Biological Drugs in EoE and Their Targets

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Eosinophilic esophagitis (EoE) is a multifaceted disease characterized by a wide heterogeneity of clinical manifestations, endoscopic and histopathologic patterns, and responsiveness to therapy. From the perspective of an effective approach to the patient, the different inflammatory mechanisms involved in the pathogenesis of EoE and biologics, in particular monoclonal antibodies (mAbs), targeting these pathways are needed. Currently, the most relevant is dupilumab, which interferes with both interleukin (IL)-4 and IL-13 pathways by binding IL-4 receptor α, and is the only mAb approved by the European Medicine Agency and US Food and Drug Administration for the treatment of EoE. Other mAbs investigated include mepolizumab, reslizumab, and benralizumab (interfering with IL-5 axis), cendakimab and dectrekumab (anti-IL-13s), tezepelumab (anti-TSLP), lirentelimab (anti-SIGLEG-8), and many others.

Keywords: biological drugs ; benralizumab ; cendakimab ; dupilumab ; eosinophilic esophagitis

1. Dupilumab: The Anti-IL-4/IL-13 mAb

Dupilumab is a humanized IgG4 monoclonal antibody that binds the α subunit of the heterodimeric IL-4 receptor [1]. IL-4Rα may link to the γc chain, forming IL-4R type I (binding exclusively IL-4 and being expressed only on hematopoietic cells), or it may associate the receptor for IL-13, IL-13Rα1, forming IL-4R type II (binding both IL-4 and IL-13 and being expressed on both hematopoietic and epithelial cells) [2]. The pivotal role played by IL-4 and IL-13 released by type 2 cells in target tissues of atopic diseases, such as lung, skin, and gut, is very well-known [3][4]. As regards EoE, IL-4 and IL-13 are involved in favoring the releasing of eotaxin (CCL26) by esophageal epithelial cells, leading to eosinophils recruitment [5], Th2 differentiation, B cell IgG1 and IgE class-switching, and in epithelial to mesenchymal transition with consequent fibrosis [6][7]. Being more abundant than IL-4 in EoE, IL-13 plays a key role in the pathogenesis of EoE [8]. By binding its receptors expressed on esophageal epithelial cells (IL-4-Rα, IL-13-Rα1, and IL-13-Rα2) [8], IL-13 promotes esophageal barrier dysfunction by virtue of regulating the expression of many pivotal actors such as calpain 14, desmoglein-1, and synaptopodin [9][10]. Particularly, in vitro experiments conducted on cultured primary human esophageal cells found IL-13 to be related to altered patterns of tight junctions (intercellular junctional complexes on esophageal epithelial cells) and to mediate a down-regulation of the filaggrin expression, a key protein in the bond of the cytoskeleton of contiguous cells [11]. Furthermore, IL-13 overexpression leads to epithelial–mesenchymal transition, characterized by lower expression of tight junctions and E-cadherins and higher expression of depolarized cytoskeletal proteins (both typical of the epithelial cells), and to increased collagen deposition in the esophageal extracellular matrix (more typical of activated fibroblasts and myofibroblasts) [12][13]. As suggested in in vivo experiments on an eosinophil-deficient mouse with IL-13 overexpression, IL-13 may drive esophageal fibrosis independently of its role in eosinophil recruitment [14].

By targeting and blocking such a strategic pathway, dupilumab has proved to attenuate or abrogate disease chronicity and severity so much that, currently, it is the only biologic agent approved by both the EMA and FDA for the treatment of EoE in patients over 12 years of age and 40 kg of weight. Unlike in the US, duplumab can be employed in Europe only in case of failure of or contraindications to conventional EoE treatments [15][16].

