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ORIGINAL ARTICLE

Gastroenterology: Eosinophilic Gastrointestinal Disorders

Cost-utility analysis of sequential therapies for pediatric-onset eosinophilic esophagitis

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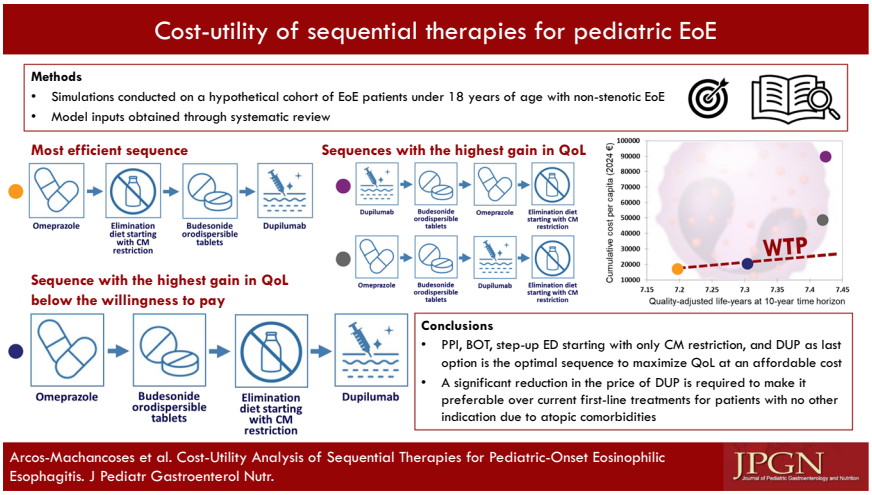
Abstract

Objectives: Topical corticosteroids, proton-pump inhibitors (PPI) and elimination diets (ED) are equally recommended as first-line therapies for pediatric eosinophilic esophagitis (EoE). Dupilumab (DUP) is usually used for refractoriness. We aim to assess the cost-utility of all potential sequential treatments for EoE.

Methods: A Markov model under the payer's perspective was used to describe induction, maintenance, and reinductions for nonresponders over 10 years. Dietary options included step-up restriction starting from two foods, and from cow's milk (CM). Topical corticosteroids viscous solutions, or budesonide orodispersible tablets (BOT) were considered. Nonresponsiveness led to esophageal dilation. Simulation parameters were defined by systematic review. We deterministically selected the most cost-effective permutation as reference. Incremental cost-utility ratios (ICUR) of each alternative sequence were compared to a willingness-to-pay (WTP) threshold of €30,000. Sequences with the highest number of quality-adjusted life-years (QALY) and the highest QALY below WTP were probabilistically explored. Sensitivity analysis was performed.

Results: PPI-ED(CM)-BOT-DUP was the most cost-effective sequence, resulting in €2373/QALY and 7.20 QALY at the time horizon. DUP-BOT-PPI-ED(CM) gave the uppermost QALY, 7.42, but any iteration was cost-effective, yielding a median ICUR of €323,774/QALY. PPI-BOT-ED(CM)-DUP, however, had a higher chance of being under the WTP (83%), showed a median ICUR of €25,156/QALY and provided 7.31 QALY. An 83% reduction of DUP price was needed to make DUP-BOT-PPI-ED(CM) and PPI-BOT-ED(CM)-DUP equally as efficient.

Conclusions: BOT and CM-starting step-up ED are present in both effective and cost-effective sequential treatments for EoE. The option PPI-BOT-ED (CM)-DUP succeeded in approaching the most effective alternative while balancing costs.



