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EOSINOPHILIC ESOPHAGITIS: TARGETS, THERAPIES, AND UNMET NEEDS

A literature review

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Abstract

Eosinophilic Esophagitis (EoE) is an emerging disease. It is a chronic, allergen-mediated disease, characterized by the accumulation of eosinophils in the esophageal epithelium. The impaired barrier function, caused by genetic predisposition, exposure to environmental factors and inflammation is a hallmark of the disease. The disrupted epithelial barrier allows for the passage of allergens, triggering an inflammatory immune response. The chronic inflammation may eventually lead to remodeling of the esophageal epithelium in EoE patients. Although the role of many components in the EoE pathogenesis have been well defined, there are still many parts that remain unclear. It is important to unravel the exact mechanism of EoE, since the key components in the disease mechanism form a target for EoE treatment strategies. Currently, EoE treatments consist of elimination diets, proton pump inhibitors (PPIs), swallowed topical corticosteroids (STCs) and endoscopic dilation. Recently also dupilumab (a monoclonal antibody blocking IL-4Rα) was approved by the Food and Drug Administration (FDA) and the European Commission (EC) as the first biologic in the treatment of EoE. However, these therapies do not offer an effective remedy for every individual, which is why several biologics are being tested in clinical trials for the treatment of EoE. Most of them block a part of the immune response and thereby diminish eosinophilic inflammation of the esophagus. The current and upcoming treatments all have their benefits and limitations. This is why EoE treatment should be personalized for every individual patient, taking into account their EoE phenotype and personal preferences. Research into the mechanism and new therapies of EoE, will provide more and better options for EoE patients.

Plain Language Summary

Eosinofiele oesofagitis (EoE) is een ziekte die steeds vaker voorkomt. Het is een chronische ontsteking van de slokdarm, veroorzaakt door een allergische reactie. De allergische reactie wordt meestal veroorzaakt door een deel van een bepaald voedingsmiddel (voedselallergeen). Eosinofielen zijn cellen van het immuunsysteem, die voorkomen bij een allergische reactie. Bij eosinofiele oesofagitis hopen deze cellen zich op in de slokdarm, op de plek van de ontsteking. De ziekte wordt gekenmerkt door een niet functionerende barrière van de slokdarm, waardoor de (voedsel)allergenen door deze barrière heen kunnen komen. De dysfunctionele barrière wordt veroorzaakt door genetische aanleg en schadelijke deeltjes uit de omgeving. Bijvoorbeeld in tandpasta, zeep en schoonmaakmiddel zit een stofje (SLS) wat deze barrière aantast. Als de barrière beschadigt is, kunnen de (voedsel)allergenen er makkelijker erdoorheen komen. Eenmaal door de barrière heen, veroorzaken ze de allergische reactie. Bij een allergische reactie worden heel veel cellen van het immuunsysteem geactiveerd. Deze cellen kunnen cytokinen produceren, die weer andere cellen aansturen en de reactie versterken. Uiteindelijk zorgt deze allergische reactie voor het verder verzwakken van de barrière en een chronische ontsteking in de slokdarm. Uiteindelijk zorgt deze chronische ontsteking voor het vervormen van de slokdarm, waardoor EoE patiënten slikproblemen en /of pijn met slikken hebben. Hoewel er al veel bekend is over het mechanisme van de ziekte, zijn er ook delen waarvan de experts nog niet zeker weten hoe het precies in zijn werk gaat. Dit is waarom er nog steeds veel onderzoek gedaan wordt naar het exacte mechanisme van EoE. Het is belangrijk om te weten hoe het mechanisme van EoE precies in elkaar zit, om zo betere medicijnen te kunnen ontwikkelen. Om mensen met EoE te behandelen, bestaan er momenteel verschillen strategieën; een eliminatiedieet, protonpompremmers, corticosteroïden en verwijding van de slokdarm. Deze behandelingen voorzien helaas niet alle patiënten van een passende, effectieve oplossing. Daarom is het belangrijk dat er onderzoek gedaan wordt naar andere medicijnen voor het behandelen van EoE. Dupilumab is een medicijn, dat recentelijk goedkeuring heeft gehad in Europa en de Verenigde Staten. Het medicijn blokkeert een deel van het afweersysteem, waardoor de ontsteking in de slokdarm minder wordt. Verder zijn er nog meer van dit soort medicijnen, die een deel van het immuunsysteem blokkeren, die momenteel worden onderzocht in klinische onderzoeken. Elke behandeling en elk medicijn heeft zijn eigen voor- en nadelen. Het is belangrijk dat er veel onderzoek gedaan wordt naar nieuwe medicatie voor het behandelen van EoE, zodat er meer en betere opties zijn voor EoE patiënten. De kenmerken van de ziekte variëren van persoon tot persoon. Ook kunnen patiënten een bepaalde voorkeur hebben, bijvoorbeeld of ze wel of geen medicijnen willen slikken. Daarom is het belangrijk dat elke patiënt een gepersonaliseerde behandeling krijgen, waar gekeken wordt naar de specifieke ziektekenmerken en de voorkeuren van de patiënt.

List of Abbreviations

APC	Antigen presenting cells
CAPN14	Calpain 14
CLDN7	Claudin-7
CRTH2	Chemoattractant receptor-homologous molecule on T-helper type 2 cells
DSG-1	Desmoglein-1
EC	European Commission
EDC	Epidermal Differentiation Complex
EMT	Epithelial-mesenchymal transition
EoE	Eosinophilic Esophagitis
eos/hpf	Eosinophils per high power field
FDA	Food and Drug Administration
FED	Food elimination diet
FLG	Filaggrin
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony stimulating factor
Ig	Immunoglobin
IL	Interleukin
IL-4Rα	Interleukin-4 receptor alpha
IL-5Rα	Interleukin-5 receptor alpha
ILC2	Group 2 innate lymphocytes
iNKT	Invariant natural killer T
IVL	Involucrin
MBP	Major basic protein
NGF	Nerve growth factor
OSM	Oncostatin M
PAI-1	Plasminogen activator inhibitor 1
PLN	Phospholamban

PPI	Proton pump inhibitor
PPI-REE	PPI-responsive esophageal eosinophilia
SDS	Sodium dodecyl sulphate
SPINK7	Serine peptidase inhibitor Kazal-type 7
SPRR	Small proline-rich protein
STC	Swallowed topical corticosteroid
TEER	Transepithelial electrical resistance
TGF-β	Transforming growth factor beta
Th	T-helper
Th2	T-helper type 2
TSLP	Thymic Stromal Lymphopoietin

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Introduction

Eosinophilic esophagitis (EoE) is a chronic allergen-mediated esophageal disease. It leads to a local allergic inflammation in the esophagus, during which the epithelial surface becomes hyperplastic and accumulates eosinophils.[1] The antigen(s) causing the allergic reaction is/are often food-based.[2] EoE is characterized clinically by symptoms of feeding problems, vomiting, and abdominal pain in children, and by dysphagia and food impaction in adolescents and adults. Histologically it is characterized by eosinophil-predominant inflammation, with eosinophil counts higher than 15 per high power field (eos/hpf).[3] To clinically define EoE, other causes of esophageal eosinophilia and symptoms must be ruled out.

Epidemiology

EoE has been reported from infancy to almost 100 years of age. The most cases however, are in children, adolescents and adults under the age of 50.[4] EoE has been reported more frequently in Caucasian populations and it has affected males more commonly than females with a ratio of 3:1.

The population-based incidence and prevalence vary widely across individual studies. It is highly dependent on the population studied, the definition of EoE that was used and the study methodology (prospecive vs retrospective).[4] The incidence and prevalence of EoE has primarily been investigated in Europe and North America in population-based studies.[5] An overview of the incidence and prevalence trends of these studies are shown in Figure 1. An overall pooled incidence rate of 3.7 cases per 100,000 inhabitants per year was calculated with a meta-analysis where they included 13 population-based studies from North America, Europe and Australia.[6] The pooled prevalence of EoE was calculated to be 22.7 cases per 100 000 inhabitants.