A recent phase 3 trial proved the effectiveness of weekly subcutaneous administrations of dupilumab in the improvement of both histologic and clinical outcomes in patients 12 years or older with a documented diagnosis of EoE despite at least 8 weeks of therapy with PPIs [17]. More specifically, this trial was conducted in three parts. In part A, patients underwent a 1:1 randomization (subcutaneous administration of dupilumab 300 mg weekly vs. placebo), while in part B, a 1:1:1 randomization (subcutaneous administration of dupilumab 300 mg weekly vs. subcutaneous administration of dupilumab 300 mg every two weeks vs. placebo); both parts A and B lasted 24 weeks. In part C, all patients who completed parts A or B, including the ones in the placebo groups, were administered dupilumab 300 mg subcutaneously every week up to week 54. In both parts A and B, a significant histologic complete remission (≤6 eosinophils/hpf) was shown in all groups involving patients administered with dupilumab compared to placebo. In part C, patients of parts A and B who were

administered dupilumab weekly had a sustained remission even at week 54, and those who were part of the placebo group reported a significant remission [17].

2. Cendakimab and Dectrekumab: The Anti-IL-13 mAbs

Cendakimab, also known as RPC4046 and CC-93538, is an IgG1k humanized monoclonal antibody that recognizes IL-13 and inhibits its binding to both IL-13-receptor specific subtypes (IL-13-Rα1 and IL-13-Rα2) [18]. A multicenter study (HEROES) was performed on adult patients with active EoE treated with weekly subcutaneous administrations of 180 mg, 360 mg of cendakimab, or placebo. Significant improvements in both histopathologic (<6 eosinophils/hpf and Eosinophil Histologic Scoring System—EoEHSS) and endoscopic (EREFS) outcomes at week 16 were reported in patients treated with cendakimab compared to placebo. Regarding the clinical outcomes, no significant amelioration in dysphagia was achieved, but in the high-dose group, a significant positive effect on the global assessment of disease severity score was reported. The most common adverse events were headache and upper respiratory tract infections [19], the latter confirmed, together with nasopharyngitis, as the most reported in the open-label extension (52 weeks) of the trial [20]. More specifically, all patients who completed the double-blind induction phase were administered cendakimab 360 mg weekly, achieving a positive trend in symptom remission (symptom-based EoE activity index score ≤ 20) in all three previous groups [20]. Furthermore, esophageal samples obtained from patients in the HEROES trial were characterized for their epithelial–mesenchymal transition at week 16, and a trend in the mean percentage of vimentin-positive cells that was inversely proportional to the dose administered of cendakimab was found. On the contrary, E-cadherin expression was increased, thus, as a whole, suggesting a potential role of IL-13 inhibition in a reduction in fibrostenotic risk in EoE [21].

More clarifications about such promising results will come from three more ongoing studies regarding cendakimab. One is a double-blind trial involving not only adults but also adolescents (ClinicalTrials.gov Identifier: NCT04753697) [22], for which is already planned an open label long-term extension (ClinicalTrials.gov Identifier: NCT04991935) [23], while another one investigates drug–drug interactions with selected cytochrome P450 substrates (ClinicalTrials.gov Identifier: NCT05175352) [24].

3. Mepolizumab, Reslizumab and Benralizumab: The Anti-IL-5 mAbs

IL-5 and its receptor (IL-5-R) have been interesting targets for the management of patients affected by EoE for a long time. IL-5 is the most specific eosinophilic cytokine. It is secreted by Th2 cells, mast cells, innate lymphoid cells of type 2 (ILC2s), and eosinophils, and by binding the α subunit of IL-5-R (CD125), it modulates eosinophilic activities from the proliferation of their progenitors to priming of cytotoxicity by mature cells and delaying their apoptosis [25]. As a consequence, the prolonged release of pro-fibrotic factors such as TGF-β1 and fibroblast growth factor 9 (FGF-9) is very strategic in all those processes underlying epithelial remodeling and esophageal dysmotility (i.e., basal zone hyperplasia, fibrosis of the lamina propria, and expansion of muscularis propria) [26]. A study conducted on the esophageal specimens of 312 patients highlighted a non-direct proportion between higher levels of IL-5 and both histological and endoscopic abnormalities. More specifically, higher expression of IL-5 in active cases of EoE was found, but without a linear transition. Patients passed, in fact, from an IL-5 low milder phenotype to an IL-5 high phenotype developed in response to inflammatory or antigenic triggers, up to an IL-5 intermediate phenotype more typical of the latter fibro-stenosing phase of the disease [27].

