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Original Article

Efficacy of Biologic Therapies for Eosinophilic Otitis Media: A Systematic Review and Meta-analysis

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BACKGROUND: Eosinophilic otitis media, first reported in Japan, is a viscous, intractable otitis media often linked to bronchial asthma and chronic rhinosinusitis, characterized by highly viscous middle ear effusion. Its pathological mechanism remains unclear and the condition occasionally does not respond to steroids. It is now recognized as a rare type 2 inflammatory disease and should be treated specifically to enhance quality of life. This systematic review and meta-analysis evaluated the efficacies of biologic treatments.

METHODS: We searched PubMed, SCOPUS, Embase, Web of Science, and Cochrane databases up to September 2023. We retrieved ear examination findings, otitis media-related and symptom scores, air–bone gaps and hearing thresholds, serum eosinophil, and immunoglobulin E (IgE) levels before and after biologic treatments.

RESULTS: Biologics treatment significantly improved subjective otitis media-related scores, compared with control group (standard mean difference (SMD) −1.62; 95% confidence interval (CI) [−2.24; −1.01], $I^2 = 54\%$). Additionally, the serum eosinophil counts and IgE levels significantly decreased (SMD −1.40; 95% CI [−1.99; −0.81], $I^2 = 0\%$) after 6-12 months of biologic treatments, but the hearing thresholds did not significantly change. There were no significant differences between groups treated with dupilumab and groups treated with other biologics.

CONCLUSION: Biologics treatment for eosinophilic otitis media significantly improved subjective otitis media-related scores and decreased serum eosinophil and IgE levels, but no significant changes in hearing threshold. More randomized cohort studies are needed to confirm the efficacies of biologics in patients with refractory eosinophilic otitis media.

KEYWORDS: Eosionophilic otitis media, biologics, dupilumab, type 2 inflammation

INTRODUCTION

Eosinophilic otitis media can be an intractable disease; eosinophil-dominant exudates accumulate in the middle ear cavity or middle ear mucosa, accompanied by inflammation.[1] Exudates with high proportions of eosinophils may be quite viscous. The condition was first described in 1952 by Derlacki.[2] Lino et al[3] suggested diagnostic criteria; the major criterion is an eosinophil-dominant middle ear exudate or otitis media with effusion.[4] At least 2 of 4 minor criteria should also be met: viscous middle ear exudate, bronchial asthma, nasal polyposis, and/or refractory disease.[2-4] A pathological diagnosis with formalin-fixed, paraffin-embedded middle ear mucosa was evaluated for eosinophil activation and degranulation in the effusion.[3,4]

Eosinophilic otitis media usually responds well to topical or systematic steroids.[5] If it does not respond to these treatments, the disease persists and may be accompanied by neurological hearing loss, especially at high frequencies.[4,6,7] The hearing threshold at 4 kHz for patients with eosinophilic otitis media may be about 10 dB higher than for patients with chronic otitis media.[8] This hearing loss may be due to severe inflammatory changes or extensive exudate in the mucous membrane.[1]

Although the pathophysiological mechanism of eosinophilic otitis media remains unclear, chemoattractants secreted by eosinophils, such as interleukin (IL-5) or eotaxin, are presumably involved.[9] According to the minor criteria of eosinophilic otitis media, eosinophilic otitis media is often accompanied by and highly correlated with asthma and diffuse type 2 chronic rhinosinusitis with nasal polyp.[10-12] Rhinosinusitis/polyposis is also associated with increased levels of immunoglobulin E (IgE), IL-4, IL-5, IL-13, and eosinophils.[13] Biologic treatments seek to reduce IgE, IL-4, IL-5, and IL-13 production in patients with refractory type 2 chronic

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rhinosinusitis with nasal polyposis.[14] Previous studies showed that, after biologic treatments, eosinophil levels decreased with improved status of asthma, nasal polyps, or eosinophilic otitis media.[15-20]

Biologics that reduce IL-4, IL-5, IL-13, or IgE levels have not been approved as treatments for eosinophilic otitis media; there have been no relevant studies. Biologics effectively treat uncontrolled asthma and type 2 chronic rhinosinusitis with nasal polyposis. However, no study has explored whether chemoattractant reduction can alleviate eosinophilic otitis media. The aim of the presented meta-analysis was to study the effectiveness of biologics in patients with eosinophilic otitis media.

