Management of eosinophilic otitis media in the era of biological therapy: systematic review and proportion meta-analysis

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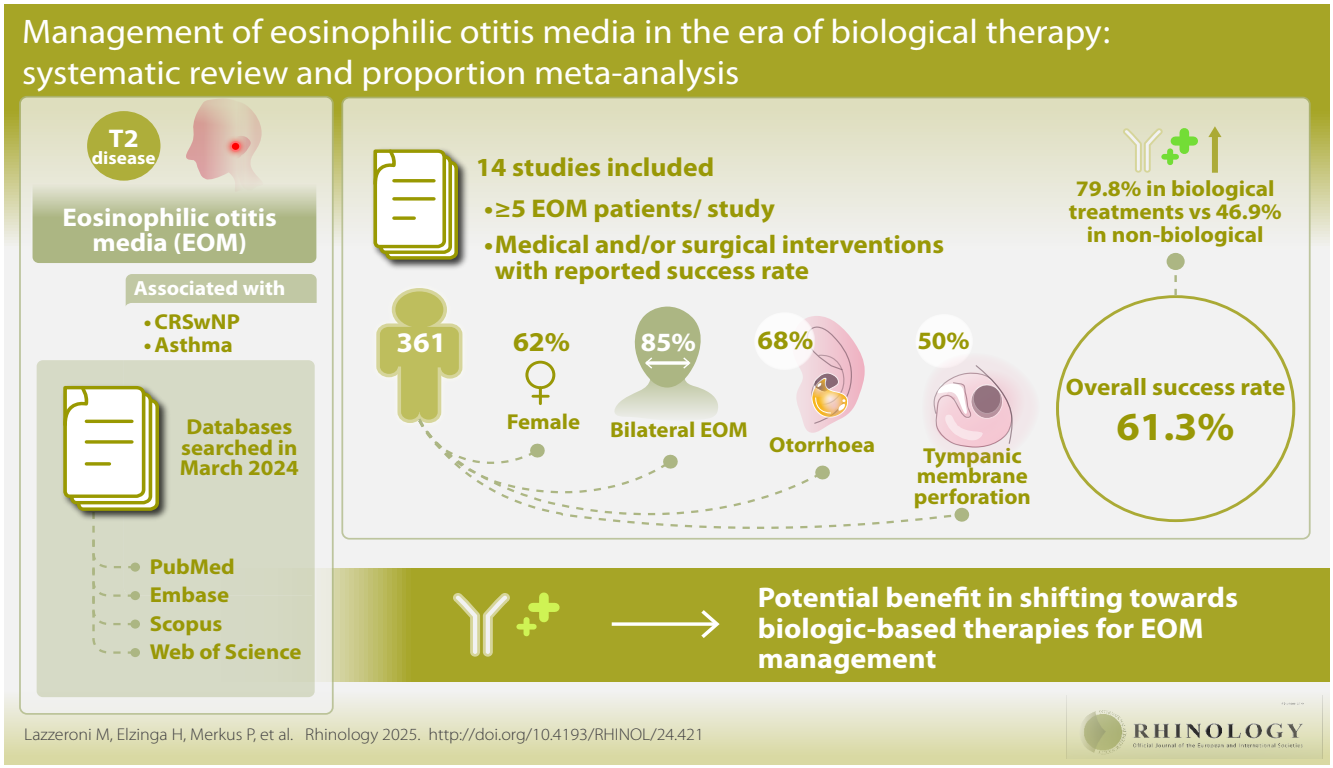

Abstract

Background: Eosinophilic otitis media (EOM) is a recently recognised type 2 inflammatory disease, strongly associated with asthma and chronic rhinosinusitis with nasal polyps. Known as a difficult-to-treat condition, EOM is often refractory to traditional therapies for (chronic) otitis media. This review aims to assess the success rates of the different interventions for patients with EOM including newly available biological therapy.

