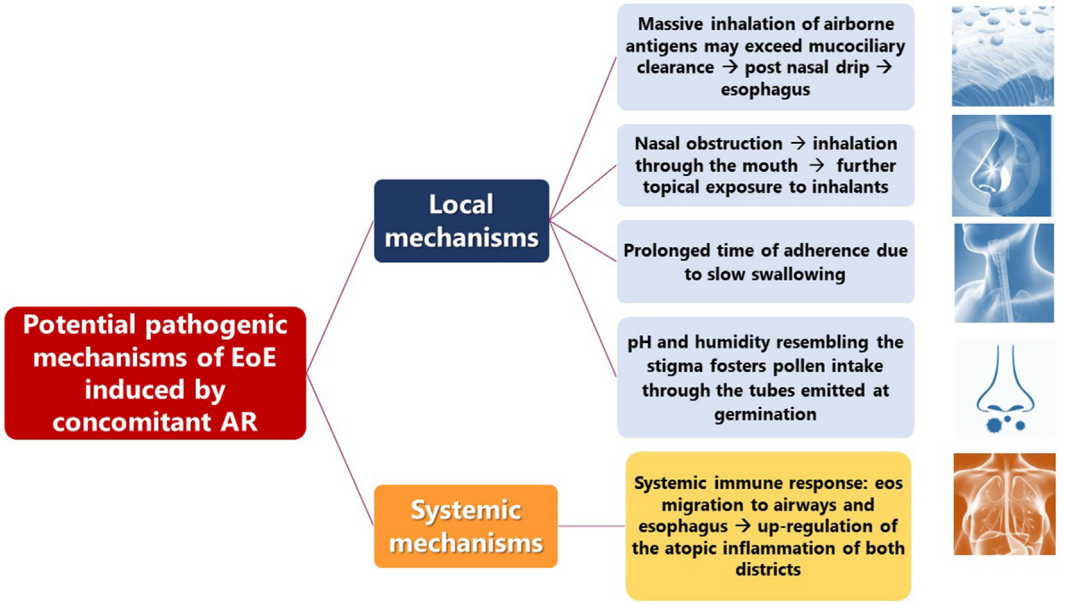

Fig. 2 Correlations among eosinophilic esophagitis, allergic rhinitis, pollen-food allergic syndrome and potential effects of SCIT and SLIT. Abbreviations: SCIT = subcutaneous immunotherapy; SLIT = sublingual immunotherapy.

Interestingly, Sunganam et al described in children and adolescents with EoE a sensitization profile transition from food to inhalant allergens according to age increase,[51] thus corroborating the concept that EoE manifestations attributed to seasonality might be amplified with age.[23,37] Such a hypothesis could be consistent with the findings of lesser effectiveness of SFED during the pollen season in EoE adult patients sensitized to birch and/or grass pollens.[44]

AR as a predisposing condition for PFAS

PFAS is an IgE-mediated reaction that usually occurs within minutes after the ingestion of plant-based foods, causing oral-pharyngeal pruritus, angioedema and itching, tingling or throat tightness. The pathogenesis of PFAS is related to cross-reactivity of pan-allergens present both in plant-foods and pollens.[52] The main responsible for PFAS in EoE patients are two pan-allergens susceptible to pepsin digestion in the stomach: profilin (birch - Bet v 2 and timothy grass - Phl p 12 homologues), and pathogenesis-related protein 10 (PR-10) (birch pollen - Bet v1 homologues), with a sensitization in adult EoE population of 40% and 39%, respectively.[53,54] Another study aimed to characterize EoE in adults based on component resolved diagnosis (CRD) reported also a relevant sensitization (28%) to lipid transfer protein (LTP),[55] major allergen of mugwort pollen, resistant to both heat treatment and pepsin digestion.[52] The most common food triggers for PFAS reported in adults with EoE were apples (containing PR-10 and LTP), carrots (profilin, PR10), peaches (profilin, PR-10, LTP), and nuts (profilin, PR10, LTP).[42]

In a cohort of 346 adults with EoE, the presence of AR has been related to a significant higher risk of developing PFAS (odds ratio – OR - 3.0, 95% CI 1.39–7.24), as well as EoE patients with PFAS reported a significant higher frequency of AR compared to patients without PFAS (86.7% vs. 64.2%).[42] The comparison to a control group of adults with AR highlighted a significantly higher prevalence of tree, grass, and/or weed pollen sensitization in adults with EoE (70% vs 82% respectively), and also a higher rate of symptomatic PFAS (7% vs 42%).[56] Mahdavinia et al proposed different possible explanations for these findings: I) epithelial barrier disruption in EoE might result in a sensitization to food proteins, including pollen-food pan-allergens, causing the sensitization to aero-allergens as an epiphenomenon; II) in adults and older children with AR, the sensitization to pollens may promote esophageal inflammation through both nasal inflammation and exposure to cross-reactive foods in the mouth and potentially in the esophagus; III) patients with EoE may be sensitized only to minor pollen-food allergens, therefore experiencing symptoms limited to gastrointestinal tract and by-passing airways.[56]

