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# Update on Biologic Therapy for Pediatric Eosinophilic Esophagitis

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## ABSTRACT

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated disease of the esophagus, marked by eosinophilic infiltration, epithelial barrier dysfunction, and fibrosis. Clinical manifestations vary by age, with infants and young children presenting feeding difficulties, vomiting, and failure to thrive, while older children and adults typically exhibit dysphagia, food impaction, and abdominal discomfort. Th2-mediated inflammation, driven by IL-4, IL-5, and IL-13, promotes eosinophil recruitment and activation, leading to tissue damage and development of symptoms. Conventional therapies – including proton pump inhibitors, corticosteroids, elimination diets, and esophageal dilation – are often insufficient, highlighting the need for targeted biologic treatments. This review summarizes the current evidence from pediatric and adult studies. Dupilumab, an IL-4Rα inhibitor, is the only biologic approved for children with EoE, demonstrating high rates of histologic remission, clinical improvement, and a favorable safety profile. Anti-IL-13 agents (cendakimab, dectrekumab) and anti-IL-5/IL-5Rα agents (reslizumab, mepolizumab, benralizumab) effectively reduce eosinophilic infiltration, though symptomatic benefit, particularly for dysphagia, is variable. Other investigational therapies, including lirentelimab, omalizumab, and etrasimod, show promise, while evidence for vedolizumab, natalizumab, and infliximab remains limited. Biologic therapies offer a novel, targeted approach for pediatric EoE, especially in refractory cases, although further studies are needed to optimize clinical efficacy and long-term safety.

**KEY WORDS:** eosinophilic esophagitis, Pediatric biologics, Eosinophil-targeted therapy

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## INTRODUCTION

Eosinophilic esophagitis (EoE) is the most common eosinophilic gastrointestinal disorder, characterized by eosinophilic infiltration and esophageal dysfunction. In infants and young children, EoE primarily presents with feeding difficulties, vomiting, regurgitation, failure to thrive, coughing after meals, and abdominal pain [1]. Adolescents and adults more frequently report abdominal and epigastric pain, but dysphagia and food impaction remain the hallmark symptoms. The pathophysiology involves Th2-type inflammation, epithelial barrier disruption, fibrosis, and altered esophageal motility, even though the precise mechanisms are incompletely understood.

The Th2 immune response in EoE is marked by elevated IL-4, IL-5, and IL-13, detected in esophageal biopsies [2-4]. IL-13, produced by Th2 cells, ILC2, and mast cells, contributes to epithelial barrier dysfunction, eosinophil recruitment, fibroblast activation, and tissue remodeling. For these reasons, it is considered one of the central cytokines in the pathogenesis of EoE. IL-4 similarly promotes Th2 polarization, IgE production, and barrier disruption [5]. Both IL-4 and IL-13 signal via the IL-4Rα receptor. IL-5 regulates eosinophil development, survival, and trafficking to the esophagus, with chemokines like eotaxin and leukotriene B4 enhancing tissue infiltration. Activated eosinophils release toxic mediators, including eosinophil-derived neurotoxin, major basic protein, and eosinophil peroxidase, which drive tissue damage and clinical symptoms [6].

**TABLE I.** Summary of completed clinical trials on monoclonal antibodies in patients with EoE included in the review. The table lists the target, route of administration, study name, study type, and age of the study population. Studies that included children are shown in bold.