Methodology: In March 2024 we systematically searched PubMed, Embase, Scopus and Web of Science for studies on >5 EOM patients undergoing any medical or surgical intervention with a reported success rate. Proportion meta-analysis on a random effect model was used to synthesize results effectively. Risk of bias was assessed through the Risk Of Bias In Non randomized Studies of Interventions tool (ROBINS-I).

Results: From 1103 potential articles, 14 studies with 361 patients were included. 62% were females and 85% had bilateral presentation. Otorrhoea was present in 68% of patients, tympanic membrane perforation in 50%. The overall success rate was 61.3%. However, interventions comprising biological agents targeting type 2 inflammatory cascade showed higher success rates compared to non-biological treatments.

Conclusions: A shift towards biologic-based therapies could be beneficial for managing the challenging condition EOM.

Key words: antibodies, monoclonal, eosinophils, meta-analysis, otitis media, systematic review

Introduction

Eosinophilic otitis media (EOM) is a rare form of otitis media that has only recently been recognized [1,2], with diagnostic criteria established by Iino et al. in 2011 [2]. EOM is a condition driven by type 2 inflammation, that has a strong association with asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) [3]. Clinically the otoscopic presentation is similar to either an otitis media with effusion (OME) or as a chronic suppurative otitis media (CSOM). Presentation can also be with granulations and/or polyps protruding into the external auditory canal in more severe cases [3,4]. A distinctive feature of EOM is the presence of highly viscous eosinophil-rich secretions in the middle ear [2,5,6]. The prevalence of EOM in Western societies is still a matter of debate. It has been reported in a tertiary otorhinolaryngology practice that up to 25% of CRSwNP patients have otitis media with effusion [7]. This figure might be influenced by selection bias, and data from large patient cohorts is lacking. Still, it is very likely that rhinologists will encounter EOM cases regularly in their practice, although they might remain unrecognized. Therefore, a sound understanding of the therapeutic challenges that EOM presents is crucial to provide optimal care for patients with overlapping type 2 inflammatory conditions.

The management of EOM has long been subject of debate due to its reputation as a difficult-to-treat condition, resistant to most common (chronic) otitis media treatments [8]. Over the years, a broad range of interventions has been proposed [2]. These comprise the use of corticosteroids (local, systemic, and/or intratympanic), antibiotics, myringotomy, placement of a ventilation tube, and myringoplasty [9]. More recently, the deepened understanding of type 2 inflammation and its related diseases resulting in the advent of biological therapies has paved the way for a significant revolution in the management strategies for asthma, CRSwNP and atopic dermatitis [10-12]. This has led to a growing interest in the possible application of biological agents for EOM. The first reports have shown promising results [9,10,13,14]. Thus far, only one systematic review [15] has tried to analyse the outcomes of the different interventions for EOM in an evidence based perspective. However, it included studies published only until 2020 and therefore does not consider the most recent publications on treatment of EOM by means of biological agents targeting the type 2 inflammatory cascade. Furthermore, no meta-analysis has yet been conducted to provide a quantitative synthesis of the individual studies' outcomes. This paper addresses these gaps by providing an up-to-date systematic review of the literature and a meta-analysis. This review aims to assess the success rates of the different interventions for patients with EOM including newly available biological therapy.

Materials and methods

The present systematic review and meta-analysis was not registered, follows the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) 2020 statement(16) and is in accordance with the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [17].

Eligibility criteria

We included studies that met the following eligibility criteria: 1) Randomised or observational studies, 2) published from 2004 until the search date, 3) on a population of a minimum of 5 patients with EOM, 4) receiving any medical and/or surgical therapy. We excluded studies i) that did not report any clinical outcome, or ii) that did not provide the overall number of patients with clinical improvement from their cohorts, as success rates could not be retrieved from this.
We considered studies to be clinically relevant within a timeframe of 20 years, and the cut-off of 5 patients was chosen to mitigate publication bias.