KEYWORDS

acceptability curve, cost-effectiveness, efficiency, quality of life

1 | INTRODUCTION

Eosinophilic esophagitis (EoE) is a Th-2 antigen-mediated clinicopathologic condition.[1] Its main clinical features are on account of esophageal dysfunction and eosinophil-predominant mucosal inflammation. However, pediatric-onset EoE may present with a different and less specific spectrum of symptoms than adults, and an unalike response to available treatments as well.[2]

International consensus on the management of EoE is consistent in recommending proton pump inhibitors (PPIs), dietary elimination, and topical corticosteroids (TCS) as first-line therapies.[3] Regarding the latter, budesonide orodispersible tablets (BOT), and viscous solution preparations of either budesonide, fluticasone or mometasone have shown efficacy in induction and maintenance of remission.[4–6] BOT is the first specific formulation approved in Europe for the treatment of adult EoE and has shown to be cost-effective compared to no treatment in patients nonresponsive to PPI.[7] The six-food elimination diet (ED), although favored over TCS in previous cost-utility analyses,[8] is currently considered an outdated first-line approach,[1] and there is increasing evidence in favor of a step-up ED starting with two foods[9] or even cow's milk restriction alone.[10,11] Furthermore, biological treatments are mainly considered as a way to treat severe or refractory cases.[12] A clinical guideline for the indication of dupilumab (DUP) in EoE suggests considering its use not only as a step-up therapy, but also as first-line therapy in cases of multiple comorbid atopic conditions, and when avoidance of dietary restriction or TCS is strongly preferred.[13]

EoE is known to have substantial direct costs and to be responsible for a significant burden of disease.[14] Moreover, the impact on quality of life is not only determined by disease activity, but is also directly influenced by treatment regimens.[15] Differences in age at onset, induction success rate, eventual loss of response, long-term treatment adherence, non-covered off-label pharmacologic indications, and sequence of therapies for non-first-line responders may have an impact in managing to get a cost-effective care.[16]

Given the availability of several equally recommended therapies, the gaining knowledge of optimal EDs, and the presumably future broadening of age indications for DUP and new TCS formulations, we aim

What Is Known?

Novel esophageal-specific formulations of steroids and biologic agents are expected to become available in Europe for on-label use in pediatric eosinophilic esophagitis.Healthcare providers and patients not showing any particular preference for any of the available treatments, might be interested in choosing a cost-effective permutation of options.

What Is New?

Proton-pump inhibitors, followed by orodispersible budesonide, a step-up elimination diet starting with cow's milk restriction alone, and dupilumab as last line for refractoriness is the optimal sequence of treatments to maximize health-related quality of life at an affordable cost.A significant reduction in the price of dupilumab would be required to make it preferable over current first-line treatments for patients with no other indication due to atopic comorbidities.

to conduct a cost-utility analysis of all potential sequences of treatments for pediatric EoE.

2 | METHODS

2.1 | Target population and search strategy for input data

The target population consisted of a hypothetical cohort of patients under 18 years of age with non-stenotic EoE diagnosed according to current guidelines.[3]

We carried out a systematic search for studies reporting: (1) induction response for every therapeutic option, (2) quality of life related to active EoE and after treatment response, (3) 1-year-term treatment sustained efficacy, (4) candidiasis event rate for TCS, and (5) clinical improvement after esophageal dilation. Medline and Embase medical studies directories were searched. Two authors independently reviewed the titles and abstracts returned by the systematic search and excluded articles based on duplication, original language other than English, objective, population, relevance, or design. In a second step, the Elicit database (Ought, CA, USA), an online tool based on artificial intelligence,[17] was searched for the most relevant articles published between 2004 and 2024. The search requested abstracts, key findings, and population summaries from the original research. The full text of selected articles was read to confirm eligibility, which was considered if they met the following criteria: (1) explicitly stated EoE diagnosis based on accepted clinical and histologic criteria, and (2) exclusively pediatric population (under 18 years of age) or including patients in this age group. The best input data were extracted from the primary sources, prioritizing recent clinical trials, pooled results from meta-analyses, and larger sample sizes. In trials with multiple doses for the same treatment, we chose the most favorable outcome. Alternatively, adult studies were considered when pediatric results were not possible to retrieve. Disagreements at each stage were resolved by consensus after discussion or consultation with a third investigator. This process was carried out from February to July 2024. A schematic of the search instructions, keywords, limits, and set operators used in each electronic database, as well as the prompts used in Elicit, are provided in Supporting Information: Digital Content S1.