MATERIAL AND METHODS

Search Strategy and Study Selection

We searched PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials up to September 2023. This analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[21] The following keywords were used: "biologics," "eosinophilic otitis media," "dupilumab," "omalizumab," "benralizumab," "mepolizumab," "reslizumab," "biologic treatment," and "eosinophils."

Two authors independently reviewed all abstracts and titles. All included studies were published in English. Both authors carefully reviewed the entire manuscript if the abstract and title did not clearly indicate fulfillment of inclusion/exclusion criteria. Prospective and retrospective studies that included symptom scores (otitis severity indices and chronic otitis media outcome tests), objective and subjective ear findings (tympanometric data, air conduction thresholds, and/or bone conduction thresholds), and serum tests (the IgE level and/or eosinophil count) were included. Subjective ear exam finding based on severity used a 3-point scale and clinically scored otitis media-related scores using 5 items with scores of 0-2 points.[15,17]

Studies were excluded if they involved patients not diagnosed with eosinophilic otitis media or patients who did not receive at least 1 biologic. Other excluded studies were duplicate works, studies with results that were difficult or impossible to quantify, and case reports with minimal or no comparative data.[20,22-24] Figure 1 summarizes the search strategy.

Data Extraction and Risk of Bias Assessment

Using standardized forms, the 2 authors independently extracted all data.[25,26] In the control, biologics, and dupilumab groups, pre- and post-treatment changes in subjective and objective ear, symptom, and disease severity scores; otitis severity indices; and chronic otitis media outcome tests were evaluated, with a particular focus on a 6-12 month follow-up comparison between pre- and post-treatment. *P*-values, patient counts, and scale scores were compared between biologic and control groups or within biologic groups before and after treatment. We used the Newcastle–Ottawa Scale to assess the risks of bias in all studies; the qualities were good or fair.

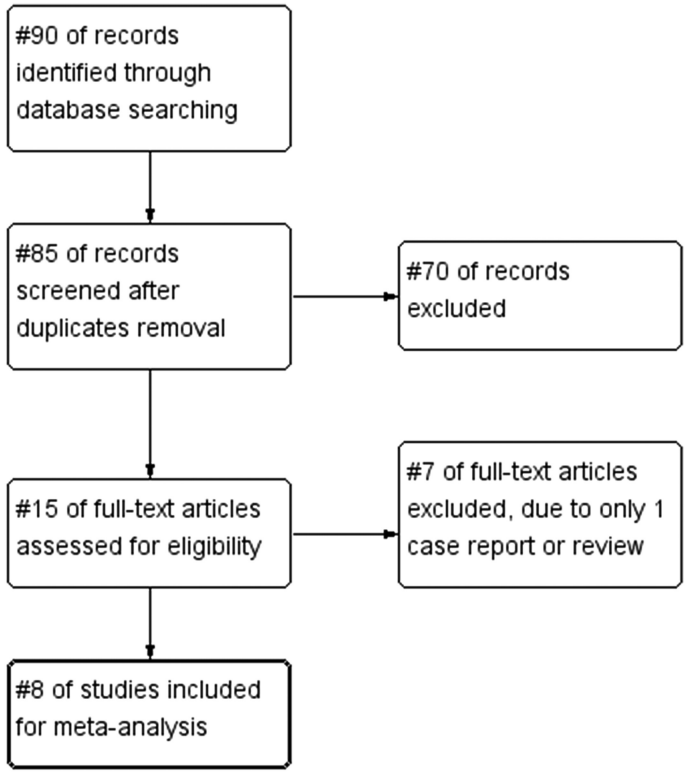

Figure 1. Study selection diagram.