Search strategy

In March 2024 PubMed, Embase, Scopus and Web of Science were consulted with the following search strategy: ("eosinophilic otitis media") OR (eosinophilic AND otitis) OR (eosinophilic AND "otitis media"). The reference list of the previous systematic review [15] was also checked for additional records. No language restrictions were applied to be as complete as possible. Two authors (ML and HE) independently performed the abstract and full text screening of the retrieved articles. Disagreements in any phase were resolved through discussion, with a third author (SR) acting as an arbiter if necessary. If there was an overlap amongst studies populations, only the largest cohort was included in the present study.

Data extraction

Two reviewers (ML and HE) independently extracted relevant data from the selected articles: name of the first author and country of origin, year of publication, study design, sample size, mean age and sex of the enrolled patients, time of follow up, otologic symptoms, otoscopic findings, comorbidities (bronchial asthma, CRSwNP), treatment and success rates. Given the known wide variety in reported outcomes between individual studies on this rare disease, the current meta-analysis was based on the reported success rate of any intervention. The success rate was broadly defined as any clinical improvement per patient and could be an improvement in disease-specific patient-reported outcomes or clinically observed improvement such as seen with otoscopy. The extracted data were then compared between the two authors and disagreements were resolved through discussion, with a third author (SR) acting as an arbiter if needed.
Some studies compared different interventions, either with or without a group receiving biological therapies directed against type 2 inflammation. For reasons of completeness, these groups

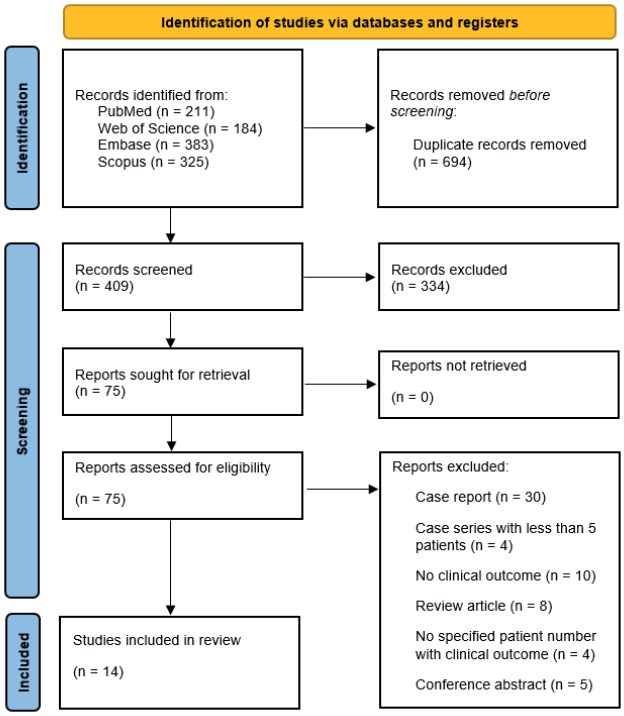

Figure 1. PRISMA flowchart of the study selection process for the present systematic review and meta-analysis.

were reported separately. Some studies reported outcomes as number of ears. However, since most reports were on numbers of patients, we converted these to number of patients to present the success rate homogeneously between studies. Conversion was done through proportions:

improved patients = (#improved ears) / (#total ears) x #total patients

Data synthesis

Demographic characteristics of patients with EOM were summarized descriptively as valid percentages. The primary goal for the present systematic review and meta-analysis was to assess the success rates of different interventions for EOM. Proportion meta-analysis was chosen. Proportion meta-analysis is usually employed to synthesize evidence from single-group studies, for example to estimate an overall disease prevalence (proportion) from studies between different populations [18]. Its methodology can also be applied to other proportions, such as in this case: success rates between studies/interventions considering the lack of comparative studies.

Study designs and interventions were deemed to be highly variable, therefore a random effect model was chosen. Results are presented on forest plots as percentages with 95% confidence intervals.

Subgroup analysis was performed to compare interventions with monoclonal antibodies targeting the type 2 inflammatory cascade to all other, non-biological agents. Heterogeneity was assessed through Cochran Q test and I^2 statistics; $p<0.10$ and $I^2>25\%$ were considered significant for heterogeneity. R statistical software (version 4.4.0, 2024-04-24) was used for the meta-analytical approach.