2.2 | Model structure and comparative treatments

All possible treatment permutations were compared using a Markov chain model. Patients who did not respond to the induction regimen, as well as those who justifiably discontinued treatment, crossed over to the next therapeutic line. Complete discontinuation after four lines resulted in esophageal dilation. The model did not include a mortality related exit option from any compartment (Figure 1).

Generic omeprazole was the sole PPI considered since the clinical importance of the subtle published differences in terms of effectivity and safety among the several alternative drugs has yet to be confirmed. Thus, the selection of a preferred PPI is recommended to be based on the acquisition cost of the drug.[18] Swallowed TCS are a mainstay of anti-inflammatory therapy in the treatment of active EoE. Budesonide viscous solution (BVS) and BOT show good outcomes regarding the efficacy of inducing and maintaining histologic, symptomatic and endoscopic remission.[19] In addition, swallowed fluticasone performs similarly to BVS when indicated for EoE.[20] Mometasone has also shown promising results in a limited number of small-scale trials.[4,5] Those four corticosteroids were taken into account. Two different stepwise ED approaches were considered: the classic 2-4-6-food ED and cow's milk restriction as a first step, followed by 4-food and 6-food elimination for those who did not respond to the previous steps. DUP was permitted even as a first-line option for exploratory reasons. Combination of treatment modalities for cases of incomplete response was not explored. Finally, as noted above, esophageal dilation was offered to patients who did not respond to standard treatment to better reflect the reality of the 5%–22% of children who ultimately require this procedure during follow-up.[21,22]

2.3 | Efficacy and safety data

Histologically, ≥15 eosinophils in a high-power field (Eo/HPF) are required to define active disease. The ultimate goal of EoE treatment is to achieve not only clinical and endoscopic remission, but also histologic improvement, as this better prevents esophageal fibrosis and is associated with a gain in quality of life.[23,24] For this reason, medical treatment efficacy

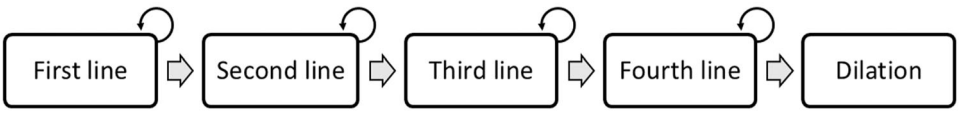


FIGURE 1 Markov model general structure for all sequential therapies.

data were retrieved from studies providing success rates based on the <15 Eo/HPF criterion. When the proportion of patients achieving remission at the end of an induction time span or a 1-year-term sustained efficacy was not explicitly stated, we manually calculated it per protocol if enough information was provided narratively, or presented in tables or in supplemental materials. Dropping out due to poor adherence was considered a treatment failure for the dietary elimination regimens. If no direct long-term efficacy was informed, any treatment persistence reported in the primary studies was assumed to have ended due to loss of response, adverse events or patient preference, unless otherwise stated.[25] Consequently, these data were used alternatively to define crossover between lines of treatment in cases with previous successful induction. Published treatment sustained efficacy was extrapolated over the entire simulated time period. Efficacy in second and subsequent lines was not regarded as different than in naïve patients. Only esophageal dilation efficacy was defined from a clinical point of view. Esophageal candidiasis risk was accounted for those patients under remission with any of the TCS. No other adverse events were considered.