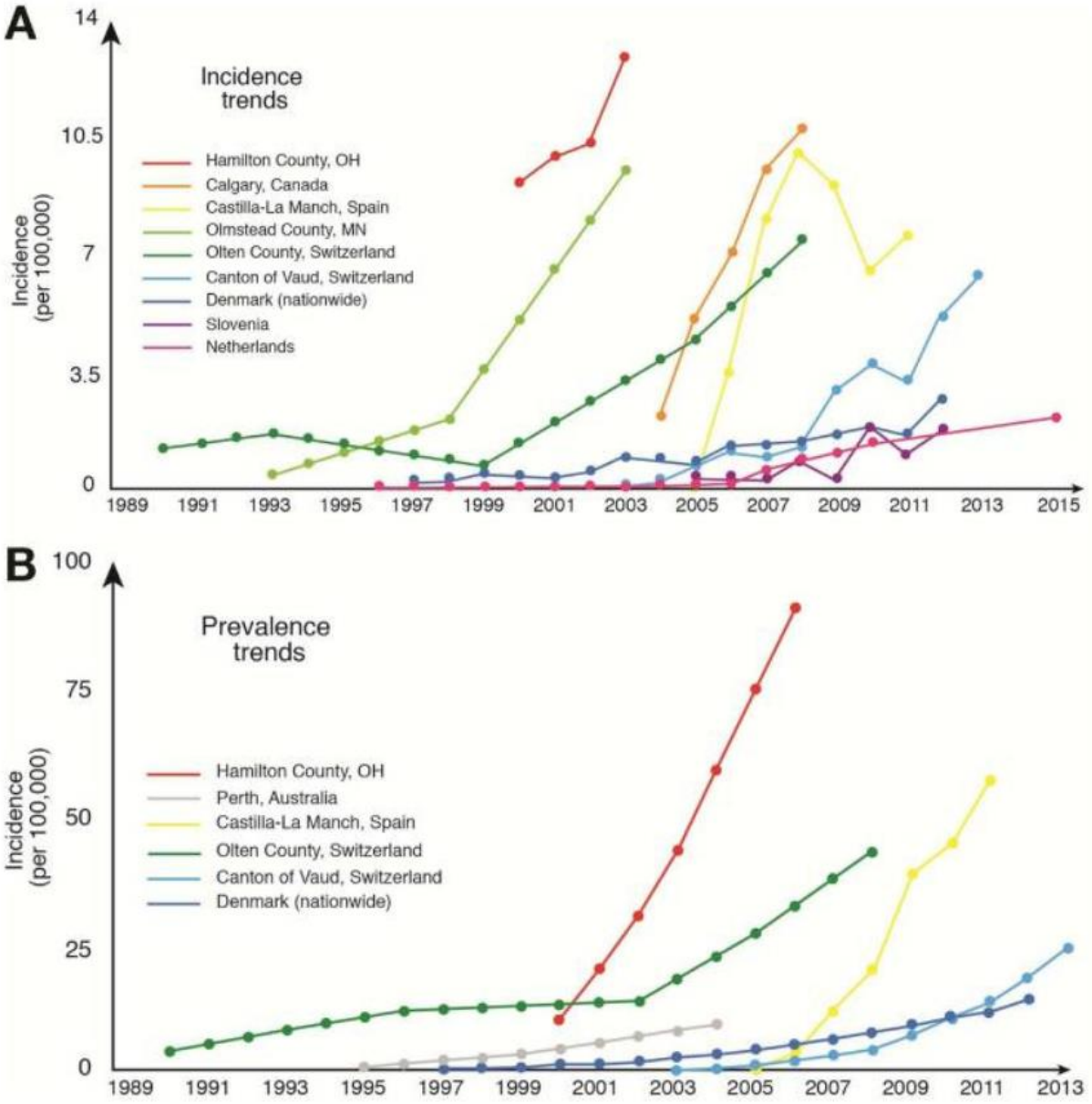

Figure 1 A) The incidence trends of EoE over time, investigated in population-based studies. B) The prevalence trends of EoE over time, investigated in population-based studies.[5]

As can be seen in Figure 1A the incidence of EoE is increasing rapidly. This can partly be explained by the increasing recognition of EoE.[4] Since there is more awareness of EoE, more esophageal biopsies are taken and there is a higher degree of suspicion when performing endoscopy, both contributing to more EoE diagnoses. However, the incidence of EoE outpaces the increase in biopsy rates, suggesting that the increasing incidence is not just an artifact of increasing surveillance and detection.[5]

Etiology

Some genetic factors have been associated with EoE. EoE has a strong familial association with a nuclear family heritability of 72%.[7] To study the contribution of genetic factors on EoE monozygotic and dizygotic twins were compared. They found that monozygotic twins have a 41% disease concordance, while dizygotic twins have a 22% concordance, a 2-fold decrease. Non-twin siblings have a 2.4% concordance. This is 10-fold lower dan for dizygotic twins, while genetically you would expect

them to have similar shared genetic influences. This difference can be attributed to early life environmental factors.[8] Moreover, genome wide association studies have reported several genes that are likely contributing to the development of EoE. These genes include thymic stromal lymphopoietin (TSLP), calpain 14 (CAPN14), EMSY, LRRC32, STAT6, and ANKRD27.[9]

Despite these genetic factors, the rapid increase in EoE incidence suggests that environmental factors might play a role in disease risk.[5] In a large database study in the United states it is shown that the prevalence of EoE steadily increases with age, to a peak value in the 35-45 age range, and then decreases.[10] This raises the question if environmental changes starting 40-50 years ago contribute to the development of EoE.[5] One explanation might be the 'hygiene hypothesis', which suggests that humans lose immune tolerance from being raised in clean environments. This is supported by the general increase in allergic diseases and auto-immune diseases in recent decades. Another explanation might be the 'epithelial barrier hypothesis', which proposes that the rise in allergic, autoimmune and other chronic conditions is an effect of the increase in epithelial barrier-damaging agents linked to industrialization, urbanization and modern life.[11] A functioning epithelial barrier is crucial for protection from infections, environmental toxins, pollutants and allergens. A damaged barrier may therefore allow for the passage of these molecules leading to development of these diseases. Lastly, there are also a number of specific etiologic factors that have been identified or hypothesized to contribute to the increase in EoE incidence.[4] These are shown in Box 1.

Box 1 Hypothesized or identified etiological risk factors for EoE.[4]

Potential etiologic risk factors for EoE

- Aeroallergens
- Food allergens
- Helicobacter pylori (protective)
- Proton pump inhibitors
- Cold or arid climates
- Population density (urban vs rural locations)
- Early life factors (antibiotic use; cesarian section)
- Connective tissue disorders

With the rising incidence of EoE the demand for therapies increases as well. Therefore, a lot of research is being done in the field of EoE, both to unravel the exact pathogenic mechanism and to develop new treatment strategies. This review aims to explore the current understanding of the mechanism underlying EoE, analyze existing and emerging therapies, and address the unmet medical needs associated with EoE. All of this is geared towards answering the question: What is required in order to improve medical care for EoE patients?

Mechanism of EoE

Epithelial Barrier dysfunction

The epithelial barrier protects the host tissue from infections, environmental toxins, pollutants and allergens.[12] The impaired barrier function is a hallmark of allergic inflammation in patients with EoE. It is characterized by dilated intracellular spaces (spongionis), basal zone hyperlasia and the loss of esophageal tissue proliferation.[13–15] The impaired barrier function may be caused by environmental toxins, inflammation and genetic predisposition.

Transcriptional dysregulation of the esophageal epithelium

The impaired barrier function seen in EoE can be caused by transcriptional dysregulation of esophageal genes. The EoE transcriptome revealed transcriptional changes at locus 1q21, which encodes for the epidermal differentiation complex (EDC).[16] The EDC is a gene complex compassing more than 50 genes, involved in the differentiation and cornification of keratinocytes, the primary cell type of the epithelium. In EoE interleukin (IL) 13 downregulates multiple structural genes in the EDC, including filaggrin (FLG), involucrin (IVL) and the small proline-rich protein (SPRR) gene family. This downregulation results in a decrease in barrier function. Another gene that is downregulated in EoE patients, is the desmosomal cadherin desmoglein-1 (DSG-1).[17] DSG-1 is an intercellular adhesion molecule of the desmosomal cadherin family. Its function is to regulate cell adhesion and promote epithelial cell differentiation. The decrease in DSG-1 levels by IL-13 thus contributes to an impaired barrier function. The reduction of DSG-1 also increases gene expression of pro inflammatory mediator POSTN, adding to the inflammation of the esophageal mucosa. Another striking feature of the EoE transcriptome is the highly enriched protease-related activities. This is caused by the overexpression of CAPN14 and the loss of serine peptidase inhibitor Kazal-type 7 (SPINK7).[16] CAPN14 is a proteolytic enzyme specific to the esophagus. Overexpression of CAPN14 by IL-13 leads to a diminished barrier function and structure. Moreover it leads to the loss of DSG1 and FLG. SPINKs regulate the activity of extracellular serine proteases. SPINK7 is specifically expressed in the esophageal epithelium. Loss of SPINK7 expression leads to increased proteolytic activity, leading to impaired barrier function.