Quality assessment

The risk of bias assessment of the included studies was performed with the Risk Of Bias In Non randomized Studies of Interventions (ROBINS-I) tool [19] in case of observational, cohort studies or case series. Lastly, quality of evidence was evaluated in accordance with the Grading of Recommendations Assessment Development and Evaluation (GRADE) handbook [20]. Two authors (ML and HE) independently performed the quality assessment, resolving conflicts through discussion and involving a third author (SR) when necessary.

Results

Study selection

Figure 1 shows the PRISMA flowchart for the study selection process. Our systematic search yielded 1103 potential articles. No additional records were retrieved from the reference list of the previous systematic review [15]. After removal of duplicate records and abstract screening, 75 remained and passed onto full text assessment. Ultimately, we included 14 [9,13,14,21-31] studies with a total of 361 patients. All the included records were observational, non-randomized studies.

Baseline characteristics

62% of the patients were females, 38% male. 85% had bilateral presentation. Detailed baseline characteristics are presented in Table 1. Amongst studies that reported on otoscopic examination, otorrhea was present in 68% of the patients, effusion in 57%, tympanic membrane perforation in 50%, aural polyps or granulations in 33%. Type 2 comorbidities were closely associated with EOM, asthma being present in 96% of the patients and CRSwNP in 84%. The overall follow-up duration amongst studies ranged from 6-57 months. The duration of biologic therapy ranged from 6 to 17.1 months.

Treatment

The included studies presented a broad range of (combinations of) interventions and outcome measures for the treatment of EOM (Table 2). Local steroid eardrops were administered to 72 patients, systemic steroids to 75, intratympanic injections of triamcinolone acetate to 139. Surgery was performed on 42 patients and, lastly, 89 patients received different types of monoclonal antibodies targeting type 2 inflammation. As shown in Figure 2, the overall success rate was 61.7 % (95% CI 44.5-76.9 I^2=87%). Patients treated with biological agents showed

Table 1. Baseline characteristics of included studies.

Study	Country	Group $	Type of biological	No. of patients	Bilateral cases	Sex (F/M)	Age (years; mean ± SD)	TM perforation	Aural polyps/ granulation	Effusion	Otorrhea	CRSwNP	Asthma	Follow up (months)
Nakashima 2023[21]	Japan	Biologics Non-biologics	Dupi	10 8	4/10 8/8	7/3 8/0	53 ± 12 56 ± 7	6/10		3/10	6/10	10/10 8/8	10/10 8/8	
Kikuchi 2023[9]	Japan	Biologics Non-biologics	Oma, Mepo, Benra, Dupi	7 11	2/7 6/11	4/3 9/2	69 ± 8 60 ± 8			3/7 3/11		3/7 7/11	7/7 10/11	
Ryder 2023[14]	USA	Biologics Non-biologics	Dupi	19 43		12/7 19/24	64 ± 19 57 ± 17	4/7 8/11				19/19 43/43	19/19 43/43	
Bartier 2023[22]	France	Biologics	Oma, Mepo, Benra, Dupi	17		8/9	52 ± 13	1/17	2/17			17/17	17/17	
De Corso 2022[13]	Italy	Biologics	Dupi, Mepo, Benra, Oma	8	1/8	5/3	54 ± 18	3/8		5/8	3/8	8/8	8/8	6
Esu 2021[23]	Japan	Non-biologics Non-biologics		12 43	12/12 43/43	8/4 23/20	64 ± 10 57 ± 11					8/12 32/43	12/12 32/43	24
Breslin 2021[24]	USA	Biologics	Mepo, Benra	9		7/2	56 ± 13			7/9		8/9	9/9	
Iino 2019[25]	Japan	Biologics Non-biologics	Mepo	9 13		5/4 9/4	66 ± 9 57 ± 13		3/9	7/9 13/13		6/9 9/13	9/9 13/13	
Fukuda 2019[26]	Japan	Non-biologics*	Oma, Mepo	11	11/11	11/0	49 ± 10			11/11		8/11	11/11	
Esu 2018[27]	Japan	Non-biologics		68	68/68	38/30	56							22
Saliba 2018[28]	Canada	Non-biologics		10	4/10	5/5	48 ± 17	10/10	7/10	0/10	10/10	8/10	10/10	
Neff 2016[29]	USA	Non-biologics		8						8/8		8/8	8/8	21
Iino 2014[30]	Japan	Biologics Non-biologics	Oma	9 8		6/3 5/3	56 ± 12 57 ± 14					6/9 6/8	9/9 8/8	12
Iino 2006[31]	Japan	Non-biologics Non-biologics		24 14	19/24 13/14	18/6 11/3	58 ± 11 46 ± 11	13+/24 5+/14		10+/24 6+/14		21/24 12/14	24/24 14/14	27 40
Total				361	191/226	218/135		50/101	12/36	76/134	19/28	247/293	281/293	
Valid percentage					85%	62%/ 38%		50%	33%	57%	68%	84%	96%	