| Drug | Target | Route of administration | Study name | Outcome of the study | Study type | Population age |
|---|---|---|---|---|---|---|
| Dupilumab | Ab anti IL-4 & IL-13 | SC | **LIBERTY EoE KIDS**<br>**LIBERTY EoE TREET** | 52 wk | RCT<br>RCT | **1-11 y**<br>**1-50 y** |
| Cendakimab | Ab anti IL-13 | SC | RPC4046<br>NCT04753697 | 16 wk<br>48 wk | RCT<br>RCT on going | 18-65 y<br>> 12 y |
| Dektrecumab | Ab anti IL-13 | IV | NCT01022970 | 21 wk | RCT | 18-50 y |
| Reslizumab | Ab anti IL-5 | IV | **NCT00381529** | 15 wk | RCT | **5-18 y** |
| Mepolizumab | Ab anti IL-5 | IV | NCT03656380<br>**NCT00358449** | 13 wk | RCT<br>RCT | 23-48 y<br>**2-17 y** |
| Benralizumab | Ab anti-interleukin-5 receptor α | SC | **NCT04543409** | 24 wk | RCT | **12-65 y** |
| Lirentelimab | Ab anti-CD33 receptor or Siglec-8 | IV | **NCT04322708** | 24 wk | RCT | **12-51 y** |
| Etrasimod | Selective sphingosine 1-phosphate receptor modulator | PO | VOYAGE | 52 wk | RCT | 18-65 y |
| Omalizumab | Ab anti IgE | SC | NCT01040598<br>**NCT00123630** | 20 wk | SAOLS<br>**RCT** | 18-56 y<br>**16-52 y** |
| Infliximab | Ab anti TNF α | IV and SC | | 4 wk | One Small Study | Adults |
| Vedolizumab | Ab anti α4β7 integrin | IV | | - | Case reports | Adults |
| Natalizumab | Ab anti integrin α4β1 and α4β7 heterodimer | IV | | - | One case report | Adults |

Ab: antibody; SC: subcutaneous; IV: intravenous; PO: oral; RCT: randomized controlled trial; SAOLS: single-arm open-label study.

Current management of EoE includes proton pump inhibitors (PPIs), topical or systemic corticosteroids, elimination diets, and esophageal dilations for stenosis. However, these approaches are not universally effective, prompting development of biologic therapies targeting Th2 cytokines or eosinophils [7]. Biologics can selectively inhibit key inflammatory pathways, potentially providing more effective treatment for patients who are refractory to conventional therapy.

## METHODS

This review focuses on pediatric EoE biologic therapies, including approved and investigational drugs with clinical trial evidence in children and adults. Because a formal meta-analysis was beyond the scope of this work, we relied on a recently published scoping review [8], which included a complete literature search up to February 11, 2024. We then updated the search to include studies published on MEDLINE and Embase between February 11, 2024, and July 5, 2025, without language or design restrictions. After screening 99 unique studies, 17 were selected for detailed analysis, focusing primarily on randomized controlled trials (RCTs). The search strategy used the following keywords and Medical Subject Headings (MeSH) terms ("biological therapy" OR "monoclonal antibodies" OR "mepolizumab" OR "omalizumab" OR "dectrekumab" OR "QAX576" OR "benralizumab" OR "lirentelimab" OR "AK002" OR "cendakimab" OR "RPC4046" OR "reslizumab" OR "infliximab" OR "vedolizumab" OR "natalizumab" "anti-interleukin" OR "Anti-IL" OR "AntiIL") AND ("Eosinophilic esophagitis" OR "eosinophilic oesophagitis" OR "EoE"). The search identified 88 articles from PubMed and 97 from Embase. After removing duplicates, a total of 99 unique records were identified. We focused primarily on clinical studies enrolling patients in randomized controlled trials (RCTs) for EoE. A total of 16 studies were included in the Review (Tab. I). In addition, we examined earlier relevant studies and guidelines by reviewing the references of published reviews and clinical trials on this topic.

## RESULTS

Twelve biologics have been evaluated for EoE, with three pediatric-only RCTs and four RCTs including both adults and children. Biologics in these studies target different immune pathways, chiefly by Inhibition of primary Th2 cytokines and disrupting eosinophil activity and movement (Fig. 1).