Environmental factors

The impaired barrier function in EoE patients might also be caused by epithelial exposure to allergens, pathogens or environmental toxins, which can damage the epithelial barrier. This is described by the previously mentioned ‘epithelial barrier hypothesis’, which proposes that a damaged epithelial barrier might be the cause for the rise in allergic, autoimmune and other chronic diseases.[11] For example processed foods have shown to increase intestinal permeability even at low concentrations. Moreover, detergents like sodium dodecyl sulfate (SDS) which are common ingredients in household products like soap and toothpaste, decrease esophageal barrier integrity. Therefore detergents may be a key environmental trigger for EoE.[18] The exposure to these environmental toxins / allergens can cause chronic epithelial inflammation, which may further increase their effects.[11]

Inflammation

Finally, the impaired barrier function may be the results of ongoing inflammation. This is supported by histological findings of actively inflamed tissue. The inflamed tissue showed dilated intracellular spaces and decreased desmosomes.[19] Cytokines play an essential role in the inflammatory response in EoE. Some of these cytokines contribute to the damaging of the esophageal epithelium. IL-13 is known to

dysregulate the epithelial transcriptome resulting in the downregulation of FLG, IVL, DSG1 and the upregulation of CAPN14, leading to a diminished barrier function.[9] Another cytokine playing an important role in the impairment of the barrier function is transforming growth factor beta1 (TGF-β1). In an *in vitro* experiment it was shown that, exposure of TGF-β1 to human esophageal epithelial cells resulted in a decreased transepithelial electrical resistance (TEER) and cellular separation.[20] Lastly IL-9 has shown to also decrease epithelial resistance of eosinophilic cells.[21] This might be caused by the downregulation of E-cadherin, which is essential for epithelial integrity and stratification. The downregulation of E-cadherin by IL-9 might lead to the decreased barrier function in EoE. Not only the cytokines, but also the immune cells that are part of the inflammatory response, might contribute to the damaging of the epithelial barrier. Mast cells are activated in EoE. Activated mast cells down regulate the expression of FLG, IVL, DSG1 and SPINK7 leading to a diminished barrier function.[22] This was confirmed by the decreased epithelial resistance and increased epithelial permeability. Once an inflammatory process starts, the epithelial barrier becomes more permissive, increasing allergenic stimulation, which contributes again to the inflammation.[11]

Epithelial alarmins

The damaged epithelial barrier caused by the transcriptional dysregulation, exposure to environmental toxins and inflammation, leads to the release of TSLP, IL-25 and IL-33 (all shown to be elevated in EoE). These epithelial alarmins promote a type 2 inflammatory response.[23,24] They can drive the polarization of naïve T-helper (Th) cells into Th type 2 (Th2) cells after activation by dendritic cells and activate group 2 innate lymphocytes (ILC2) cells.[9] Moreover TSLP activates basophils.[25] Th2 and ILC2 cells promote the type 2 immune response. This inflammatory response will continue to maintain damaged and open barriers, leading to a vicious cycle.[11]

Type 2 immune response

The type 2 immune response is triggered by the passage of a food allergen through the epithelial barrier. The fact that food allergens are a trigger for EoE, is supported by the finding that more than 90% of patients respond to an elemental amino acid-based diet and a large majority responds to avoidance of one or more foods.[26] Moreover reintroduction of the identified food allergen leads to disease recurrence. In another study, where they compared 6 observational studies, they found that elemental diets lead to histological remission (defined as <15 eos/hpf) in 93.6% of the subjects.[27]

The disrupted epithelial barrier in EoE patients can allow for the passage of allergens. The foreign food antigens will be processed and presented by antigen presenting cells (APCs), e.g. dendritic cells. The Langerhans cell, an antigen-presenting dendritic cell, may be an important APC in EoE.[24] It is a type of dendritic cell found in the squamous epithelia that drives the type 2 inflammation. The antigens will be presented to cells of the adaptive immunity such as naïve Th cells. Because of the release of TSLP, IL-25 and IL-33 these naïve Th cells will differentiate into Th2 cells, leading to a type 2 immune response. EoE patients show elevated levels of Th2 cells, ILC2 and invariant natural killer T (iNKT) cells.[28–30] These cells produce the type 2 cytokines IL-4, IL-5, and IL-13. This can trigger a type 2 immune response, exacerbating to the inflammation of the esophageal mucosa and the impairment of the barrier function.

T cells

Under the inflammatory condition, T cells migrate to the inflammation site. This is in line with the findings in EoE patients, where elevated levels of T cells are found in the esophageal tissue.[31] The most common T cells in EoE are Th2 cells. The Th2 cells express high levels of type 2 cytokines IL-4, IL-5 and IL-13.[24] However, Th2 cells are not the only T cells upregulated in EoE. The number of regulatory T cells (Tregs) and the Treg / T cell ratio is also increased in EoE patients.[31] Tregs usually have an important role in preventing allergy. However the specific role of Tregs in EoE is still unclear. Another T cell playing an important role in EoE is the iNKT cell.[32] CXCL16 is a chemokine involved in iNKT cell trafficking, that is upregulated in EoE. Moreover iNKT cell-associated cell marker Vα24 and CD1d were also upregulated in esophageal biopsies from EoE patients. The increased levels of iNKT cells correlated with the expression of inflammatory mediators.

ILC2 cells

Another cell important in the type 2 immune response is ILC2. ILC2 is activated by the epithelial alarmins. Upon activation, ILC2 produces type 2 cytokines. ILC2c cells are lineage-negative, meaning that they lack surface markers for T, B, NK and iNKT cells. However they do express the chemoattractant receptor-homologous molecule on Th2 cells (CRTH2).[29] The number of ILC2 cells in EoE patients is highly elevated and correlate with the number of esophageal eosinophils. These findings suggest an important role for ILC2 cells given their capacity to produce high levels of IL-5 and IL-13.

B cells

B cells are a key player of the adaptive immune response. They are able to produce antibodies against foreign antigens. The esophageal tissue of EoE patients shows an increased density of B cells.[33] Moreover, elevated levels of IgE-bound mast cell are found in the tissue, suggesting that B cells have a role in the IgE class switching in the EoE pathogenesis. IL-4 and IL-13, present in EoE patients, promote IgE class switching of B cells and B cell proliferation. The IgE produced by B cells can bind to the high-affinity receptor FcεR1, which is expressed on mast cells and basophils. B cells might therefore play an important role in activating mast cells and basophils.

Eosinophils, basophils and mast cells

Eosinophils, basophils and mast cells are essential components of allergic inflammation. In EoE, eosinophil levels correlate with disease severity and treatment responses. Activated eosinophils release various mediators involved in inflammation, immunoregulation and tissue remodeling and repair.[23] IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF) are important cytokines for the function of eosinophils. IL-5 promotes eosinophilopoiesis and eosinophilic trafficking to the esophagus. Moreover granulocyte-macrophage colony stimulating factor (GM-CSF) plays an important role in eosinophil proliferation, maturation, migration and degranulation.[34] In EoE eosinophils accumulate in the esophagus. Here they contribute to the local inflammation by releasing several cytokines, e.g. IL-5, GM-CSF, IL-9 and IL-13.[23] By producing IL-5 and GM-CSF they contribute to their own survival and accumulation. The role of IL-9 has been linked with mast cell numbers in the esophagus.[35] IL-13 contributes to impaired barrier function and fibrosis in the esophagus. Finally, the degranulation of eosinophils leads to the release of granule proteins, including major basic protein (MBP), damaging the epithelial barrier.[23] MBP can also induce mast cell and basophil degranulation and

activate smooth muscles and fibroblasts. This leads to inflammation and fibrosis of the epithelial barrier.

Basophils are activated by the epithelial alarmin TSLP.[25] It has been shown that basophils play an important role in the pathogenesis of EoE. In the study they show that EoE development in mice is dependent on TSLP and basophils. Moreover, they showed that humans have elevated TSLP levels and exaggerated basophil responses in esophageal biopsies. Lastly, they showed that a gain-of-function TSLP polymorphism was associated with increased basophil responses, suggesting a role for the TSLP-basophil axis.