Each cohort of patients with EOM of the included articles is described separately. + Some studies reported outcomes as number of ears. We converted these to number of patients to present the success rate homogeneously between studies. Conversion was done through proportions: #improved patients = (#improved ears) / (#total ears) x #total patients. CRSwNP = Chronic rhinosinusitis with nasal polyps; TM = Tympanic membrane; F = Female; M = Male; SD = Standard deviation; Dupi = dupilumab; Oma = omalizumab; Benra = benralizumab; Mepo = mepolizumab. If a cell is empty, then its value is not reported in the published article. $ Some studies compared different interventions, either with or without a biological group. For reasons of completeness, these groups are mentioned separately, even it means listing two non-biological intervention groups per study. * Fukuda included 1 case treated with biological therapy. The results from this case were not reported separately, however, and we decided to keep the full group as 'non-biologics'.

success rates of 79.8% (95% CI 63.3-92.9 I^2=61%), significantly higher than the ones of the non-biologics group (p=0.02, test for subgroup differences). Non-biologic therapies had worse success rates and greater heterogeneity, with a pooled effect size of 46.9% (95% CI 25.0-69.3 I^2=90%; Figure 2).

Quality assessment

According to the ROBINS-I tool the overall risk of bias of the 14 articles was "moderate" for 8 articles [13,14,23-25,27,29,31], "serious" for 3 [9,22,30] and "critical" for 3 [21,26,28] (Figure 3). Using the GRADE handbook [20], the quality of evidence for all the included 14 articles was rated as "very low" (supplementary Table S1).

Table 2. Treatment and outcomes of included studies.

Study	Group [$]	Number of patients	Steroid eardrops	Systemic corticosteroid	PEGylated Interferon	Intratympanic corticosteroids	Myringotomy	Myringoplasty	Biological agents	Successful treatment	Outcome definition
Nakashima 2023[21]	Biologics Non-biologics	10 8		10/10 8/8					10/10	10/10 [+] 2/8	EOM severity score, prednisolone intake reduction
Kikuchi 2023[9]	Biologics Non-biologics	7 11		2/7 4/11				7/7 11/11	7/7	6/7 [+] 5/11 [+]	No relapse of MEE or otorrhea
Ryder 2023[14]	Biologics Non-biologics	19 43	 43/43						19/19	13/19 6/43	Improvement in otologic examination and tympanometry
Bartier 2023[22]	Biologics	17		2/17					17/17	8/17	EOM severity score
De Corso 2022[13]	Biologics	8	5/8	2/12 8/43					8/8	6/8 [+]	Complete resolution in Otitis Severity Score Index
Esu 2021[23]	Non-biologics Non-biologics	12 43						12/12		12/12 [+]	EOM severity score
Breslin 2021[24]	Biologics	9							9/9	7/9	Resolution of middle ear effusion after intervention
Iino 2019[25]	Biologics Non-biologics	9 13		3/9 8/13		9/9 9/13			9/9	9/9	EOM severity score
Fukuda 2019[26]	Non-biologics*	11		1/11		6/11	5/11[^]		1/11	4/11 [+]	Improvement in otologic examination
Esu 2018[27]	Non-biologics	68				68/68	7/68			54/68 [+]	Improvement in otologic examination
Saliba 2018[28]	Non-biologics	10	10/10							4/10 [+]	Improvement in otologic examination
Neff 2016[29]	Non-biologics	8			8/8					4/8	Improvement in EOM grade
Iino 2014[30]	Biologics	9		8/9		9/9			9/9	6/9	Reduction in MEE and need for instillation of IT steroid
	Non-biologics	8		8/8		8/8				0/8	Improvement in symptoms and otologic examination
Iino 2006[31]	Non-biologics Non-biologics	24 14	 14/14	6/24 5/14		24/24				20/24 [+] 4/14 [+]	Improvement in otologic examination
Total		361	72	75	8	139	12	30	89	180/305	