2.4 | Utilities

Children with EoE, specially under dietary restriction and with active disease, experience a negative impact on health-related quality of life (HRQoL) as measured by either the child's self-reported PedsQL™ EoE Module Total Scale Score or the Symptoms Total Scale Score.[26,27] For this reason, the maximum utility value was considered to be that of a patient in histological remission under any drug treatment. It was set at 0.87 as this is the ratio between the PedsQL™ 4.0 Generic Core Scales of children with EoE with reference to a matched historical healthy children sample.[26] Utilities of the different health and treatment states among children with EoE were assumed to keep the same proportional relation as that of the PedsQL™ EoE between the same states. Quality-adjusted life-years (QALYs) were calculated by applying those utilities as a correction factor. Dilation non-responders were subjected to a 70% quality of life penalty.[21] No disutility values were set for esophageal candidiasis because it usually has little or no clinical impact, is easily treated, and may even be considered a potential marker of good medication adherence and histologic response.[28] No HRQoL correction factor was applied for change of treatment line. Key model efficacy and utility inputs, and supporting bibliographical references,[29–38] are presented in Supporting Information: Digital Content 2.

2.5 | Cost data

All analyses were performed from the Spanish Health System perspective. Only direct medical costs in relation to drug retail prices and public prices for healthcare services were taken into account.[39] Costs for pharmacological agents were assigned by drug dosing for an age-stratified population.[40] Induction costs for PPIs and TCS were twice the maintenance costs. Patients responding to ED were offered a progressive food reintroduction and, accordingly, costs related to repeated endoscopies were accounted. Dietitian appointment costs were also considered in patients undergoing ED. Second and subsequent esophageal dilations were charged with hospital admissions due to food impaction. For the eventuality of esophageal candidiasis, extra costs (systemic antifungal therapy and an additional endoscopic evaluation) were imputed. Prices were expressed in 2024 euros. Key model cost inputs are presented in Supporting Information: Digital Content 3.

2.6 | Discount rate

An annual discount rate of 3% was applied to both costs and health outcomes. Discount rates ranging from 0% to 5% were evaluated in the sensitivity analysis.

2.7 | Time horizon and model implementation

The analysis was conducted over a 10-year time horizon to capture the medium-term effectiveness of the sequential interventions. Each cycle of the simulation represented a 12-week time frame, analogous to a regular induction period.[41] Probabilities obtained from primary information sources were transformed into transfer rates per cycle between model compartments.

Simultaneous variations of all key parameters were performed by means of a second order Monte Carlo simulation. A total of 5000 iterations were obtained using the appropriate distributions and limits as per convention. Further details on the functions that control the probabilistic model can be found in Supporting Information: Digital Content 4. Simulations were conducted using an Excel spreadsheet (version 2016, Microsoft, WA, USA) and the XLRisk plugin.[42]

2.8 | Incremental cost-utility analysis

The most cost-effective treatment permutation was deterministically selected as the reference. The resulting incremental cost-utility ratios (ICURs, calculated by

TABLE 1 Cost-utility outcomes of the most relevant treatment sequences at 10 years.

Selected treatment permutations	Sequence	Cumulative cost per responder	Cumulative cost per capita	Quality-adjusted life-years	Cost-utility in €/QALY	Median ICUR (IQR) in €/QALY
Lowest cumulative cost per responder and per capita	**ED(CM) → PPI → BOT → DUP**	€19,995.99	€17, 048.92	7.1421	2387.11	306.46 (13.80–629.13)
Lowest cost-utility	**PPI → ED(CM) → BOT → DUP**	€20,109.03	€17,077.08	7.1970	2372.80	N/A
Highest gain of QoL below the WTP	**PPI → BOT → ED(CM) → DUP**	€23,687.56	€19,861.54	7.3073	2718.05	24,155.56 (21,320.23–28,049.53)
2nd highest gain of QoL below the WTP	**PPI → BVS → ED(CM) → DUP**	€22,658.46	€18,673.33	7.2578	2572.85	24,717.58 (15,292.81–38,640.78)
Highest gain of QALY	**DUP → BOT → PPI → ED(CM)**	€108,550.93	€91,242.70	7.4244	12,289.50	323,774.33 (282,418.31–378,862.14)
2nd highest gain of QALY	**PPI → BOT → DUP → ED(CM)**	€58,573.49	€49,180.15	7.4237	6624.74	137,840.86 (122,785.34–156,125.81)