Mast cells are inflammatory cells that are located primarily near blood vessels and at epithelial surfaces.[36] They can be activated by the binding of IgE to FcεR1. IL-4 upregulates the expression of FcεR1, thereby promoting mast cell activation. Moreover mast cells can be activated by several other factors including, C3a and C5a, stem cell factor, nerve growth factor (NGF) and IgG. Lastly, IL-9 has been linked with mast cell numbers in the esophagus, supporting a potential role of IL-9 in the activation or accumulation of mast cells in EoE.[35] Upon activation mast cells have an immediate and delayed release of inflammatory mediators such as histamine, proteases, Il-13, Il-5 and GM-CSF. Mast cell density and degranulation are increased in the esophagus of patients with EoE.[37] IgE-activated mast cells decrease epithelial resistance and increase the permeability.[22] It is suggested that this is mediated by cytokine oncostatin M (OSM), since OSM is increased by 12-fold in active EoE and associated with mast cell marker genes. Stimulation of epithelial cells with OSM leads to a decrease of FLG and DSG-1 and an increase of CPN14, which leads to a decrease in barrier function. Moreover, murine models have demonstrated that mast cells increase smooth muscle mass and play a role in esophageal remodeling via producing TGF-β1.[38]

Type 2 cytokines

As stated before the type 2 cytokines are released by the type 2 immune cells. The type 2 cytokines include IL-4, IL-5, IL-9 and IL-13. Indeed it has been shown that these cytokines show elevated levels in EoE patients, mainly in the esophagus.[39,21] Apart from having their own receptors, IL-4 and Il-13 share a receptor subunit, interleukin-4 receptor alpha (IL-4Rα).[24] This receptor is expressed on mast cells, eosinophils, macrophages, lymphocytes and epithelial cells. IL-4 and IL-13 signaling through IL-4Rα contributes Th2 effector functions and the production of type 2 cytokines IL-4, IL-5 and IL-13, amplifying its effect. IL-4 signaling contributes to B cell class switching to immunoglobin E (IgE).[40] This leads to mast cell and basophil degranulation resulting in the release of pro-inflammatory mediators. In addition, IL-4 is also able to directly activate mast cells, leading to their proliferation, survival and degranulation.[24] Another type 2 cytokine is IL-5. IL-5 is a critical factor in the maturation, differentiation and survival of EoE. First of all IL-5 upregulates eosinophilopoiesis.[41] The IL-5 receptor alpha (IL-5Rα) is expressed by eosinophils and basophils. Therefore IL-5 can promote eosinophilic trafficking to the esophagus.[42] Lastly, IL-5 mediated eosinophilia mediates collaged deposition in the mucosa and lamina propria and thickening of the basal layer, leading to tissue remodeling of the esophagus.[43] As briefly mentioned before IL-9 is known to have a function in damaging the epithelial barrier.[21] IL-9 receptor expression and mis-localized claudin-1 are upregulated, while expression of E-cadherin is downregulated. This leads to a decreased epithelial resistance and might contribute to epithelial barrier disruption.

The most prominent cytokine in the pathogenesis of EoE is IL-13. IL-13 treatment of esophageal epithelial cells in vitro induces a gene expression profile that overlaps with the EoE transcriptome, showing that IL-13 is involved in the upregulation and downregulation of specific genes in the esophagus. First of all IL-13 signaling promotes eosinophil recruitment by upregulating the CCL26 gene. CCL26 is the most upregulated gene in EoE patients, compared with healthy individuals.[44] It encodes the eosinophil-specific chemoattractant eotaxin-3, which is involved in eosinophil trafficking to the esophagus via receptor CCR3. Therefore by upregulating CCL26, IL-13 production leads to the accumulation of eosinophils in the esophagus. Moreover, IL-13 disrupts the epithelial barrier by dysregulating the EDC (downregulating FLG and IVL), downregulating DSG1 and upregulating CAPN14.[9] Lastly, IL-13 signaling is involved in the induction of TGF-β1, leading to esophageal fibrosis.[45]

Mixed IgE or non-IgE mediated pathway

The exact mechanism of EoE is still not well defined. Both IgE-mediated and non-IgE mediated pathways may be involved. Classically, mast cell degranulation is induced by cross-linking of membrane bound IgE by specific antigens.[36] The elevated mast cell degranulation in EoE patients might therefore be an indication of an IgE-mediated mechanism. In a study from Mulder, et al, they found that IgE-bearing mast cells are only increased in atopic EoE patients and not in non-atopic EoE patients.[46] Indicating that IgE-sensitization is common in at least a sub-group of EoE patients. In another study they showed that indeed, IgE levels are increased in some EoE patients, but not all of them.[47] In this study they measured the plasma IgE concentration, while the immune response in EoE may be a local response. The lacking IgE in some patients might therefore be explained by the fact that the IgE are located at the esophageal tissue and not in the plasma. Indeed, in a study where endoscopic biopsies from the esophagus were taken, elevated levels of IgE-bound mast cells were found.[33] In their study they show a supporting the role of local immunoglobin class switching to IgE and IgE production in the esophageal mucosa of EoE patients.

Other evidence might suggest that IgE does not have a prominent role in the pathogenesis of EoE. The levels of food specific IgE are increased only relatively modestly compared to patients with food anaphylaxis. Moreover measuring specific IgE levels and skin prick testing, were not able to predict EoE-triggering foods.[9] Lastly, a murine study showed that B-deficient mice were still able to develop EoE and the anti-IgE therapy in EoE patients was not effective.[48,49] This might however be explained by the several pathways in the mechanism of EoE. If only the IgE-mediated pathway is blocked, the other pathways might still lead to a decreased epithelial barrier function and in increase in esophageal eosinophilia. Bloking one specific pathway might therefore not be beneficial in EoE therapy.

The way that the mast cells are activated in EoE is still unclear. IgE mediated mast cell activation is not the only way mast cells can be activated. As stated above, eosinophils can release IL-9 which has been linked with mast cell numbers in the esophagus. Another proposed pathway includes IgG4, an antibody isotype that is upregulated by IL-4. EoE patients have elevated systemic serum levels and increased local cell expression of IgG4.[50] IgG4 usually has a protective role in allergy by acting as a blocking antibody (competing with IgE for allergen binding) and therefore inhibiting mast cell degranulation.[51] However, oral immunotherapy (OIT) has been shown to induce EoE in about 2.7% of the patients undergoing this treatment.[52] The elevated IgG4 levels and the development of EoE whilst undergoing OIT, indicate a role of IgG4 in EoE pathogenesis. The exact role of IgG4 is however still unclear.

In conclusion, the activation of the type 2 immune response triggered by a passing food allergens leads to the downstream release of type 2 cytokines. These cytokines promote further inflammation and epithelial barrier dysfunction, driving a positive feedback loop. This results in a chronic inflammation of the esophagus, which may lead to esophageal fibrosis and tissue remodeling. The EoE mechanism is shown in Figure 2.