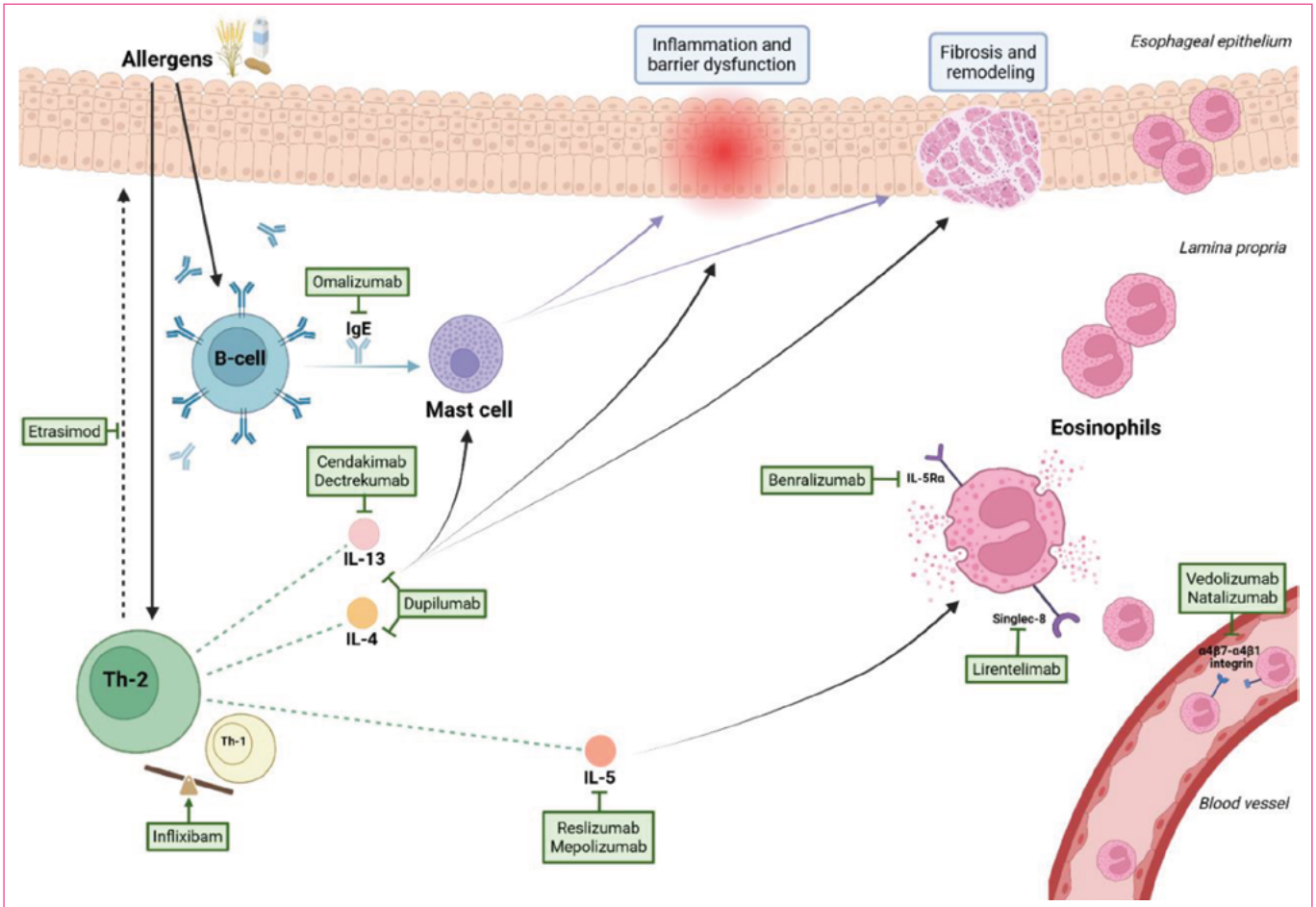



**FIGURE 1.** Schematic representation of immune pathogenesis in EoE. Allergens activate Th2 cells, which release cytokines (IL-4, IL-5, IL-13), leading to eosinophil and mast cell activation. This causes esophageal tissue damage, barrier dysfunction, fibrosis and remodeling. Monoclonal antibodies reduce inflammation by targeting these pathways.