Statistical Analysis

RevMan Manager software version 5.4.1 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used. The 95% CIs of weighted mean differences (MDs) are reported. The *P*-values of chi-squared test results and the I^2 values were used to determine statistical heterogeneity. At breakpoints of 40% and 60%, I^2 heterogeneity was classified as low, medium, or high. When heterogeneity was high, a random-effects model was used. When heterogeneity was low or medium, a fixed-effects model was utilized. The threshold for statistical significance was defined as $P < .05$. Treatment effects were assessed by deriving MDs or standard mean differences (SMDs) if the variables were continuous.

RESULTS

Finally, we retrieved 8 relevant studies.[5,15,-19,27,28] Figure 1 shows data regarding the 171 included patients. The study characteristics are summarized in Table 1.

Changes in Ear Examination Findings and Otitis Media-Related Scores

Subjective ear examination findings and disease severity scores were available for 142 patients. Ear examinations evaluated otorrhea, granulation, retraction, effusion, and eardrum perforations; total scores ranged from 3 to 10. Pre- and post-treatment scores were

MAIN POINTS

- This systematic review and meta-analysis assessed the effectiveness of biologics treatment on eosinophilic otitis media.
- Biologics treatment for eosinophilic otitis media improved subjective scores and decreased serum eosinophil count and immunoglobulin E (IgE) levels, but had no significant effect on hearing threshold level.
- More randomized cohort studies are needed to confirm biologic efficacy in patients with refractory eosinophilic otitis media.

Table 1. Summary of Included Studies

Study	Design	Nation	Number of Patients (n)	Indication of Biologics Use	Comparison	Time Frame of Follow-up	Time Frame of Follow-up	Analyzed Outcomes	Reported Side Effects
Iino 2012	Prospective study	Japan	8	EOM patients associated bronchial asthma	Omalizumab (0.016 mg/kg per IU/mL of IgE per 4 weeks, every 2 or 4 weeks)	More than 3 months	3, 6, 12 months	Bone conduction threshold (at speech range and 4kHz) and asthma control test score before and after treatment	No side effects
Iino 2014	Retrospective chart review	Japan	9	EOM patients associated bronchial asthma	Omalizumab (0.016 mg/kg per IU/mL of IgE per 4 weeks, every 2 or 4 weeks)	3 months or more than 1 year	3, 12 months	Eosinophil cationic protein and IgE level in middle ear effusion and serum, IL-4 and IL-5 level in middle ear effusion before and after treatment	No side effects
Iino 2019	Retrospective chart review	Japan	9	EOM patients associated bronchial asthma	Mepolizumab (100 mg, every 28 days)	More than 6 months	More than 1 year	Changes in otitis media severity score, bone conduction threshold (at speech range and 4kHz), symptom score, serum eosinophil and IgE level before and after treatment	N/A
Breslin 2021	Retrospective chart review	USA	9	EOM patients	Benralizumab or mepolizumab	Mean 17.1 months	N/A	Serum eosinophil count before and after treatment	Fatigue, myalgia
Iino 2021	Retrospective chart review	Japan	3	Severe refractory EOM patients associated bronchial asthma	Dupilumab (600 mg at first time, and then 300 mg, every 2 weeks)	More than 6 months	3, 6, 9, 12 months	Symptom score, computed tomography scan score, and air conduction threshold (at speech range), serum eosinophil and IgE count before and after treatment	No side effects
De Corso 2022	Retrospective observational study	Italy	8	Refractory EOM patients associated severe eosinophilic asthma or severe uncontrolled chronic rhinosinusitis with nasal polyp	Duplinumab with/without omalizaumab, mepolizumab, or benralizumab	N/A	6 months	Changes in otitis media severity index, chronic otitis media outcome test (COMOT-15), nasal polyp score, SNOT-22, sniffin' stick test, and peak nasal inspratory flow before and after treatment	N/A
Ryder 2023	Retrospective chart review	USA	30	Refractory EOM patients associated type 2 chronic rhinosinusitis with nasal polyp, or asthma	Duplinumab with/without benralizumab, mepolizumab, or reslizumab	More than 18 months	N/A	Changes in objective (tympanometry) and subjective ear findings, air–bone gap, and subjective nasal endoscopic findings before and after treatment, post-treatment serum eosinophil level (k/UI)	N/A
Nakashima 2023	Retrospective chart review	Japan	8	EOM patients associated recurrent chronic rhinosinusitis with nasal polyp or bronchial asthma	Duplinumab with/without omalizumab, mepolizumab, or benralizumab	More than 6 months	Mean 57 months	Changes in air–bone gap, air and bone conduction threshold (at speech range and 4kHz) before and after treatment	No side effects