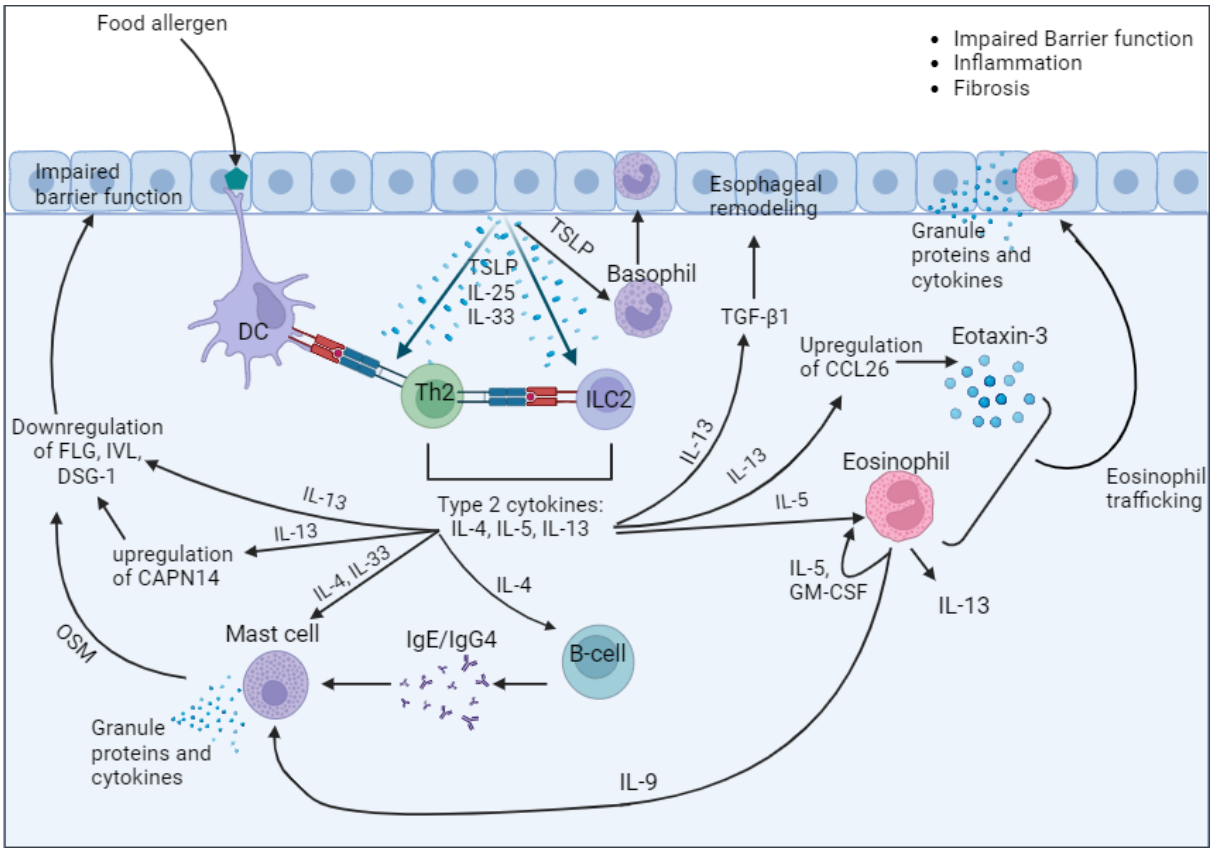

Figure 2 The type 2 immune response, triggered by the passing food allergen in the esophageal epithelium of EoE patients. The food allergen passes the disrupted barrier and is recognized by an APC. The APC presents the antigen to a naïve Th cell which will, with the release of TSLP, IL-25 and IL-33, differentiate into a Th2 cell. Moreover the epithelial release of TSLP, IL-25 and IL-33 will lead to activation of basophils and ILC2. cells Together these type 2 immune cells will produce type 2 cytokines. The production of IL-5 activates eosinophils, that will produce several cytokines, enhancing the type 2 immune response. IL-4 activates mast cells directly and via B cell class switching to IgE, leading to mast cell degranulation. This will in turn contribute to the impaired barrier function in EoE. The release of IL13, leads to the upregulation of CAPN14, and the downregulation of FLG, IVL and DSG-1 all contributing to the impaired barrier function. Moreover IL-13 upregulates CCL26, leading to the overexpression of eotaxin-3 which promotes eosinophil trafficking to the esophagus Lastly IL-13 also induces esophageal remodeling via TGF-β1. In total the type 2 immune response will lead to the inflammation, impaired barrier function and remodeling of the esophageal epithelium in EoE patients.

Esophageal remodeling

If left untreated, the chronic esophageal inflammation in EoE patients will eventually lead to esophageal remodeling. This includes changes of basal zone hyperplasia, dilated intercellular spaced and subepithelial fibrosis and angiogenesis in the lamina propria.[53] TGF-β1, induced by IL-13, plays a large role in this process. TGF-β1 is increased in active EoE, leading to a diminished barrier function by esophageal remodeling and fibrosis. In an in vitro experiment on human esophageal epithelial cells, it was shown that TGF-β1 reduces the expression of tight junction molecule, claudin-7 (CLDN7).[20] Reduced expression leads to a diminishing barrier function. In another study it was shown that TGF-β1 induces phospholamban (PLN) expression, which alters the smooth muscle cell contraction in EoE, contributing to the remodeling of the esophagus.[54] Lastly, TGF-β1 expression induces the expression of

the serine protease inhibitor plasminogen activator inhibitor 1 (PAI-1), which promotes tissue fibrosis in the esophageal epithelium in patients with EoE.[53] Overall, the elevated levels of TGF-β1 lead to esophageal remodeling and fibrosis in EoE.

The barrier dysfunction, allergen disposure and type 2 inflammation all reinforce each other, adding on to the pathogenesis of EoE (Figure 3Figure 3**Error! Reference source not found.**). Finally the chronic inflammation will lead to esophageal remodeling and fibrosis.

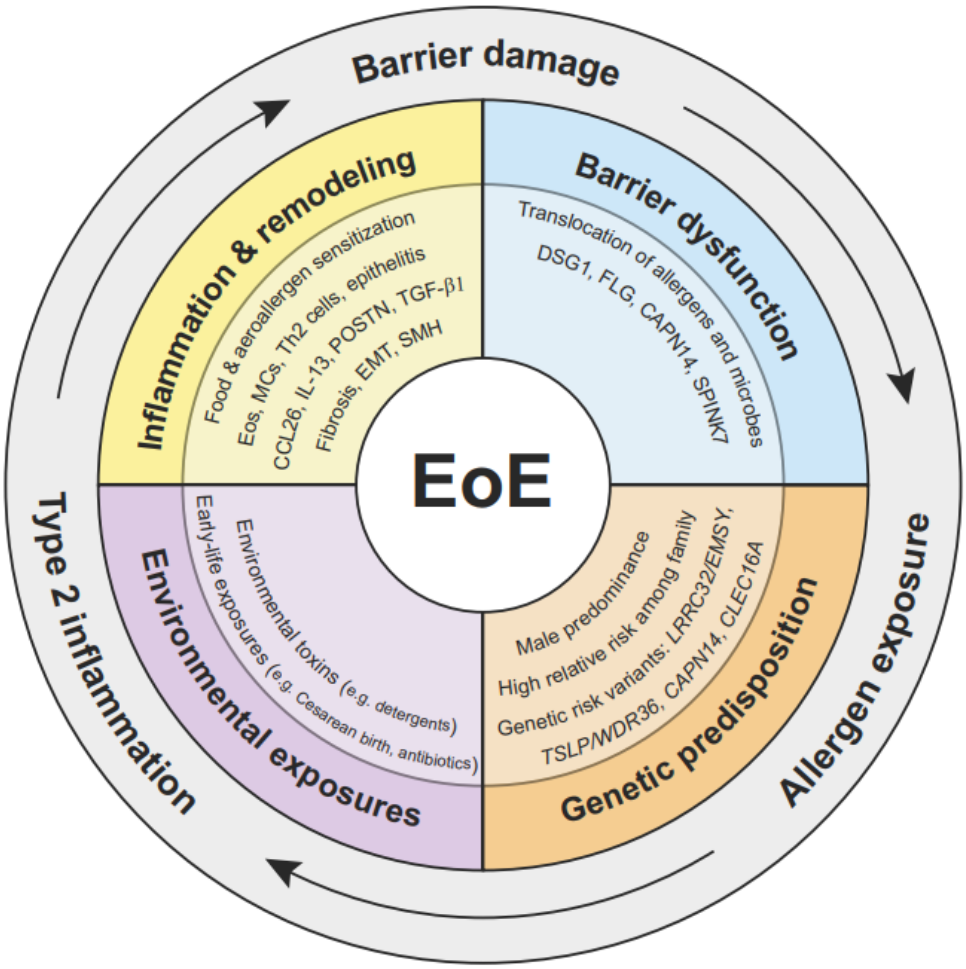

Figure 3 The vicious cycle representing the EoE pathogenic development. The damaged barrier, caused by environmental exposure, inflammation or genetic predisposition, leads to the exposure of allergens. This leads to a type 2 immune response, in which immune cells are activated and type 2 cytokines are produced. These will induce transcriptional changes and inflammation of the esophagus, that will further damage the epithelial barrier. The resulting esophageal inflammation will finally lead to the esophageal fibrosis and remodeling.[55]

Over the years a lot of research has been done on the mechanism of EoE. Different parts of the mechanism have been clarified. Several triggering genes, proteins and cytokines have been revealed. Since the mechanism exists of many different triggers and pathways that all influence each other, it is difficult to clarify the exact mechanism. Therefore some parts, for example the activation of mast cells (IgE-mediated or not), still remain unclear and need further research.