Each cohort of patients of the studies is described separately. Numbers of patients within the cohorts are provided per treatment option. [$] Some studies compared different interventions, either with or without a biological group. For reasons of completeness, these groups are mentioned separately, even it means listing two non-biological intervention groups per study. [+] Some studies reported outcomes as number of ears. We converted these into number of patients to present the success rates homogeneously. Conversion was done through proportions #improved patients = (#improved ears) / (#total ears) x #total patients. IT = Intratympanic; EOM = eosinophilic otitis media; MEE = middle ear effusion. * Fukuda included 1 case treated with biological therapy. The results from this case were not reported separately, however, and we decided to keep the full group as 'non-biologics'. [^] With or without tube placement.

Discussion

In the present systematic review and meta-analysis of 14 studies and 361 patients we have investigated the demographic characteristics of patients with EOM, their comorbidities, treatments and outcomes. Our main result was the finding of a statistically significant difference between success rates of treatments for EOM favouring biological agents targeting the type 2 inflammatory cascade over conventional treatments.

Traditionally, EOM has been considered a difficult-to-treat condition, to the extent of which Iino et al. [2] have included resistance to conventional treatments as an item in their diagnostic criteria. Amongst the broad range of treatment modalities that have been proposed for EOM, authors have reported on the efficacy of local or systemic administration of corticosteroids to reduce inflammation in the middle ear [28]. Surgical options have proved to have only a marginal role in the management of this condition, because of high recurrence rates [15] and myringoplasty is generally contraindicated in presence of active otorrhoea [9]. Other explored surgical procedures were resection of granulation tissue and ventilation tube placement [9,15,23,27]. Notably, according to Esu et al. [27] surgery should be considered only for refractory or severe cases.