## 1. Anti-IL-4 and IL-13

**Dupilumab**, an IL-4Rα antibody inhibiting IL-4 and IL-13 signaling, is the only biologic approved for pediatric EoE in children aged 1-11 years. In the phase 3 "EoE KIDS" study [9], dupilumab led to histologic remission, defined as peak of esophageal intraepithelial eosinophil count, ≤ 6 per high power field (HPF) at week 16, in 68% of children versus 3% with placebo, along with endoscopic and clinical improvements. One-year follow-up indicated sustained remission in 53-63% of patients. Real-world retrospective studies in refractory pediatric cases showed 82% symptom relief, 73% endoscopic improvement, (calculated with the change in EoE endoscopic reference scoring system (EREFS) scores from the baseline to 3 months), and 90% histologic remission after three months (< 10 eos/HPF) [10]. Another phase 3 trial evaluated the efficacy and safety of dupilumab, over 52 weeks, at a dose of 300 mg weekly or every two weeks versus placebo, in patients aged 12 years or older with EoE. The study found that weekly subcutaneous administration of dupilumab led to improved histologic outcomes and reduced disease symptoms. Adverse events were generally mild, including injection site reactions, headache, cough, conjunctivitis and mild infections. Dupilumab is recommended by Clinical Guidelines from American College of Gastroenterology and from an expert panel of Italian Society of Pediatric Gastroenterology, Hepatology, and Nutrition (SIGENP) after failure of conventional therapy and may be considered first-line in severe, multi-atopic cases [11,12]. The recommended doses are 200 mg subcutaneously every other week (15-30 kg), 300 mg subcutaneously every other week (30-40 kg) and 300 mg subcutaneously every week (> 40 kg) [13-15].

## 2. Anti-IL-13

**Cendakimab (RPC4046)** and **dectrekumab (QAX576)** target IL-13. In adults with steroid-resistant EoE, Cendakimab reduced eosinophil counts and improved endoscopic features at week 16, though symptom improvement, assessed by questionnaire scores, was modest [16]. Dectrekumab, in a small adult RCT, decreased eosinophil infiltration by 60% versus a 23% increase in placebo, and improved

dysphagia scores [17,18]. Both drugs had favorable safety profiles, but pediatric data are currently lacking.

## 3. Direct eosinophil-targeting biologics

The mechanisms used are blockade of IL-5 or IL-5 receptor α or of another eosinophilic receptor, named CD33 or Siglec-8 (sialic acid-binding immunoglobulin like lectin 8). **IL-5 inhibitors** include **reslizumab**, **mepolizumab**, and **benralizumab**. Mepolizumab and reslizumab act by binding to IL-5, neutralizing it before it attaches to its receptor. Benralizumab works by binding to the anti-interleukin5 receptor α. **Lirentelimab** targets Siglec-8/CD33.

**Reslizumab** was tested in a multicenter RCT with 226 children (ages 5-18) who had moderate-to-severe EoE [19]. The co-primary efficacy measures were changes in peak esophageal eosinophil count and physician's global assessment score at week 15 (end of therapy). IV infusions reduced peak esophageal eosinophil counts by up to 67%, but clinical symptom improvement was limited. An open-label extension showed reductions in dysphagia, abdominal pain, and vomiting, with patients maintaining a relatively unrestricted diet [20]. No serious adverse events were attributed to the drug. In addition, patients receiving reslizumab maintained a relatively unrestricted diet.

**Mepolizumab** has demonstrated histologic benefit in adults and children, though symptom relief was modest. A pediatric international, multicenter, double-blind, randomized, prospective study has been carried out involving 59 children (2-17 years) receiving three different doses (0.55, 2.5, or 10 mg/kg) of mepolizumab via intravenous infusion IV. The study was designed such that any patient who had responded to treatment, defined by a reduction in peak esophageal eosinophil counts to 5/hpf, progressed into the short-term follow-up phase, which lasted 8 weeks. The study showed a significant mean reduction in eosinophil counts (122.5 → 40.2 per hpf), but complete response was achieved in only 8.8% [21]. Clinical improvement was minimal, with most adverse events being gastrointestinal. In another RCT enrolling 66 fibrostenotic patients, aged 16-75 with fibrostenotic disease, mepolizumab improved histology but not dysphagia, evaluated with change in Eosinophilic Esophagitis Symptom Activity Index, a validated outcome metric, from baseline to month 3 [22]. Subgroup analysis suggested that a larger greater in symptoms was observed in patients with shorter duration of EoE (< 6 years since diagnosis) and fewer overall dilations (< 5), suggesting that earlier intervention in patients with less treatment experience may be more effective on symptoms.

**Benralizumab**, an anti-IL-5Rα antibody, rapidly depletes eosinophils through antibody-dependent cell-mediated cytotoxicity [23]. It is approved as an add-on maintenance therapy for patients aged 12 years of age or older with severe eosinophilic asthma [24,25]. Case reports in adults with asthma and EoE showed clinical and histologic improvement [26].