Treatment of EoE

Current treatment strategies

Current treatments for EoE consist of elimination diets, proton pump inhibitors (PPIs), swallowed topical corticosteroids (STCs) and endoscopic dilation.[56] European guidelines have been proposed for the clinical treatment of EoE, as shown in Figure 4Figure 4. The short-term goals of EoE treatments are to reduce symptoms and to attain a histological remission, defined as an eosinophil count of < 15 eos/hpf. A long term goal is to prevent dysmotility and strictures. Therefore, treatments that prevent fibrosis and tissue remodeling are of interest.[57]

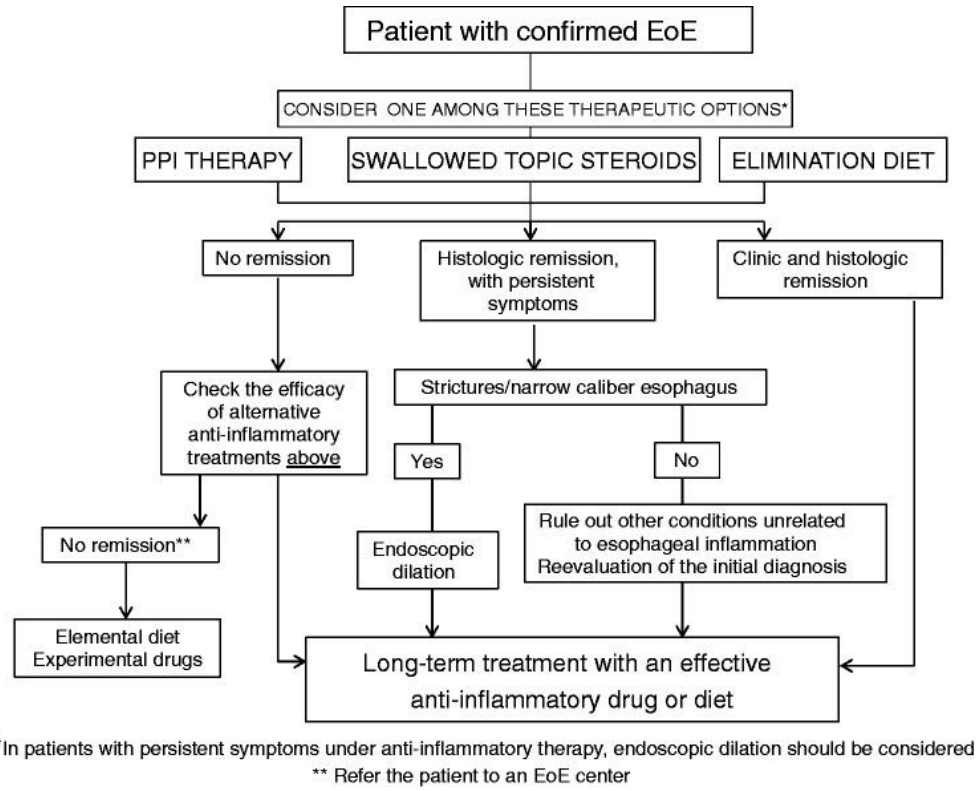

Figure 4 Therapeutic algorithm proposed for eosinophilic esophagitis in clinical practice.[58]

Elimination diets

Elemental diets, test-directed elimination diets and empiric elimination diets are used to treat EoE.[59] All these diets have their own benefits and limitations. Patients taking the elemental diet receive only an amino acid-based formula, to make sure they completely eliminate dietary antigens. If histological remission is achieved, foods are reintroduced to identify potential triggers. The clinical symptoms and esophageal histology (by endoscopy) are assessed. This diet is very effective in decreasing esophageal eosinophilia and improving clinical symptoms. However, it is also very limiting on the quality of life, since the diet is very restrictive and multiple endoscopies are required. The test-directed elimination diet uses skin prick and atopy patch testing to identify EoE food triggers. After finding the specific triggers, these foods are removed from the patient's diet. This diet is less restrictive on the patient's life. The efficacy however is very modest, since it results in a histological remission of only 50%. The empiric elimination diet consists of eliminating foods known to be common allergens. This diet starts by eliminating 2, 4 or 6 food groups from the patient's diet. Histological remission rates for these food elimination diets (FED) were 74% (6-FED), 64-54% (4-FED) and 43% (2-FED). After achieving histological

remission, foods are reintroduced one at a time. Clinical symptoms and esophageal histology are assessed after each food group, to identify the food triggers. This diet is less restrictive than the elemental diet, but still might be difficult to follow. Moreover several endoscopies are required to follow remission and identify specific food triggers.

Proton pump inhibitors

The subgroup responsive to PPI treatment is called the PPI-responsive esophageal eosinophilia (PPI-REE). It is hypothesized that both EoE contributes to or causes gastroesophageal reflux disease (GERD) and that GERD contributes to or causes EoE. The first hypothesis is supported by the theory that esophageal dysmotility in EoE patients may contributes to reflux which leads to acid exposure in the esophagus. The second hypothesis is supported by the fact that the gastric acid in GERD patients damages the mucosal barrier which might lead to the development of EoE.[60]

PPI therapy is a safe and practical initial step in treating EoE and is easily administered. In a systemic review with meta-analysis, including 33 studies with 619 patients, they showed that PPIs led to a histological remission (<15 eos/hpf) in 50.5%, and to a clinical response in 60.8% of the patients.[61] However, the authors caution about the interpretation of these findings, because of poor-quality evidence, heterogeneity and publication bias. Although the lowest effective dose should be used to minimize potential complications, long-term PPI use is well-tolerated. Low-dose PPI maintenance therapy among children and adults have a sustained 1-year remission rate of 70-80%, showing the value of PPIs as maintenance agents.[62,63]

Topical Corticosteroids

Topical corticosteroids non-specifically inhibit the Th2 immune response. Upon treatment the expression of inflammatory cytokines (IL5, IL13, eotaxin-3, periostin, TSLP) decreased and the expression of barrier integrity proteins (FLG, DSG-1) increased.[64] Leading to an improved mucosal barrier integrity. Moreover the treatment leads to reduced esophageal remodeling and decreased fibrosis.[65]

Randomized trials conducted in children and adults confirm the efficacy of topical steroid therapy in histological remission.[58] For example in an observational study of 20 pediatric patients they showed that upon topical corticosteroid treatment the eosinophil count reduced from 34.2±9.6 to 1.5±0.9 eos/hpf. Moreover they showed great clinical response, with 13 patients becoming completely asymptomatic and 6 patients showing improvement of symptoms.[66] At the 12 month follow-up 50% of the patients remained asymptomatic.

Dupilumab

Recently the novel drug Dupixent (dupilumab) was approved by the Food and Drug Administration (FDA) and the European Commission (EC) to treat EoE. Dupilumab is a human monoclonal antibody (mAb) blocking IL-4Rα and thereby blocks IL-4 and IL-13 signaling. The efficacy and safety of Dupixent was tested in a phase III clinical trial on EoE patients 12 years of age or older.[67] This was a randomized double-blind, placebo-controlled trial. In the study weekly dosing, dosing every two weeks and a placebo were compared. A histological remission occurred in 60% of the patients from both the group receiving the dose weekly and the group receiving the dose every two weeks. Histological remission

only occurred in 5-6% of the patients receiving the placebo. The clinical symptoms were improved in the patients receiving the weekly dose, but not in the patients receiving dupilumab every two weeks. Serious adverse events occurred in 7 of the 122 patients receiving weekly dosing. In conclusion, weekly administered dupixent improves histological and clinical outcomes in EoE patients. Currently dupilumab is being investigated in a phase IIII trial to determine the long-term efficacy and safety.[68]

Therapeutic challenges

The current treatment strategies used in treating EoE still have some limitations. The big downside of PPIs and topical corticosteroids, is that upon therapy cessation, recurrent symptoms are reported.[69,70] Therefore these treatments are suboptimal for long-term management. Moreover, treatment with PPI's is only successful is a subgroup of EoE patients. Up until now, the newly introduced Dupilumab has shown very promising results. However, not all patients are responsive to this treatment. The elimination diets offer a treatment for patients that do not want to take medicine. However the diets are often hard to follow and require multiple endoscopies. To improve EoE treatments, research is being done to find alternative treatments for EoE.

Biologic treatments for EoE on the horizon

Currently, a lot of biological drugs are being tested in clinical trials. Biologics are monoclonal antibodies that block a certain cytokine / receptor. In EoE they are used to block a specific target of the type 2 immune response. By blocking part the immune response, the researchers expect to see less eosinophilic accumulation in the esophagus and improved clinical outcomes. In this paragraph, different biologic treatment options will be discussed, both those that are already a long way into phase II and III clinical trials and those that are just beginning their initial stages of investigations.