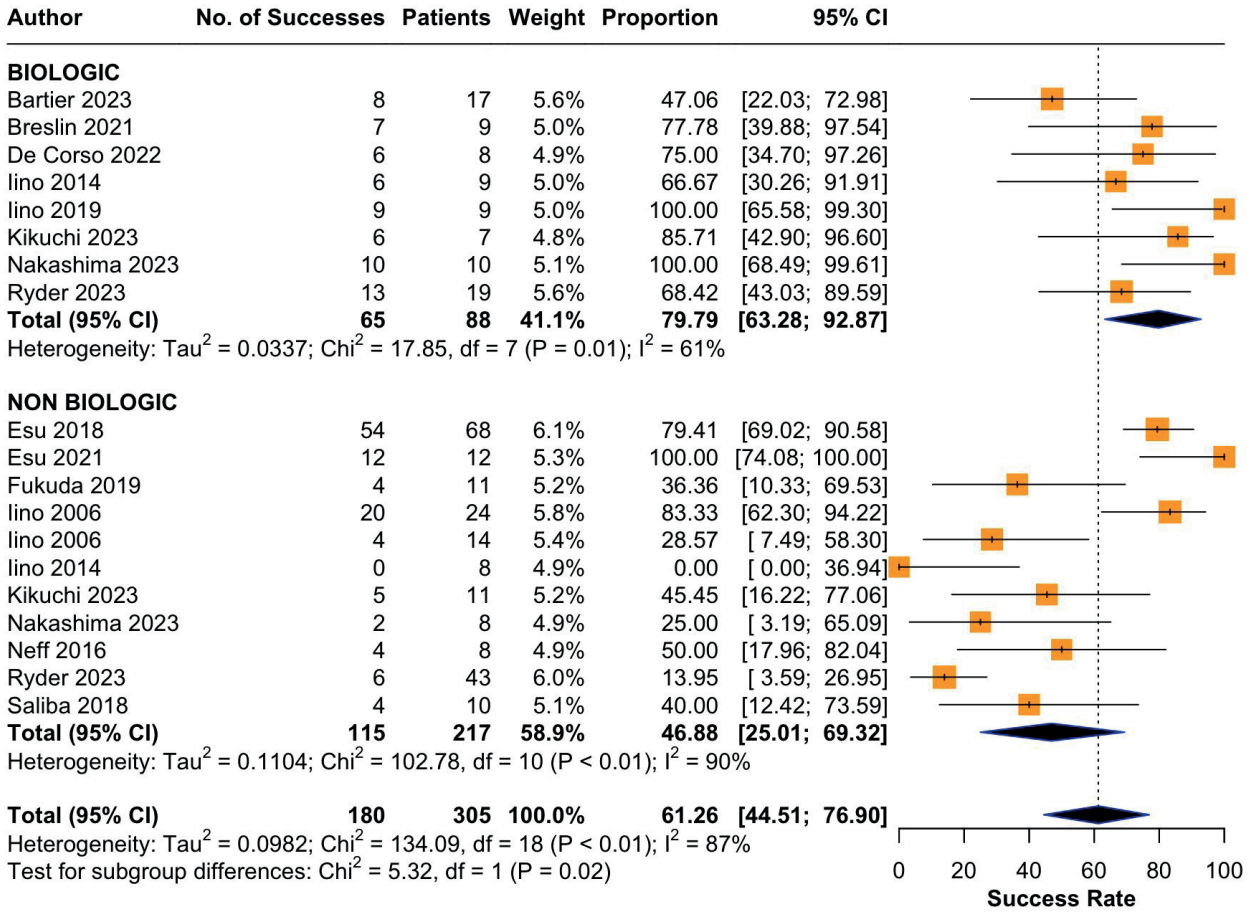

Figure 2. Success rates of treatments for EOM. Results are presented in percentages with their 95% confidence interval. Studies were divided into two groups: those which comprised monoclonal antibodies directed against the type 2 inflammation cascade (BIOLOGIC), and those which did not (NON BIOLOGIC).

Over the last years different monoclonal antibodies have been approved for the treatment of upper and lower airway inflammatory diseases, such as asthma or CRSwNP [11]. Literature addressing the use of biologics for EOM are mainly reports in which biologics were prescribed in light of the comorbid asthma or CRSwNP [8,12,14,22,24]. Our meta-analysis shows that biological therapies can achieve better results than traditional treatments for EOM. However, the success rates vary amongst studies, as well as the clinical manifestations. This could be related to the underlying molecular mechanisms of the type 2 inflammation [32] or the presence of so-called mixed endotypes. The current data does not allow for a comparison between the various biologics, which could also play a role in the variation of success rates in the biological group. Also, separate analyses of individual treatments were not possible due to a lack of reporting of success rates for individual patients, and due to an often mixed strategy with multiple treatments in the same patient.