A phase 3 RCT assigned patients, aged 12 to 65 years, with symptomatic and histologically active EoE in a 1:1 ratio to receive subcutaneous benralizumab (30 mg) or placebo every 4 weeks [26]. The primary efficacy endpoints were histologic response (< 6 eosinophils per hpf) and reduction of baseline symptoms score on the Dysphagia Symptoms Questionnaire (DSQ) at week 24. The study showed a more frequent histological response in the benralizumab-treated group (87.4%) versus placebo (6.5%), though symptom scores did not differ significantly [26].

**Lirentelimab (AK002)** targets Siglec-8/CD33 on eosinophils and mast cells [27]. A phase 2/3 trial in adults and adolescents demonstrated significant histologic remission (88-92% *vs*. 11% placebo), though clinical symptom endpoints, defined by > 30% improvement in symptoms recorded with the DSQ, were not met. Of the 276 patients who completed the study, 51 were adolescents (12-17 ys). In this subgroup, a trend toward improved symptom scores over placebo was observed [28].

## 4. Other mechanisms

**Omalizumab** an anti-IgE antibody, showed inconsistent outcomes. In a prospective, randomized, double-blind, placebo-controlled trial in 30 adults, it failed to reduce eosinophils or symptoms. On the other hand, homogenates of esophageal tissues from patients with EoE showed a 45-fold increase in IgG4 compared with controls. Therefore, the authors conclude that in adults, EoE is associated with IgG4 rather than being an IgE-mediated allergic response [29]. In a previous open-label trial conducted on 24 patients that also included children (average age at enrollment was 20.4 years, ranging from 12 to 71 years of age, partial histologic remission was achieved [30]. Stratifying patients based on age (pediatric < 18 years of age, adult > 18 years of age), only one of four adult subjects demonstrated full remission. In pediatric patients, histological remission was evident in four out of 11 cases. The results of this study suggest an IgE-driven disease in a subset of children.

**Etrasimod**, an oral S1P1,4,5 receptor modulator, plays a part in regulating lymphocyte migration, reducing tissue infiltration of Th2 cells, and decreasing the expression of proinflammatory cytokines and eosinophilic inflammation [31]. Efficacy and safety have recently been studied in a three-arm, phase 2, randomized, double-blind in adults with eosinophilic esophagitis and histologically active disease [32]. The primary endpoint was percentage change from baseline in esophageal peak eosinophil count (PEC) at week 16. It significantly decreased eosinophil counts and improved symptoms over 52 weeks in patients without prior esophageal dilatation and was well tolerated. Pediatric studies are pending.

**Vedolizumab** and **natalizumab**, two integrin inhibitors, reducing leucocyte and eosinophil recruitment to the inflamed tissues and gastrointestinal mucosa, have only anecdotal evidence in EoE, primarily from adult case reports [33,34]. **Infliximab**, an anti-TNF-α antibody, a key proinflammatory cytokine in many autoimmune and chronic inflammatory diseases, showed variable symptom improvement in three adult patients without resolving eosinophilia [35].

# DISCUSSION

Among the 12 biologics, seven have been studied in pediatric populations. Dupilumab is the only fully approved therapy for children aged 1-11 years and older with active disease unresponsive to proton pump inhibitors and who weigh at least 15 kg, demonstrating consistent histologic and clinical benefit with a favorable safety profile. Furthermore, the SIGENP guideline [12] notes that, in selected cases

of severe disease or in presence of multiple atopic comorbidities, biologic therapy may be considered as an initial treatment option.

Other biologics – cendakimab and dectrekumab in adults and reslizumab, mepolizumab, benralizumab, lirentelimab and omalizumab also in children – generally reduce eosinophilic infiltration but have limited effects on symptoms, particularly dysphagia. EoE is a heterogeneous disease with different inflammatory and fibrostenotic phenotypes. Early intervention may improve outcomes for IL-5-targeting therapies. Dysphagia remains challenging to treat due to established tissue remodeling, and eosinophil-targeted therapies alone may not address all pathogenic mechanisms [36]. The disease phenotype (inflammatory vs. fibrosthenotic) and the duration of the disease significantly influence the response to biological therapies, in particular to anti-interleukin-5 (IL-5) agents. They are less effective in patients with advanced disease and fibrosthenic phenotype than in those with inflammatory phenotype and short-lived disease. Thus, early intervention may improve outcomes for IL-5-targeting therapies. Etrasimod also shows potential in early-stage disease by improving both infiltration and clinical symptoms.