Blocking IL-13

The IL-13 blockers are still under investigation. QAX576 is an anti-IL-13 mAb that has been tested in a phase II clinical trial.[71] It significantly improved the esophageal eosinophil counts and the expression of EoE transcripts. However the primary end-point was not met. Another IL-13 blocker is currently being investigated in a phase III trial.[72] RPC4046 is a humanized anti-IL-13 mAb that blocks the binding of IL-13 to the receptor subunits IL-13Rα1 and IL-13Rα2.[73] In a randomized, double-blind, placebo-controlled phase II study the safety and efficacy was tested. In the trial they included 99 adults with active EoE that were treated for 16 weeks. After treatment with RPC4046 there was a significant reduction in esophageal eosinophil count. Moreover, histological and endoscopic features were reduced and the patients experienced less dysphagia. A sub-study of this phase II trial showed that RPC4046 also reduces epithelial-mesenchymal transition (EMT).[74] In total the phase II study shows RPC4046 is well tolerated in patients and it can reduce inflammation and remodeling of the esophagus. A follow-up study was done to test the efficacy and tolerability for one year of treatment. In this study they showed that one year of treatment with RPC4046 is well tolerated and results in continued improvement / maintenance of histologic, endoscopic and clinical outcomes.[75] Therefore RPC4-46 in now being investigated for its long term safety and efficacy in a phase III trial.

Blocking IL-5

Benraluzimab is a monoclonal antibody that targets IL-5Rα and might therefore deplete eosinophils from gastrointestinal (GI) tissue.[76] Benraluzimab has been investigated in a phase II and a phase III trial.

The phase II trial included 26 patients aged 12–60 years. The patients were randomized into receiving a 30mg dose benraluzimab or placebo. A histological remission was achieved in 77% of the patients receiving benraluzimab, compared to 8% receiving the placebo. Moreover, significant improvements were seen in peak gastric eosinophil counts, eosinophilic gastritis histology total score, inflammatory histology score and blood eosinophil count. However, there was no significant difference in histology structural score, EG-REFS score or in patient-reported outcomes. The most common adverse events included nausea, vomiting and headache. The phase III trial of benraluzimab on EoE patients has been terminated. The results of the trial did not meet one of the two primary endpoints. A statistically significant improvement in histological disease remission was seen, but there was no significant improvement in dysphagia symptoms, compared to placebo. Since there was no clinical benefit for the EoE patients when taking benraluzimab, the study has been stopped.[77]

Another IL-5 blocking biologic therapeutic is Mepoluzimab. Mepoluzimab is a humanized monoclonal antibody against IL-5. First a phase I/II safety and efficacy study was conducted.[78] The study only included 4 adult patients. There was a significant decrease in peripheral blood and esophageal eosinophilia and an improvement in clinical outcomes. After that a phase II trial was done.[79] It was a randomized, double-blind, placebo-controlled clinical trial. Mepoluzimab was effective in improving eosinophil counts and endoscopic severity. However it did not meet the endpoint of improving dysphagia symptoms.

The fact that the IL-5 blockers significantly decrease eosinophil counts, but seem unable to improve clinical outcomes, suggests that there are other eosinophil-independent pathogenic mechanisms contributing to the symptoms of EoE. Therefore in order to improve the symptoms of patients with EoE a broader targeting of the type 2 immunity is necessary.

Blocking TSLP

Tezepulemab is a first in class human monoclonal antibody inhibiting the action of TSLP.[80] It already received its first approval in de USA as an add-on treatment for patients (> 12 years) with severe asthma. In October 2021 Tezepulemab received an orphan drug designation by the FDA for the treatment of eosinophilic esophagitis. Currently the drug is being investigated in a phase III study.[81] It is a randomized, double-blind, placebo-controlled trial including about 360 patients 12-80 years of age.

Blocking IgE

Omalizumab is a humanized monoclonal anti-IgE antibody that blocks the binding of free IgE to its corresponding FcεRI receptor on mast cells and basophils. In this way, their activation by allergens is inhibited. In a phase I study of omalizumab, it was suggested that this anti-IgE therapy may results in disease remission.[82] However in a phase II study it was demonstrated that treatment of EoE with omalizumab is unsuccessful.[49] It was a randomized, placebo-controlled, double-blind phase II trial including 30 subjects. Treatment with omalizumab did not reduce eosinophil counts nor did it improve symptoms compared to placebo. Therefore it seems that blocking IgE is not an effective treatment in EoE. In the study the authors do suggest a potential role of IgG4 in the pathogenesis of EoE.

Blocking Siglec-8

Lirentelimab is a humanized monoclonal antibody against Siglec-8. Siglec-8 is a cell surface receptor that is expressed on human mast cells and eosinophils.[83] Lirentelimab can upon binding to Siglec-8

inhibit mast cell activity and cause depletion of eosinophils. In a phase II / III study lirentelimab was tested for its safety and efficacy against EoE.[84] 277 adults and adolescents with active EoE participated in the study. In the study the histological endpoint of achieving a proportion of tissue eosinophil responders (≤6 eos/hpf in peak esophageal hpf) was achieved. However the clinical endpoint was not met, since there was no absolute change in Dyshpagia Symptom Questionaire (DSQ) score.

Blocking KIT

The receptor tyrosine kinase KIT is required for the function and survival of mast cells.[85] Barzolvolimab is a humanized monoclonal antibody blocking this receptor with high specificity. Therefore, barzolvolimab can stop the activation and even survival of mast cells. The antibody is currently being tested in a phase II trial to test the efficacy and safety in adult EoE patients.[86] The study will include 60 patients that will be randomized into receiving either barzolvolimab or placebo.

Blocking TNF-α

TNF-α is a cytokine that is upregulated in EoE.[87] It is a pro-inflammatory cytokine expressed by the keratinocytes of the esophageal epithelium in patients with EoE. TNF-α also induces eotaxin-3 production. Infliximab is a chimeric monoclonal antibody that can inhibit both soluble and membrane-bound TNF-α. Inflixumab has been tested in a pilot-trial to evaluate its efficacy in adults with severe EoE.[87] This trial included only three patients with EoE. In the study, treatment with infliximab did not induce a resolution of the eosinophilic tissue infiltration and it did not reduce symptoms. Detailed analysis however, showed that it did evoke a heterogenous reaction. Further studies with alternative application modes, and dosages are needed to evaluate the therapeutic options for infliximab in patients with EoE.

Other potential therapeutic strategies for EoE

Apart from the biologic treatments, there are also other potential targets that are being investigated for EoE treatments. Moreover, one of the studies that is being done is focussed on improving the diagnostic tools to diagnose, monitor and manage treatment of EoE.

Blocking CRTH2

CRTH2 is a receptor expressed by Th2 cells, ILC2 cells, eosinophils and basophils that is involved with the activation and chemotaxis of these cells.[9] OC000459 is a selective CRTH2 antagonist and may therefore suppress eosinophilic tissue inflammation in EoE patients. In order to test the efficacy and safety of OC000459 in these patients a proof-of-concept phase II study was performed.[88] The study included 26 adult patients that were treated with OC000459 or placebo for 8 weeks. The treatment with OC000459 showed a decrease in esophageal eosinophil load and improved clinical outcomes. Moreover, no serious adverse events were observed. Despite the fact that the outcomes of this phase II trial seemed promising for the treatment of EoE, no further clinical trials have been performed with OC000459.

Trypsin inhibitor

Zemaira is an alpha-1 trypsin inhibitor.[89] It acts similar to the protease inhibitors lacking in EoE. Currently Zemaira is being investigated in a phase II trial in which 15 adults with active EoE will be participating. The study is being conducted to test the safety and efficacy of Zemaira in adults with

EoE. They will investigate if Zemaira accumulates in the esophagus and reduces the activity of proteases that contribute to the impaired barrier.

Etrasimod

Etrasimod is a selective S1P receptor modulator that is being developed to treat immune-mediated inflammatory disorders.[90] Currently, it has been evaluated in a phase II trial in the treatment of EoE. 108 patients with active EoE were randomly assigned to either receiving estrasimod or placebo.[91] The treatment with estrasimod improved endoscopic features and clinical symptoms and it was well tolerated.[92] This supports further evaluation of estrasimod in EoE patients.

Radiopharmaceutical agent NDX-3315

NDX-3315 is a radiopharmaceutical that is currently being investigated in a phase I trial.[93] It will be used as an imaging diagnostic to detect, diagnose, monitor and manage treatment of EoE. The big advantage of NDX-3315, compared to the current means of monitoring disease status where they do periodic endoscopies with biopsies, is that NDX-3315 is non-evasive. In the phase I trial the researchers will test for the safety, tolerability and diagnostic performance of NDX-3315. In order to do this, they will include both healthy participants and patents with EoE.