Abbreviations: BOT, budesonide orodispersible tablets; BVS, budesonide viscous solution; DUP, dupilumab; ED(CM), step-up elimination diet starting from cow's milk restriction; ICUR, incremental cost-utility ratio; IQR, Interquartile range; N/A, not applicable as this is the reference sequence; PPI, proton pomp inhibitors; QALY, quality-adjusted life-year; QoL, quality of life; WTP, willingness to pay.

dividing the difference in costs by the difference in health effects between two interventions) of each alternative sequence were compared to a willingness-to-pay (WTP) threshold of €30,000/QALY, as recommended locally.[43] The two sequences with the highest number of QALYs and the two sequences with the highest gain in incremental QALYs below the WTP were then probabilistically examined. Incremental cumulative costs per responder were also calculated. Finally, a one-way sensitivity analysis was performed.

3 | RESULTS

Deterministic cost-utility data and probabilistic ICURs of the most relevant treatment permutations are shown in Table 1. Among the 144 possible treatment sequences, the one with the lowest cumulative cost per responder and the lowest cumulative cost per patient was the stepwise ED starting with only cow's milk restriction, ED(CM), followed by PPI-BOT-DUP. PPI-ED(CM)-BOT-DUP was the most cost-effective sequence, resulting in €2373/QALY and 7.20 QALY at the end of the time horizon, and was therefore selected as the reference. In comparison, the permutation with the highest gain in QALYs below the WTP was PPI-BOT-ED(CM)-DUP, yielding 7.31 absolute QALYs with a median ICUR of €24,156/QALY. These three sequences together formed the efficient frontier. PPI-BVS-ED(CM)-DUP was close to this frontier but offered decremental QALYs compared to PPI-BOT-ED(CM)-DUP with a cost reduction of €1188 per patient at 10 years, higher ICUR, and lower probability of being below the WTP (52% vs. 83%). In addition, ED(CM)-PPI-BOT-DUP was not more cost-effective than PPI-ED(CM)-BOT-DUP in any of the simulated iterations (Figure 2). An increase in the WTP of up to €153,881/QALY would be required to identify the next sequence of treatments that would outperform PPI-BOT-ED(CM)-DUP in incremental QALYs below the new WTP: PPI-BOT-DUP-ED(CM). In fact, this was the second permutation in absolute gain of QALYs (7.42 at a cost of €6625/QALY), and the first if sequences with DUP as first-line treatment were excluded. DUP-BOT-PPI-ED (CM) yielded the uppermost QALYs (less than one healthy day over the previous sequence) at €12,290/QALY. In none of the simulated iterations were either DUP-BOT-PPI-ED(CM) or PPI-BOT-DUP-ED (CM) cost-effective, even when considering WTP up to €80,322/QALY (Figure 3). Between 7.8% and 15.0% of children required esophageal dilation at the end of the time horizon.

Sensitivity analysis showed that an 83% and 71% reduction in the price of DUP was needed to make DUP-BOT-PPI-ED(CM) and PPI-BOT-DUP-ED(CM), respectively, as efficient as PPI-BOT-ED(CM)-DUP.