Regarding the role of PFAS in EoE response to the treatment, a study conducted on children with EoE reported that a subset of 7 patients with PFAS achieved a significant faster first histologic remission vs non-PFAS (4 vs 14 months) after a treatment of at least 6 weeks involving dietary elimination, topical steroids, PPI or a combination of them.[57] This is in contrast with the finding of Letner et al. that found elimination diet (avoidance of dairy, wheat, and eggs) failed to induce remission in 46% of EoE-PFAS adults, in most cases also despite strict avoidance of PFAS trigger foods in addition.[42] Besides the difference of the cohorts age of the two studies, it should be noted also that, compared to controls, in the study conducted on children the subset of PFAS-EoE patients was characterized by a lower peak of eos/hpf on initial endoscopy.[42,57]

EOE AND ALLERGEN IMMUNOTHERAPY (AIT): THE SUBLINGUAL-SUBCUTANEOUS PARADOX

Supporting evidences of an AIT inducing effect on EoE

Based on the above, one may speculate that the treatment of AR in patients with EoE might alleviate their esophageal symptoms. Hence, there might be a role for allergen immunotherapy (AIT) to this purpose. AIT is a treatment aimed to induce tolerance to allergens through an induction phase requiring the administration of increasing amounts of allergen extract, followed by reiterated administrations of maintenance dose over a period of at least 3 years.[58] The main routes of administrations for inhalant allergens are subcutaneous (SCIT) and sublingual (SLIT), and mechanisms underlying the desensitization to inhalants involve a deviation

from Th2 to Th1 immune responses culminating in the induction of T and B regulatory cells, and of IgA, IgG (ie, IgG4) competing with IgE in the bond with allergens.[58,59]

Currently, much is still unknown about the relationship between AIT and EoE, and most of the information comes from case reports. As summarized in Table 2, several cases support the concept that, in the context of AIT, particularly the sublingual administration might be involved in triggering the onset or the recurrence of EoE, regardless of the type of allergens employed in the extracts.[60–69] The vast majority of the patients, in fact, had to opt for SLIT discontinuation,[60–68] while only few of them resisted with the treatment but switching from swallowing to spitting the tablets after minutes.[66,69] Only in the case of Wells et al relapse occurred during the induction phase of grass pollen SCIT performed in winter months in a ten years male with a history of seasonal exacerbations of EoE. Notably, the child already failed 2 previous attempts with SLIT.[65] Remarkably, all patients developed EoE symptoms at most after few weeks from the start of AIT, as well as they reported symptomatic and/or histologic remission in 1–2 months after the discontinuation.[60–69]

It is worthy to highlight that, in some cases, elimination diets did not induce remission, which might exonerate foods as triggers in this instance, except for the eventual contribution of non-eliminated pan-allergens, ie, profilin and PR-10. All of this may suggest a causative effect currently not yet confirmed by targeted trials.

Much clarity probably will come from a systematic review and metanalysis about EoE as a side-effect of AIT (both SLIT and oral immunotherapy involved in food desensitization), whose protocol has been recently proposed.[70]

Supporting evidences of an AIT ameliorating effect on EoE

Compared to SLIT, even less is known about the effect of SCIT on EoE, which of only few cases are described to our knowledge.[65,71–74] Contrarily to SLIT, both symptomatic and histologic remissions were described in the majority of the case reports,[71–74] thus leading to speculate an ameliorative effect on the esophageal tract (Table 3). Despite this, one of the few studies performed on EoE patients could not identify relevant differences regarding efficacy or safety outcomes between the group treated with SCIT versus controls. In this regard, it is important to state that the retrospective nature of the study, the limited number of EoE patients involved (10), as well as the non-reported duration of the SCIT for each one might have affected such results.[73] These findings were consistent with a subsequent larger retrospective study performed on about a thousand patients reporting no difference in steroids use and histological response between the EoE-SCIT patients and the control group (EoE not on SCIT). On the other hand, it also confirmed the non-worsening effect of SCIT on EoE.[75]