EOM, eosinophilic otitis media; IgE, immunoglobulin E; IL, interleukin; N/A, not available; SNOT, sino-nasal outcome test.

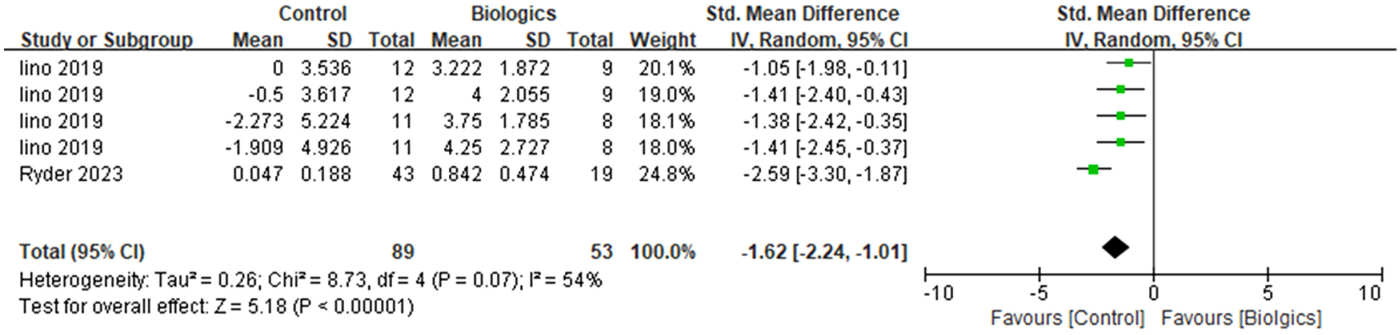

Figure 2. Forest plot of changes in ear examination findings and otitis media-related scores.

recorded for control participants and patients treated with biologics. A forest plot is shown in Figure 2. The ear examination severity scores improved by 1.6 points in patients treated with biologics compared with control participants; the difference was statistically significant [SMD −1.62; 95% CI (−2.24; −1.01), I^2 = 54%]. Subgroup analysis of 6-12-month follow-up data revealed that the severity score improved by 1.2 points, with low heterogeneity [SMD −1.40; 95% CI (−1.99; −0.81), I^2 = 0%].

Otitis Media Symptom Scores Before and After Biologic Treatments

Subjective scores—the symptom score (maximum 35) and chronic otitis media outcome score (maximum 75; based on ear symptoms, hearing, and mental health)—were compared in 29 patients before and after biologic treatments. Otitis media symptoms were significantly more severe before than after such treatments [SMD 2.41; 95% CI (1.67; 3.160, I^2 = 0%] (Figure 3).

Changes in Air–Bone Gap and Hearing Threshold

Pure-tone audiometric data of 30 patients were compared before and after biologic treatments. A forest plot is shown in Figure 4. Neither the air (at speech range) nor bone (at speech range and 4 kHz) threshold levels significantly changed after biologic treatments. The air–bone gap did not differ between patients treated with biologics and control participants.

Serum Eosinophil and Immunoglobulin E Levels Before and After Biologic Treatments

Absolute eosinophil counts in peripheral blood and serum IgE levels were compared before and after biologic treatments in 4 studies. A forest plot is shown in Figure 5. The serum eosinophil count was significantly higher before than after biologic treatments [SMD 1.83; 95% CI (0.89; 2.76), I^2 = 84%]. The serum IgE level was also significantly higher before than after biologic treatments [MD 281.53; 95% CI (123.22; 439.85), I^2 = 0%]. These results were derived using only data acquired from 6-12 months of biologic treatments.