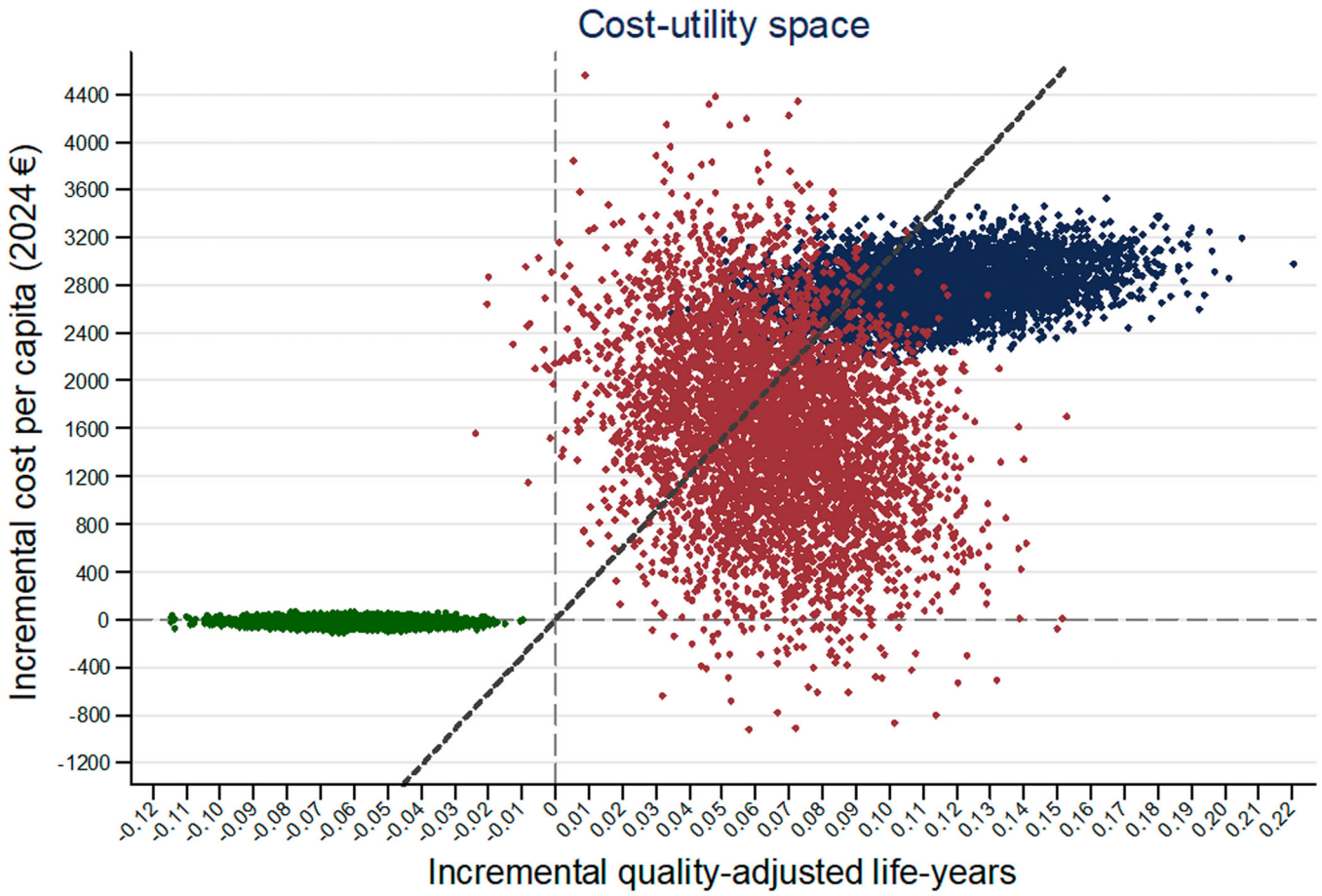


FIGURE 2 Incremental costs and quality-adjusted life-years in 5000 probabilistic analysis iterations comparing the most cost-effective sequential treatment for pediatric EoE, PPI-ED(CM)-BOT-DUP, with: 1) blue dots: PPI-BOT-ED(CM)-DUP (permutation with the highest gain of QALYs below the WTP), 2) red dots: PPI-BVS-ED(CM)-DUP (permutation with the second highest gain of QALYs below the WTP), and (3) green dots: ED(CM)-PPI-BOT-DUP (permutation with the lowest cumulative cost per responder and cost per capita). The bold dashed diagonal line represents the WTP at €30,000. BOT, budesonide orodispersible tablets; BVS, budesonide viscous solution; DUP, dupilumab; ED(CM), step-up elimination diet starting from cow's milk restriction; EoE, eosinophilic esophagitis; PPI, proton pomp inhibitors; QALY, quality-adjusted life-year; WTP, willingness to pay.