As can be seen, there are quite some drugs that are being investigated for their use in treating or diagnosing EoE. Table 2 gives an overview of all the clinical trials discussed in this review.

Table 2 Overview of several medicines that have been or are currently being tested in clinical trials. The table shows the target that is blocked by the specific drug, the study design, population size, duration, dosage and whether the trials were successful in achieving clinical and histological improvements.

Target	Drug	Study	Design	Population (N)	Duration (weeks)	Dosage	Clinical response	Histologic response	Comments
IL-4, IL-13	Dupilumab	Hirano I, et al[94]	Phase 2	Adults (47)	12	300 mg weekly	+	+	
		Dellon E, et al[67]	Phase 3	Adolescents and adults (321)	52	300 mg weekly	+	+	
		NCT04394351	Phase 3	Children (102)	160	Dose based on body weight	n/a	n/a	Study is ongoing
		NCT06101095	Phase 4	Adults (64)	128	Not defined	n/a	n/a	Study is ongoing
IL-13	QAX576	Rothenberg M, et al[71]	Phase 2	Adults (25)	12	6 mg/kg every 4 weeks	+	+	Primary endpoint was not met
	RPC4046	Hirano I, et al[73]	Phase 2	Adults (99)	16	180 or 360 mg weekly	+	+	
		Dellon E, et al[75]	Phase 2	Adults (66)	52	360 mg weekly	+	+	
		NCT04753697	Phase 3	Adolescents and adults (399)	48	360 mg weekly	n/a	n/a	Study is ongoing
IL-5	Benraluzimab	Kliewer K, et al[76]	Phase 2	Adolescents and adults (26)	12	30 mg every 4 weeks	-	+	
		NCT04543409	Phase 3	Adolescents and adults (211)	52	Not defined	-	+	Study was terminated since primary

									endpoint was not met
	Mepoluzimab	Stein M, et al[78]	Phase 1/2	Adults (4)	12	750 mg monthly	+	+	
		Dellon E, et al[79]	Phase 2	Adolescents and adults (66)	26	100 mg or 300 mg monthly	-	+	
TSLP	Tezepulemab	NCT05583227	Phase 3	Adolescents and adults (360)	52	Not defined	n/a	n/a	Study is ongoing
IgE	Omaluzimab	Loizou D, et al[82]	Phase 1	Adolescents and adults (19)	12	Varying doses	+	+	Since this study is open label there is the potential for bias.
		Clayton F, et al[49]	Phase 2	Adolescents and adults (30)	16	Dose based on IgE level and weight	-	-	
Siglec-8	Lirentelimab	Dellon E, et al[84]	Phase 2/3	Adolescents and adults (277)	26	1 or 3 mg/kg monthly	-	+	
KIT	Barzolvolimab	NCT05774184	Phase 2	Adults (60)	24	300 mg every 8 weeks	n/a	n/a	Study is still ongoing
TNF-α	Infliximab	Straumann A, et al[87]	Phase 2	Adults (3)	8	2 infusions of 5 mg/kg within 2 weeks	-	-	
CRTH2	OC000459	Straumann A, et al[88]	Phase 2	Adults (26)	8	100 mg twice daily	+	+	
α1-trypsin	Zemaira	NCT05485155	Phase 2	Adults (15)	12	120 mg/kg weekly	n/a	n/a	Study is still ongoing

S1P receptor	Etrasimod	NCT04682639	Phase 2	Adults (108)	24	1 or 2 mg daily	+	+	
n/a	NDX-3315	NCT05757856	Phase 1	Adults (24) (EOE and healthy individuals)	10	Not defined	n/a	n/a	Study is still ongoing, diagnostic tool instead of treatment

Unmet medical needs

The current treatment options have shown several downsides in treating EoE patients. The elimination diets offer a good treatment option to patients that do not want to take medicine for the rest of their lives. However, the diets are often very restrictive, need multiple endoscopies and do not improve clinical and histological improvements in all patients. The PPI therapy is only effective in a subgroup of EoE patients and upon therapy cessation the symptoms will recur. This means that patients will have to take PPIs, with all of its side effects, for the rest of their lives. The STCs show great histological remission and improvement of symptoms in a large part of EoE patients. However, just as with the PPI therapy, symptoms recur after therapy is stopped. Which means that again, patients will have to take medicine their whole lives. The currently approved dupilumab targets IL-4Rα thereby blocking both IL-13 and IL-4 signaling pathways. IL-13 is the most abundant cytokine in the pathogenesis of EoE. It activates a lot of pathway in the pathogenesis. Dupilumab is therefore a very promising therapeutic. Nevertheless it still showed histological remission in only 60% of the patients. Therefore dupilumab cannot be used to treat all EoE patients.

The current clinical trials mainly investigate the effectiveness of potential biologics in the treatment of EoE. One of the downsides of all biologics (including dupilumab) is that they are very expensive. Moreover, the biologics target only one molecule involved in the EoE pathogenesis. By blocking only one molecule, the remaining molecules can still signal for the other pathways involved in the mechanism. For example by blocking IL-5 it could be seen that eosinophil counts were down, but the clinical symptoms remained. This can be explained by the presences of other eosinophil-independent pathways involved in EoE. Therefore only targeting one molecule will not be enough. In order to reduce pathogenic features and improve clinical outcomes, more molecules should be targeted. Another way to solve this problem is to target molecules that are higher up the inflammatory cascade. For example the blocking of TSLP is very promising, since it is one of the first cytokines involved in the disease development. Lastly, since these biologics are focused on blocking the type 2 immune response, it is not known if they restore the epithelial barrier function. This might be important in order to make sure that symptoms do not recur in patients after therapy cessation.

Discussion and conclusion

In order to provide better medical care for EoE patients it is important that there is more clarification on the pathogenesis of the disease. The most pathways of the disease have already been understood, but some still remain unclear. For example, it is currently still unclear what the first cause of the barrier dysfunction is. Moreover the exact mechanism of the mast cell activation and degranulation also still remains unclear. Is it IgE-mediated, IgG4-mediated, are there other IgGs playing an important role? These are some of the main questions that need to be answered in order to develop better treatments for EoE patients. Therefore it is important that more research is done, in order to fully understand the pathogenesis of EoE.

Another aspect that needs further investigation is the effect of biologics (e.g. dupilumab) on the restoration of the epithelial barrier function. The biologics that are currently investigated block part of the immune type 2 response. By blocking this inflammatory response, the pathogenic mechanism of EoE is diminished. However, the epithelial barrier is already damaged and it is not known if the biologics can restore the barrier function. Studies will have to be done, to check if the biologics restore

barrier function. If not, it is important that apart from blocking the inflammatory response other medication is given as well to restore barrier function.

Restoring barrier function might also be a possible treatment strategy in general. Instead of blocking the immune response, focusing on the improvement of the barrier function might reduce EoE pathogenesis. This can be done by restoring the regular protein levels of FLG, IVL, DSG-1 and CAPN14. The can be done by increasing the expression of FLG, IVL and DSG-1, or by decreasing expression or blocking protein CAPN14. Specific nutritional components might also be beneficial in restoring barrier function. In a recent study they investigated the influence butyrate and propionate in restoring barrier function.[95] In the study they showed that indeed in the in vitro tests, butyrate and propionate can restore the barrier function after an inflammatory insult. In another study they evaluated the role that vitamin D might play in the pathogenesis of EoE.[96] In the study they found that vitamin D might function as a natural IL-13 antagonist. Indeed, vitamin D supplementation reversed IL-13-induced epithelial hyperproliferation, reduced barrier permeability and increased expression of FLG and IVL. Moreover, they showed that vitamin D levels inversely correlate with severity of esophageal eosinophilia and epithelial histopathology. Nutraceuticals may therefore be of therapeutic benefit in treating EoE.

What is probably most important is that EoE treatment should be personalized for every individual patient. Patients can have a preference in whether they prefer taking medication or following an elimination diet. Moreover, patients might respond better to different medication. EoE patients have a specific EoE phenotype determined by age, comorbidities, response to therapy, natural history and disease severity. A personalized treatment strategy should be made in which the phenotype and personal preferences are taken into account. The development and research into the mechanism of EoE and new therapies, will be needed to give patients more and better options for their treatment.

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