Changes in Ear Examination Findings and Otitis Media-Related Scores Among Patients Treated with Dupilumab and Other Biologics

We performed subgroup analyses regarding the otitis severity index and chronic otitis media outcome test scores of patients treated with dupilumab and non-dupilumab biologics (Figure 6). Patients treated with dupilumab exhibited slightly larger improvements in subjective scores after treatment [SMD −0.30; 95% CI (−0.92; 0.33), I^2 = 43%]. However, the difference was not statistically significant.

DISCUSSION

Eosinophilic otitis media is poorly understood, underdiagnosed, and often difficult to treat.[1,5] However, no definitive treatment of choice is currently available.[5] The treatment should be tailored to enhance the quality of life for those with eosinophilic otitis media, patients associated with bronchial asthma, and type 2 chronic rhinosinusitis with nasal polyps, with further research focusing on phenotypes and treatment strategies.[29] Here, we explored whether biologics that effectively treat type 2 chronic rhinosinusitis with nasal polyposis could demonstrate efficacy in patients with eosinophilic otitis media.

In our study, patients treated with these biologics exhibited significantly greater improvements in subjective otitis media severity scores compared with control participants. An important diagnostic criterion for eosinophilic otitis media is a high eosinophil count in the middle ear effusion.[3] Therefore, eosinophilic otitis media may be an extension of asthma, chronic rhinosinusitis with nasal polyposis, and diffuse type 2 inflammation.[30] A previous study showed that the levels of the eosinophil-derived neurotoxins IL-4 and IL-5 were significantly elevated in middle ear effusions.[31] Eosinophilic otitis media may improve when Eustachian tube function is enhanced by

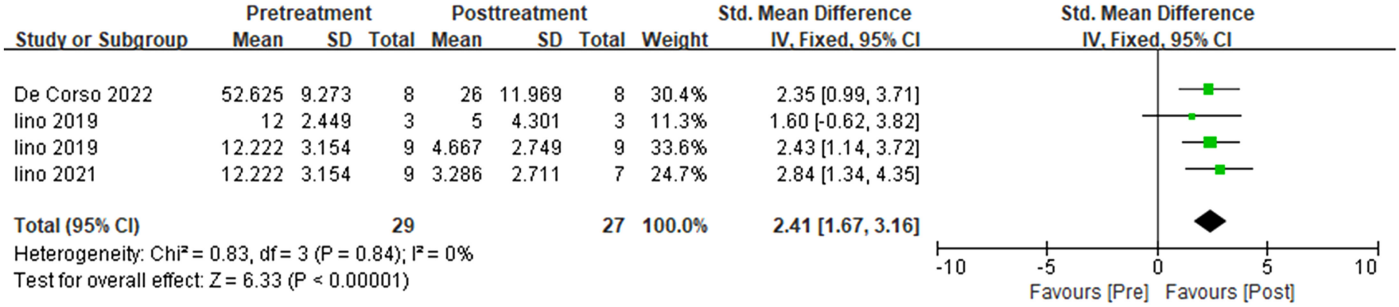

Figure 3. Forest plot of otitis media symptom scores before and after biologic treatments. CI, confidence interval; SD, standard deviation.