No other treatment permutation turned out to be selectable despite modifying either other costs or the discount rate within the range considered acceptable for probabilistic analysis. When considering rising prices for diagnostic endoscopies, the ICURs of PPI-BVS-ED(CM)-DUP and PPI-BOT-DUP-ED(CM) gradually approached one another until reaching a point of parity at values close to €1,000 per procedure (Supporting Information: Digital Content 5).

4 | DISCUSSION

Current treatment algorithms for pediatric EoE accept several treatment modalities to be chosen after discussion with patients and their caregivers.[3] Some previous cost-effective analyses have been carried out in adult population base cases. One study compared TCS with the 6-food ED as first-line therapy and concluded that both treatments were similarly effective, but that dietary elimination was more cost-effective given its lower cost.[8] More recently, BOT has also proven to be cost-effective for both induction and maintenance of clinicohistological remission after failure of PPIs.[7] However, those experiences do not address the question of what would be the optimal sequence of treatments for the pediatric population, taking into account all currently available options, including off-label indications.

The results of this study demonstrate that new formulation of orodispersible budesonide and CM-starting step-up ED are consistently present in both effective and cost-effective sequential treatments for pediatric EoE. Similarly to what has already been published, first and second line dietary elimination led to the less expensive and more efficient treatment permutation, respectively. In particular, the best dietary option has turned out to be a 1-4-6 step-up strategy starting from CM elimination. Step-down diet has not even been

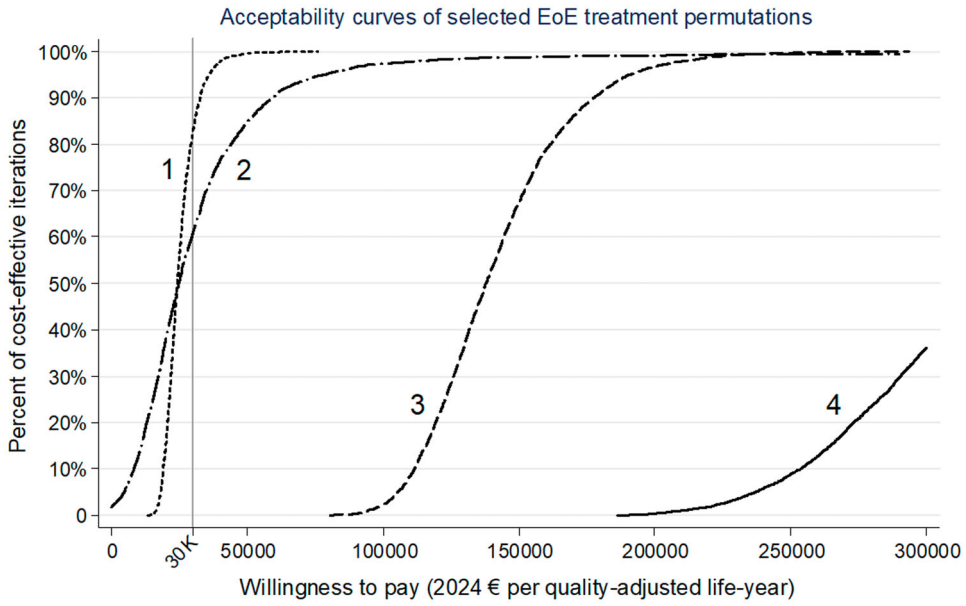


FIGURE 3 Cost-effectiveness acceptability curves comparing the most cost-effective sequential treatment for pediatric EoE, PPI-ED(CM)-BOT-DUP, with: 1) short dashes: PPI-BOT-ED(CM)-DUP (permutation with the highest gain of QALYs below a €30,000 WTP), 2) long dashes and dots: PPI-BVS-ED(CM)-DUP (permutation with the second highest gain of QALYs below a €30,000 WTP), 3) dashes: PPI-BOT-DUP-ED (CM) (permutation with the second highest gain of QALYs), and 4) solid line: DUP-BOT-PPI-ED(CM) (permutation with the highest gain of QALYs). BOT, budesonide orodispersible tablets; BVS, budesonide viscous solution; DUP, dupilumab; ED(CM), step-up elimination diet starting from cow's milk restriction; EoE, eosinophilic esophagitis; PPI, proton pomp inhibitors; QALY, quality-adjusted life-year; WTP, willingness to pay.