Mepolizumab is an IgG1k humanized monoclonal antibody that, as well as the IgG4k humanized mAb reslizumab, binds circulating IL-5 and, therefore, prevents its bond to IL-5R [25]. In the first trial concerning the use of an anti-IL-5 mAb in EoE, mepolizumab was administered (3 monthly infusions of 750 mg) to four adults with a history of long-standing EoE and oesophageal strictures. A significant reduction in the mean oesophageal eosinophilia (about 9-fold) has been reported, but never under the threshold level for the complete EoE remission (<5 eosinophils/hpf). As regards the improvements described in clinical outcomes (i.e., dysphagia) and quality of life scores, it is difficult to verify if they resulted from the biologic treatment or the previous and concomitant traditional therapy with steroids, PPIs, and elimination diet [28]. Latter trials performed on mepolizumab, in fact, confirmed a trend regarding histopathologic improvements, but they never [29] or rarely (5/57 patients) [30] achieved complete histopathologic remission, even despite higher doses (2 weekly infusions of 750 mg followed by 2 more infusions of 1500 mg at the 5th and 9th weeks) [29]. Furthermore, patients did not report a significant symptomatic improvement [29][30]. Lastly, a phase 2 trial investigating the effectiveness of mepolizumab via subcutaneous route confirmed the trend performed by this mAb, which is a discrepancy between the reduction in the eosinophilic infiltration of the oesophageal epithelium and a trend to non-progression of the endoscopic outcomes, compared to the lack of tangible improvements in the clinical picture assessed through the EoE Symptom Activity Index (EEsAI) [31].

Unfortunately, a study on reslizumab involving children and adolescents with EoE did not help much in denying what was already stated for mepolizumab, at least in the short term. Once again, the anti-IL-5 provided a significant reduction in intraepithelial esophageal eosinophilia without significant clinical improvements [32]. On the contrary, another small trial provided a larger vision of the long term by considering a follow-up of 9 years in which patients all showed a considerable clinical amelioration (absence of vomiting), with none of them reporting esophageal narrowing or strictures and achieving a complete histopathologic remission [33].

Benralizumab is an IgG1k mAb directed to the α subunit of IL-5-R [25], which received orphan drug designation status from the FDA for the treatment of EoE. Compared to the anti-IL-5 biologics, benralizumab performs a further mechanism beyond the blockage of the IL-5 axis, which is the recruitment of natural killer (NK) cells, macrophages and neutrophils, and the induction of antibody-dependent cell-mediated cytotoxicity (ADCC) for eosinophils and basophils [34]. Despite this, the only single trial performed to investigate the subcutaneous administration of benralizumab 30 mg monthly in patients with EoE over a period of 24 weeks (the MESSINA study; ClinicalTrials.gov Identifier: NCT04543409) did not show a direct correlation between histopathologic and endoscopic improvements assessed through EREFS and clinical amelioration assessed through DSQ [35]. In this regard, it is interesting to note that in a previous study, IL-5R was found to be lower expressed in tissue eosinophils compared to blood eosinophils [36].

4. Tezepelumab: The Anti-Thymic Stromal Lymphopoietin (TSLP) mAb

TSLP is a member of the IL-2 cytokine family and acts as an alarmin, performing a regulation of the Th2 response by driving the production of IL-4, IL-5, IL-9, and IL-13, as well as having pro-inflammatory effects. TSLP is produced by epithelial cells and, at a lower rate, by basophils, mast cells, and dendritic cells of the skin, lung, and gut. Its receptor is a heterodimer consisting of the IL-7 receptor α-chain (IL-7Rα) and the TSLP-R chain [37]. TSLP acts directly on dendritic cells, $CD4^+$, and $CD8^+$ cells, exerting effects also on granulocytes, mast cells, ILC2s, NK cells, smooth muscle cells, and tumor cells [37][38]. A recent trial showed that in esophageal-derived memory $CD4^+$ T cells from patients with EoE, the receptor for TSLP directly responded at a higher rate compared to placebo, as well as circulating memory $CD4^+$ T cells. Particularly, TSLP increased the proliferation of $CD4^+$ T cells, enhanced type 2 cytokines production, induced the expression of its own receptor, and modulated the expression of several other genes, providing, in this way, a feed-forward loop [39].