The reasons of the discrepancy of EoE response to SLIT and SCIT might be multiple. A viable hypothesis is the continuous inflammatory stimulation due to the direct and reiterated exposure of the esophagus to aeroantigens. Further, pollen extracts administered through the sublingual route were found to induce IL-5 expression, pivotal for the recruitment of eosinophils in esophagus.[76] Moreover, the role of pan-allergens should be attentive considered, as inferable from the report of De Swert et al in which patient symptoms decreased after strict avoidance of PR-10–containing plant-foods. Despite a regular recurrence during pollen season in the first 2 years of birch pollen SCIT, the patient achieved a complete esophageal symptomatic and histologic remission at the end of the 3 years of immunotherapy, reporting IgG4 levels for Bet v1 of 9.8 mg/L (vs 2.8 mg/L before the beginning of SCIT).[71] This is in agreement with the finding that IgE-inhibitory activity is predominantly mediated by IgG4 in SCIT, while by IgA1 and IgA2 in SLIT.[77] Nonetheless, this is in contrast to the well-known association between IgG4 levels and EoE activity.[78] In this respect, deepened analysis concerning the pathogenic mechanisms underlying EoE response to AIT will be required. Fig. 2 summarizes the potential correlations among EoE, AR, SCIT, and SLIT.

A real-life experience

A 21 years old male was referred to the Allergy Service of Parma University Hospital in May 2017

because of chronic dysphagia onset about 2 months earlier, and recent episodes of food bolus impaction. He presented a history of rhino-conjunctivitis worsening during spring and treated with cetirizine in cycles, and asthma in therapy with ICS-LABA to the need. Both skin prick tests and CRD revealed a sensitization to grass pollen, HDM, cat and dog dander, parvalbumin (Gad c1) and tropomyosin (Ani s3, Pen a1, Der p10). Patch tests for foods were found negative. The EGDS highlighted a trachealized mucosa with multiple de-epithelialized areas and the histologic evaluation confirmed the diagnosis (25 eos/hpf in 6 biopsies). SFED, oral budesonide and high doses of rabeprazole were prescribed until the subsequent visit. In October 2017 the patient reported a partial remission of symptoms, therefore pharmacological treatment was prolonged and a gradual re-introduction of the avoided foods (except fish and crustaceans) was recommended. Due to the improvement of the clinical picture, in January 2018 the topical steroid was suspended with a relapse of dysphagia in three weeks. For this reason, budesonide was reintroduced, and in May 2018 the patient reported a remission of symptoms with low doses of PPI, topical steroids, and dietary exclusion of fish and crustaceans. Few months later, he started the administration of SLIT for grass pollen (®Grazax). In the following months, with a rapid worsening of esophageal symptoms non-responsive to PPI induced to suspend immunotherapy achieving an immediate improvement of the condition. In the following two years the patient reported fluctuating control of dysphagia, with both EoE and AR relapses during pollen seasons and amelioration in winter months. In November 2020, we agreed a new try for grass pollen immunotherapy, this time SCIT (®Anallergo), well tolerated during both the induction and the maintenance phases. Currently, the patient is at the fourth year of immunotherapy with a nearly complete and steady control of esophageal symptoms, for which he follows a fish/crustaceans elimination diet and takes low doses of PPI during the pollen season. He also achieved a relevant amelioration of rhino-conjunctivitis.

Our experience is consistent with the previous findings of De Swert et al., Ramirez et al. and Iglesia et al, while discordant with the one of Wells et al.[65,71–73] If SLIT appears to trigger EoE, on the other side SCIT might perform an ameliorative effect,[79] but no certainties can be guaranteed. Furthermore, the seasonal pattern of dysphagia in our patient supports the abovementioned hypothesis of a causative role for inhalant antigens in EoE relapsing.

BIOLOGIC AGENTS AS A FUTURE OPTION FOR THE EOE-AR COMORBIDITY TREATMENT

Biologic agents are usually considered as a last-line therapy for EoE in patients refractory to dietary elimination, PPI and oral topical steroids, and one of the reasons is probably related to the economic costs. On the other hand, biologics already revealed as valuable tools in the treatment of atopic diseases by interfering with common type 2 pathogenic mechanisms, and this may acquire increasing relevance in the case of multiple morbidity,[78] as in a concomitant EoE and AR condition.

Currently, dupilumab represents the only biologic therapy for the treatment of EoE, and it is approved by both US Food and Drug Administrations (FDA) and European Medicines Agency (EMA).[80,81] Dupilumab is a monoclonal antibody binding the α subunit of the IL-4 receptor, which is involved also in the IL-13 receptor formation, leading to an inhibition of both IL-4 and IL-13 pathways.[82] Thanks to its effect on such pivotal mediators of type 2 inflammation, dupilumab achieved the approval also for the treatment of atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyposis.[80,81] Regarding perennial AR, most of the trials reported an improvement of rhinitis symptoms in patients that were already administered with dupilumab for atopic co-morbidities, such as asthma[83–85] and atopic dermatitis.[86] The response to dupilumab in the case of seasonal AR was investigated, instead, in comparison with the response to allergen immunotherapy. In a multicenter study, the patients were randomized 1:1:1:1 to timothy grass SCIT, dupilumab (300 mg/2 weeks), SCIT + dupilumab, and placebo. After 16 weeks no relevant difference in total nasal symptom score (TNSS) after nasal allergen challenge (NAC) was achieved for the dupilumab group compared to placebo. Compared with SCIT

alone, the dupilumab + SCIT group showed an improvement in SCIT tolerability.[87] Another trial performed on grass pollen allergic patients is still ongoing, and it is assessing TNSS after 2 years of therapy with SLIT + dupilumab (ClinicalTrials.gov Identifier: NCT04502966).[88]