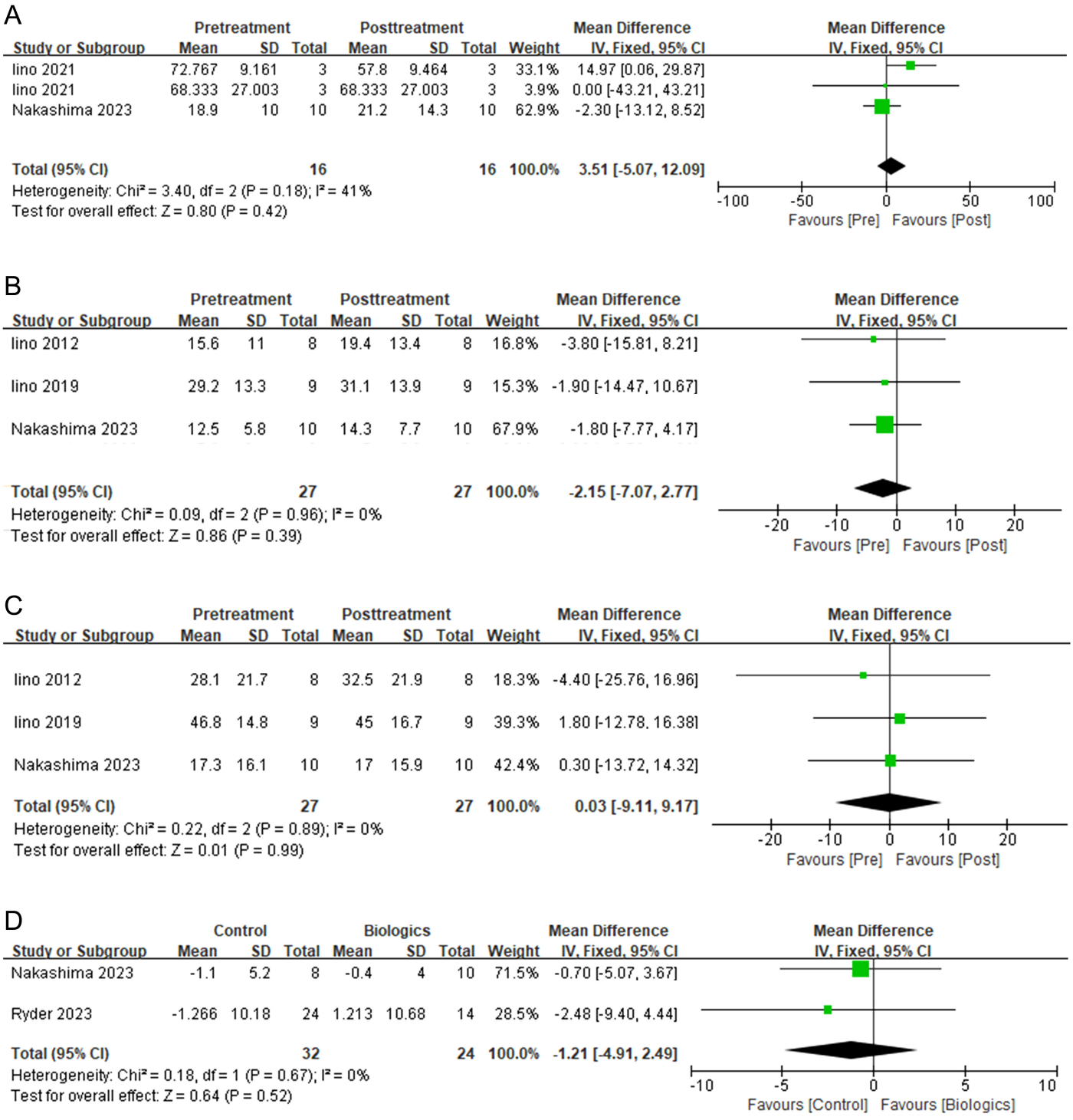

Figure 4. A-D. Forest plot of changes in air conduction threshold at speech range (A), bone conduction threshold at speech range (B), bone conduction threshold at 4 kHz (C), and air–bone gap at speech range (D).

biologics.[32,33] However, unlike computed tomography, chronic otitis media outcome scores and subjective severity stratifications via ear examinations are not objective.

Corticosteroid therapy may be the treatment of choice for eosinophilic otitis media, and intratympanic steroids were reported as the most effective treatment for eosinophilic otitis media.[4] However, there have been few systematic reviews of biologic treatments (with the exception of omalizumab) for eosinophilic otitis media.[4] Severe eosinophilic otitis media associated with high-level periostin expression does not respond well to corticosteroids.[34]

The biologic treatment indications for eosinophilic otitis media remain unclear; no consensus regimen is available.[5,27] In our study, the subjective scores, serum eosinophil counts, and serum IgE levels significantly decreased over 6-12 months after biologics treatment, compared with values recorded before treatment. The selection of appropriate biologics to treat eosinophilic otitis media is still unclear.