Tezepelumab is an IgG2λ human mAb targeting circulating TSLP and preventing its bond to the receptor. It recently received the orphan drug designation from the US FDA for the treatment of EoE [40], and, at the moment, a 52-week trial designed to assess the effectiveness and safety of tezepelumab in adults and adolescents with EoE is ongoing (ClinicalTrials.gov Identifier: NCT05583227).

5. Lirentelimab: The Anti-Sialic Acid-Binding Immunoglobulin-Like Lectins-8 (SIGLEC-8) mAb

Lirentelimab, also known as AK002, is a humanized non-fucosylated IgG1 antibody against SIGLEC-8, a receptor selectively found on mast cells, eosinophils, and, to a lesser extent, on basophils, that upon activation mediates acute and chronic inflammatory response. Lirentelimab is involved in the inhibition of mast cell activity and in eosinophil reduction mediated by a dual mechanism involving both ADCC and apoptosis [41][42][43]. Moreover, a significant reduction in neutrophils and immune cell-recruiting cytokines, like IL-6, CCL2, CXCL2, IL-13, and TNF, was reported in mice given an anti-SIGLEC-8 mAb and IL-33 [44]. Furthermore, unlike IL-5Rα, the expression of SIGLEC-8 is stable between blood and tissue compartments [42], suggesting it is an important target.

In the ENIGMA trial, patients with eosinophilic gastritis (EoG) and duodenitis (EoD) were randomized 1:1:1 (lirentelimab low dose—up to 1 mg/kg; lirentelimab high dose—up to 3 mg/kg; placebo) and received four monthly infusions. The lirentelimab combined group reported a significant treatment response (reduction >30% in total symptom score and reduction >75% in gastrointestinal eosinophil count). Notably, patients with concomitant EoE and treated with lirentelimab also reported an improvement in dysphagia [45]. Otherwise, the recent KRYPTOS trial evaluated more specifically the effect of lirentelimab high and low dose compared to placebo on patients ≥ 12 years old with EoE, reporting a significant effect of lirentelimab in achieving complete histopathologic remission (88% for high dose, 92% for low dose, and 11% for placebo), even higher when considering only adolescents. Unfortunately, the symptomatic endpoint (mean change in DSQ) did not achieve a proportional improvement [46].

A recent meta-analysis on seventeen randomized control trials comparing the efficacy of all drugs versus each other or placebo in adults and adolescents with active EoE ranked lirentelimab 1 mg/kg monthly as first for histopathologic

complete remission, but not for endoscopic and symptomatic remission [47].

6. Other mAbs

IL-15 is a master immune checkpoint in gut immunology released by several cells of the innate immune system (i.e., dendritic cells and macrophages) but also by fibroblasts and epithelial cells, thus making it another interesting target for the treatment of EoE [48]. IL-15 was found to be particularly expressed in the basal layers of the epithelium in active EoE [49]. CALY-002 is an anti-IL-15 mAb, and it is currently under study to evaluate its safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with EoE or celiac disease (ClinicalTrials.gov Identifier: NCT04593251) [50].

Another ongoing trial (the EvolvE study) is assessing the effect on adults with EoE of barzolvolimab, also known as CDX-0159 [51], a humanized mAb that specifically binds the receptor tyrosine kinase KIT and strongly inhibits its activity, which is required for mast cell function and survival (ClinicalTrials.gov Identifier: NCT05774184) [52].

A previous study aimed to assess the effect of omalizumab, an anti-IgE mAb, reported histological and clinical improvement in only 33% of patients [53], consistent with the concept that EoE is not an IgE-mediated disease; otherwise, it is associated with IgG4 [54]. No significant improvements were reported with infliximab, an anti-TNFα IgG1 mAb [55].

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