Clinical and cohort studies have shown that the inflammatory phenotype is more common in young and early patients, while the fibrosthenotic phenotype, characterized by esophageal remodeling and stricture, is more frequent in adults and patients with long-term disease [13-15]. Early intervention (shorter disease duration, less fibrosis) appears associated with better histologic and symptomatic outcomes. Omalizumab may benefit pediatric patients with IgE-driven EoE, reflecting disease heterogeneity. The results of the Loizou study [30] suggest that in a subset of EoE patients, above all in pediatric age, IgE plays a role in the pathophysiology of the disease and that anti-IgE therapy with omalizumab may result in disease remission [6]. This is worth of note since in pediatric populations, IgE-associated cases of EoE are observed with greater frequency.

Evidence for vedolizumab, natalizumab, and infliximab is limited and off-label, requiring careful monitoring.

Safety data for pediatric biologics are generally favorable. Common adverse events include injection site reactions and respiratory infections. Serious adverse events are rare and not directly attributed to treatment. The common side effects of biologics used in EoE are largely overlapping with those seen in patients with asthma or atopic dermatitis treated with the same drugs. Serious reactions like anaphylaxis are uncommon in EoE, but occur more often with omalizumab, mepolizumab, and benralizumab in asthma. Some specific adverse effects (alopecia, lichen planus, herpetic infections, autoimmune conditions) have been reported in asthma registries for biologics, but have not been consistently observed in EoE studies, probably due to the lower number and duration of follow-up [37,38]. Adult FAERS database studies highlight the potential for serious events with some biologics, underscoring the need for long-term safety monitoring [8].

## Real-world considerations and cost-effectiveness

The practical use of biologic therapies in pediatric EoE is influenced by multiple real-world barriers. Accessibility for these patients depends on regulatory approval: in the United States, dupilumab is FDA-approved for children aged ≥ 1 year and ≥ 15 kg, whereas in many European countries it is approved only for those aged ≥ 12 years, and use in younger children remains off-label or limited to compassionate use programs, restricting broader access [13] . These discrepancies create substantial variability in treatment availability across regions. Reimbursement often requires prior failure of conventional therapies and insurance coverage may be limited, particularly for off-label use or in resource-constrained health systems. Cost represents a significant barrier, as biologics like dupilumab are much more expensive than first-line treatments. Cost-utility analyses suggest that, despite clear clinical and histologic benefits, dupilumab for now is only cost-effective in refractory cases, and price reductions would be necessary to justify its use as a first-line option [13].

## Limitation of current evidence and future research directions

The clinical trials examined in this study have some limitations. As set out above, in the studies examined evaluation of response to treatment, histological and endoscopic criteria was carried out variably in different studies and this limits the possibility of comparing the results of different drugs. Standardization of endpoints in future studies would improve interpretative clarity.

The sample of pediatric patients is mostly small, the clinical scores for evaluating response to drugs are not set for the pediatric population, and the inclusion and response evaluation criteria are heterogeneous and difficult to compare with each other.

Evidence remains limited on the impact of long-term biologic therapy in children, particularly concerning infection risk, immune response to vaccines, and effects on growth.

Studies involving larger pediatric populations and adequately long follow-up would be useful in the future to assess tolerability, efficacy, and long-term effects on growing subjects, as well as the development of more specific response assessment scores for children. It would also be useful to compare the efficacy and tolerability of individual agents in targeted comparative trials and to explore the cost-benefit ratio and actual implementation in real-world pediatric care.

In conclusion, dupilumab is the only biologic approved for pediatric EoE, demonstrating robust histologic and clinical efficacy. Other biologics reduce eosinophilic infiltration but often fail to improve symptoms, especially in longstanding disease with fibrosis. Early intervention and patient selection based on disease phenotype and stage may optimize outcomes. Further research is needed to define comparative efficacy, long-term safety, and optimal strategies in both pediatric and adult populations.

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None.

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## Conflicts of interest statement

The authors declare no conflicts of interest.

## Author's contributions

All authors contributed equally to the conception, literature search, data analysis, drafting, and revision of this manuscript. All authors read and approved the final version.

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