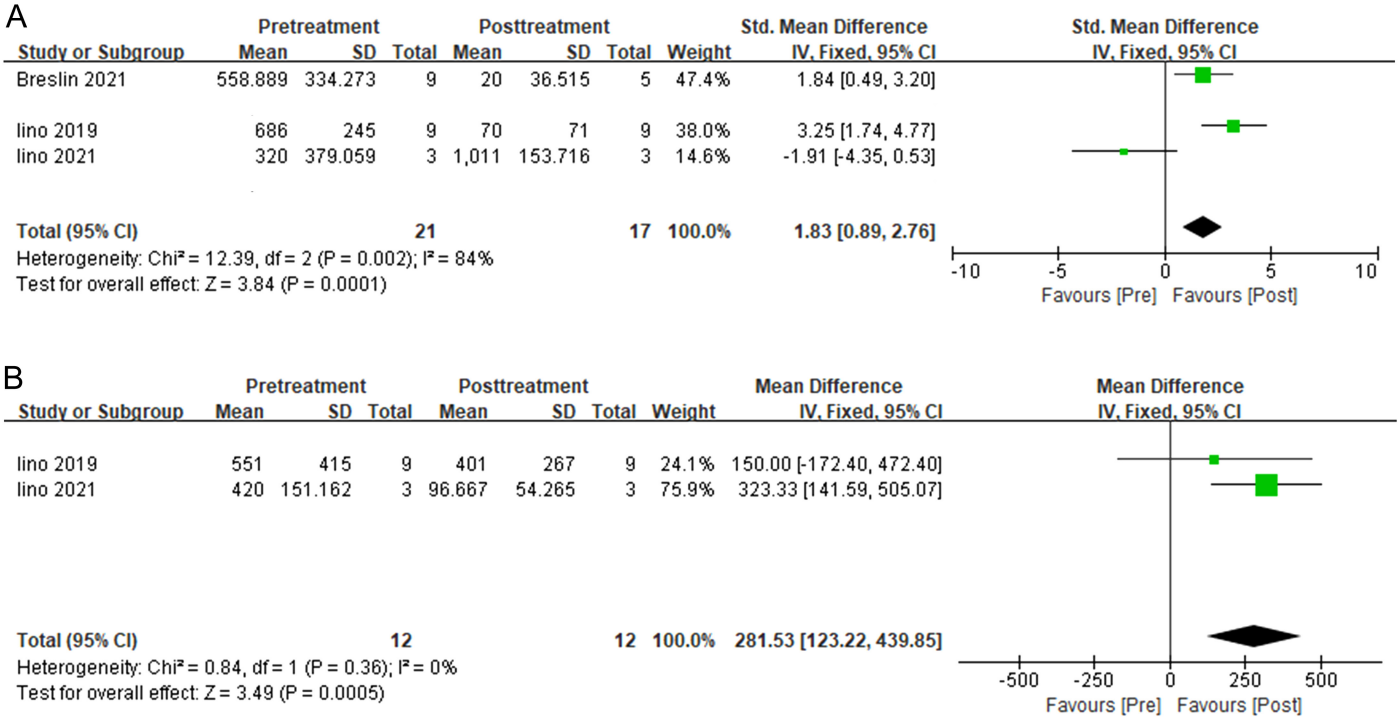

Figure 5. A, B. Forest plot of serum eosinophil (A) and immunoglobulin E levels (B) before and after biologic treatments.