Drawing general conclusion from our results should be done with caution due to the limitations and the bias of the included articles, which were all observational studies with high inconsistency in terms of design, interventions and outcomes. Such diversity led to the incorporation of several definitions for a successful treatment: improvements in EOM severity scores [23], resolution of otorrhea, tympanic perforation closure [26] or reduced oral steroid intake [21]. Some studies [27] also reported the outcomes in terms of ears instead of patients, and their number had to be converted in order to be included in our meta-analysis. Most studies were of retrospective non-comparative nature or simple case series on limited numbers of patients; this prevented us to construct a pairwise meta-analysis. Additionally, the included studies employed different treatments strategies for EOM, that for our analysis we classified into two main groups (biologic and non-biologic). These variations among studies are responsible for the high heterogeneity observed in our results (Figure 2), which is common in a proportion meta-analysis, and prevented us from exploring further differences among treatments with subgroup analysis and highlighted the need for standardized methodologies in future research.

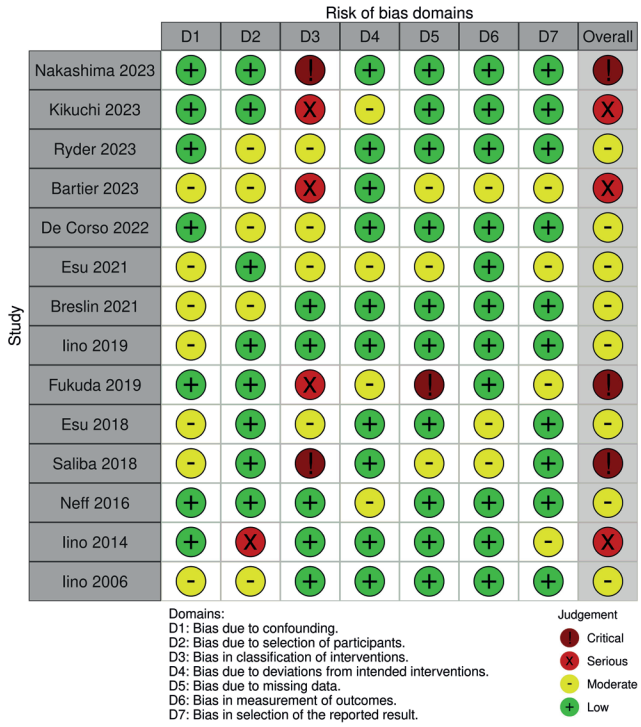

Figure 3. Results from the risk of bias assessment through the ROBINS-I tool. Several domains are assessed, the last column gives the overall judgment on the risk of bias of the individual study.

Conclusion

Given the sparse literature on this rare disease, the current meta-analysis represents in our view the best possible approach to attain some degree of certainty on treatment outcomes for EOM. As such, the promising results of biological treatment should prompt health care providers dealing with this condition to consider if any indication for biologics can be set, either for the often comorbid asthma, or CRSwNP.

Acknowledgement

None.

Authors' contributions

ML: Data curation; Formal analysis; Investigation; Methodology; Roles/Writing - original draft. HE: Data curation; Investigation; Methodology; Writing - review & editing. PM: Supervision, Validation, Methodology. EvS: Supervision, Validation, Methodology. WF: Supervision; Writing - review & editing. SR: Conceptualization, Project administration; Validation; Supervision; Writing - review & editing.

Funding

None.

Conflicts of interest

ML, EH, PM and EvS have no conflict of interest to declare. WF is an advisory board member of Sanofi, GSK, and Dianosic. SR has acted as a consultant and/or advisory board member for Sanofi, GSK, and Novartis. The department of Otorhinolaryngology and Head/Neck Surgery of the Amsterdam UMC has received research funding from Sanofi, GSK, and Novartis.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Summary of findings for the GRADE quality assessment.

Quality assessment						
Participants (studies)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
361 patients from 14 non-randomised studies	serious [a]	serious [b]	not serious	not serious	serious [c]	⊗○○○ Very low

[a] The influence of confounding factors was not addressed in any of the 14 included studies [8,12,13,20-30]. In Bartier et al. [21] patients switched between different biologics; deviation from intended intervention was rated as serious. In 5 studies [21,22,23,25,27] there was bias due to missing data. [b] Interventions varied greatly among studies and this is reflected in the high heterogeneity found with I^2. [c] Because of small sample sizes of some individual studies [12,23,25,27,28].