considered as it leads to more endoscopies, poor patient compliance and an increase in lost school and workdays.[1,3] However, by using BOT after failure to PPIs we achieved the optimal treatment permutation below the WTP threshold. Interestingly, switching budesonide to its presentation in viscous solution did not have a significant reduction in costs and, moreover, less QALYs were obtained. Although a relatively low willingness-to-pay threshold was used compared to studies in other developed countries, even raising it to a reasonably higher threshold, a different sequence would not have been selected as the optimal. Indeed, PPI-BOT-ED(CM)-DUP maximized incremental QALYs at an affordable cost. Additionally, promoting DUP as a first-line treatment or even as a first alternative following the failure of other medications, despite the favorable outcomes observed, would not be cost-effective unless there was a substantial reduction in price.

We have performed, to our knowledge, the first cost-utility analysis of sequential therapies for pediatric EoE and also the first to evaluate the role of the novel orodispersible formulation of budesonide, DUP, and a step-up ED starting with CM restriction alone in this age group. If possible, a measurement of patient-reported HRQoL has been used to estimate QALYs for every health state. This resulted in penalization of patients with active disease, undergoing dietary elimination, and not clinically responding to esophageal dilation to represent their lower reported HRQoL.[26,44] Because children on the CM-only diet show better HRQoL than that described in the multifood avoidance studies, they were considered separately.[10] In addition to these efforts to better reflect pediatric specificities in the model, another strength of this study is that the efficacy inputs were obtained through a systematic review, although the paucity of data for the target population did not allow the use of pooled results by meta-analysis.

Nevertheless, there are some limitations to be pointed out, all of them in relation to the oversimplification to which the modeling forces us to. First, to ensure comparability of the efficacy of the various treatments, we have used a purely histological definition of treatment effectiveness. Specifically, remission was accepted to be <15 Eo/HPF, as proposed by COREOS consensus and as widely used in therapeutic and observational studies.[45] However, a more restrictive criterion at <6 Eo/HPF, or improvement measured by clinical questionnaires, could also have been valid success definitions. Histologic remission is, undoubtedly, a goal in the management of EoE, but there is well known discrepancy between clinical and histologic response, and the required need for step-up or treatment change needs to be decided on individual basis. Furthermore, the option of combing therapies, especially PPI with TCS or ED, has not been acknowledged due to lack of data despite being useful in selected cases.[3] It is also to be noted that the efficacy of treatment in second and subsequent lines may differ from that in naïve patients. If failure to previous treatments predicted lesser response rates for the following

therapeutic attempts, it would be expected that sequences starting from BOT and DUP would have been favored. Finally, the flow of patients towards the esophageal dilation state has not been designed in a fully realistic way due to lack of understanding of the real reasons why some patients are more prone to develop a fibrostenotic phenotype. The inclusion of this option for cases of refractoriness to treatment was done in recognition of the fact that duration of non-controlled disease is an important risk factor for developing esophageal strictures.[46] Even so, the proportion of simulated patients who underwent esophageal dilation was similar to that described in large series.[21,22,47]

5 | CONCLUSION

Given the aforementioned considerations, in situations where the patient shows no particular preference for any of the available treatment options, the sequence PPI-BOT-ED(CM)-DUP might have a long-term positive effect in balancing costs while approaching the most effective alternative.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

ETHICS STATEMENT
The study did not require an ethics committee approval since it was designed as an economic evaluation not involving human participants and not using data obtained as part of regular patient care.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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