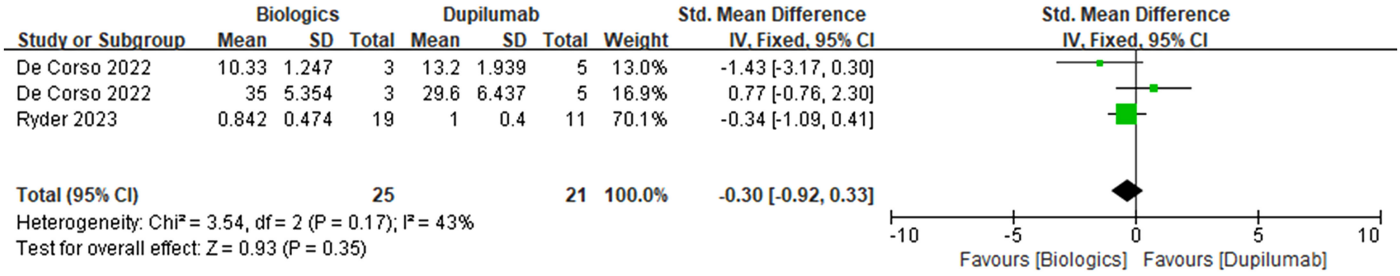

Figure 6. Forest plot of changes in ear examination findings and otitis media-related scores among patients treated with dupilumab and other biologics.

One previous report showed that dupilumab effectively treated severe asthma, refractory eosinophilic chronic rhinosinusitis, and eosinophilic otitis media.[33,35] However, mepolizumab and benralizumab yielded conflicting results.[33,35] These results suggest that the pathology of eosinophilic otitis media may be related to IL-4 and IL-13. However, our subgroup analysis revealed no significant differences between the dupilumab-treated group and the other biologics treated group in terms of ear examination findings or otitis media-related scores. Further studies regarding the effects of biologics on eosinophilic otitis media are essential to define the pathological mechanism involved and to derive indications for such treatments, as well as appropriate regimens.

In our study, heterogeneity was observed upon comparison of serum eosinophil counts. Dupilumab does not affect IL-5-induced eosinophil release from bone marrow; instead, it blocks IL-4- and IL-13-induced eosinophil survival, activation, and tissue recruitment. Thus, the serum eosinophil count may be elevated after treatment with dupilumab.[16,36,37]

Patients with eosinophilic otitis media have a high risk of hearing loss, compared with patients who exhibit chronic otitis media; the hearing thresholds at 4 kHz may differ by approximately 10 dB.[8,17] It has been reported that biologics treatment can control hearing status in eosinophilic otitis media.[27] On the contrary, we found no significant treatment-related changes in hearing threshold, air conduction, or bone conduction (both speech range and at 4 kHz). However, some patients may have taken corticosteroids, which prevent hearing loss. The hearing thresholds before treatment may also have differed in each patient. Additionally, prior surgery to treat eosinophilic otitis media or tympanic membrane perforation may have affected the air–bone gap.

This study had several limitations. First, the number of studies and patients was small. The included studies enrolled fewer participants compared with studies regarding the effectiveness of biologics in patients with severe asthma and atopic dermatitis. Although further studies with larger cohorts are needed, eosinophilic otitis media is not very common. As more randomized controlled studies or comparative studies on eosinophilic otitis media are added to international journals, further meta-analysis is needed. Second, the use of systemic corticosteroids, which can affect the middle ear mucosa and hearing threshold, may have differed among patients. Third, prior surgeries to treat eosinophilic otitis media may not have been reported; many

studies also did not control for the use of non-biologic medications. Fourth, otitis media severity was assessed in different ways (i.e., via ear examinations or subjective patient reports). Finally, most patients were Asian. The middle ear anatomical structure may vary according to ethnicity; more international studies are required to generalize the results.

In conclusion, biologic treatments for eosinophilic otitis media significantly improved the subjective scores compared with the scores of control participants. After 6-12 months, the subjective scores, serum eosinophil counts, and serum IgE levels significantly decreased. No significant changes in hearing thresholds were apparent. Ear examination findings and the otitis media-related scores of patients treated with dupilumab and patients treated with other biologics did not significantly differ. Further randomized cohort studies are needed to confirm the efficacies of biologics in patients with refractory eosinophilic otitis media.

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