Tezepelumab is an anti-TSLP antibody driving the production of IL-4, IL-5, IL-9, and IL-13, and that, in particular cases, may exert a type 2 pro-inflammatory effect.[82] It received the orphan drug designation from the FDA for the treatment of EoE,[89] and, at the present time trial designed to assess its safety and effectiveness in EoE adolescents and adults is in the recruiting phase (ClinicalTrials.gov Identifier: NCT05583227).[90] On the AR side, a study reported a significant decrease in TNSS after one year of treatment with tezepelumab compared to placebo, and a reduction of serum IL-5 and IL-13 also after a year from tezepelumab suspension. Moreover, a reduction in TNSS in patients treated with both cat SCIT and intravenous tezepelumab for 1 year compared with the SCIT group was reported, and this improvement may last a year after Tezepelumab suspension.[91]

As to other monoclonal antibodies, none of the anti-IL-5 (mepolizumab, reslizumab, benralizumab) highlighted a clear correspondence between the histologic improvement and the upgrading of the clinical picture in EoE.[92–99] Omalizumab, an anti-IgE antibody, did not even achieve a histologic amelioration.[100]

Among the biologics still under investigation, it is interesting to mention Lirentelimab, an anti-Sialic Acid-Binding Immunoglobulin-Like Lectins-8 (SIGLEC-8) antibody. SIGLEC-8 is a receptor involved in the inhibition of mast cells activity and in eosinophils decrease.[82] Despite no significant improvement in Dysphagia Symptom Questionnaire (DSQ) a complete histologic remission in patients with EoE was reported.[101] For as concerns AR, a decrease of 66% of symptoms was described after 6 monthly Lirentelimab infusions.[102]

To our knowledge, no studies dealing with the effect of biologic agents on concomitant EoE and AR were performed, and this may represent an interesting cue for future investigation.

CONCLUSION

The literature of the last years increasingly describes inhalant antigens as reliable triggers for the exacerbation and the recurrence of EoE, with AR fostering this activity through local and systemic mechanisms and through the relevant association to PFAS. Unfortunately, no diriment direction has been achieved on the effective role of inhalants and their eventual seasonality on EoE, probably owing to the retrospective design and the inappropriate surrogate EoE markers of the studies on this argument. Further, due to its shifting activity from Th2 to Th1 inflammation, even the effect of AIT on EoE requires more in-depth investigation (Fig. 2). Lastly, a watchful eye should be reserved to monoclonal antibodies as a potential future option for concomitant EoE and AR. In light of the above, an attentive evaluation of allergic history of the patient with EoE reveals itself as pivotal, and future perspectives should be addressed on prospective studies targeted to shed light on causative relations among airborne antigens, AR, AIT and EoE, as well as to viable comprehensive treatments.

Abbreviations

AIT, allergen immunotherapy; APC, antigen-presenting cells; AR, allergic rhinitis; CI, confidence interval; CRD, component resolved diagnosis; EGDS, esophagogastroduodenoscopy; EMA, European Medicines Agency; EoE, eosinophilic esophagitis; FBI, food bolus impaction; FDA, Food and Drug Administrations; HR, hazard ratio; HDM, house dust mites; Ig, immunoglobulin; IL, interleukin; ILC2, innate lymphoid cells 2; NAC,nasal allergen challenge; LTP, lipid transfer protein; PR-10, pathogenesis-related protein 10; PFAS, pollen food allergic syndrome; PPI, proton pump inhibitors; SFED, 6-food elimination diet; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; Th2, T helper 2 cells; TNSS, total nasal symptom score; TSLP, thymic stromal lymphopoietin.

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The data that support the findings of this review are available from the corresponding author upon reasonable request.

Authors contribution

ER - conceptualization, review.
FR - conceptualization, data collection, writing original draft, review; elaboration of the tables; editing of the figure.

CL – conceptualization, review, elaboration of the figure.
GP – conceptualization, review.
GS – conceptualization, review.
GWC – conceptualization, review.

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All authors have read and agreed to the published version of the manuscript.

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